CATALYSIS OF ORGANIC REACTIONS

Part I: Enhancement of a Solid State Reaction by Proper Orientation Within a Crystal

Part II: Micellar Effects on the Stereochemistry and Rate of Aqueous Solvolysis Reactions

Thesis by

Chaim N. Sukenik

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Abstract

Part I. The solid state rearrangement of methyl-p-dimethylaminobenzenesulfonate to the trimethylammoniumbenzenesulfonate zwitterion was studied by a combination of spectroscopic techniques. NMR, Field Desorption Mass Spectrometry, and X-Ray Crystallography were employed to determine the mechanism of this reaction. It was shown to be an intermolecular nucleophilic displacement whose rate is greatly enhanced by the crystallinity of the starting material.

Part II. A study of the effects of micelles on the aqueous solvolysis of alkyl-p-trimethylammoniumbenzenesulfonates revealed that anionic micelles could change the rate and stereochemistry of the solvolysis reaction. The mechanism for the observed rate retardation and induced decrease in stereochemical integrity was probed and a unified mechanistic hypothesis is presented.

Acknowledgments

I would like to thank my research supervisor Professor Robert G. Bergman for all that he has taught me both as a scientist and as a human being; for his constant encouragement and infinite patience, I am most grateful. I would like to thank Neil and Gretchen Mandel for their unselfish help in so many aspects of my work. Also, to all my colleagues in the Bergman group through the years, thank you for always being a friendly source for many discussions and ideas.

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Last but certainly not least, to my wife and daughter, for their love, understanding and patience, I can never thank them enough. I only hope that I can learn to be as generous and understanding towards them as they have been to me.

To Shelli

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דעה חכמה לנפשך
והיא כתר לראשך....

Part I: Enhancement of a Solid State Reaction by Proper Orientation Within a Crystal

I. Introduction

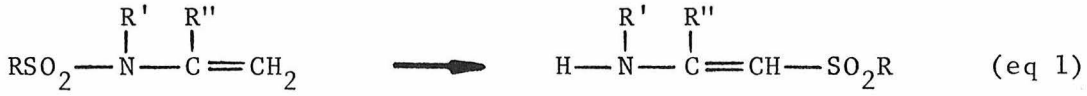
A. Background

The molecular forces which control both the inter- and intramolecular arrangement of atoms and molecules in a chemical reaction are reasonably well understood. Experimentally, however, few techniques are available which can effectively be used to generate and control those molecular orientations most favorable for chemical reaction in a given system. Perhaps the most spectacular examples of "geometrically" or topochemically controlled reactions are those catalyzed by enzymes. Nature has devised catalysts which appear to be perfectly designed to minimize both the entropic and enthalpic contributions to the free energy of the reaction transition state (1). Thus, an understanding of possible ways of controlling the reaction geometry for non-enzymic reactions would be of great value.

In this regard, the relative rigidity of the solid state has generated much speculation (2) that it could be an ideal way to simulate orientation dependent catalytic effects. In principle one could imagine two kinds of systems that would have a critical dependence on molecular orientation within a crystal. In one case, crystal packing forces could be used to constrain molecular conformation and either favor or disfavor a particular unimolecular reaction. A second possibility would be systems in which intermolecular interactions could be controlled by the relatively fixed positions of molecules within the crystal matrix (3).

The question of intermolecular orientational effects has been the

subject of much investigation. Many thoroughly studied examples of crystal directed product formation can be found in the area of solid state polymerization (4). In a wide variety of cases it has been shown that the relative orientation of monomer units dictates both the kinetics of polymerization and the nature of the polymer product. A similar use of crystal packing to propagate a more discrete chemical reaction is postulated in the radiation induced free radical isomerization of N-alkyl-N-vinylsulfonamides to N-alkyl-2-sulfonylvinylamines (eq 1). It



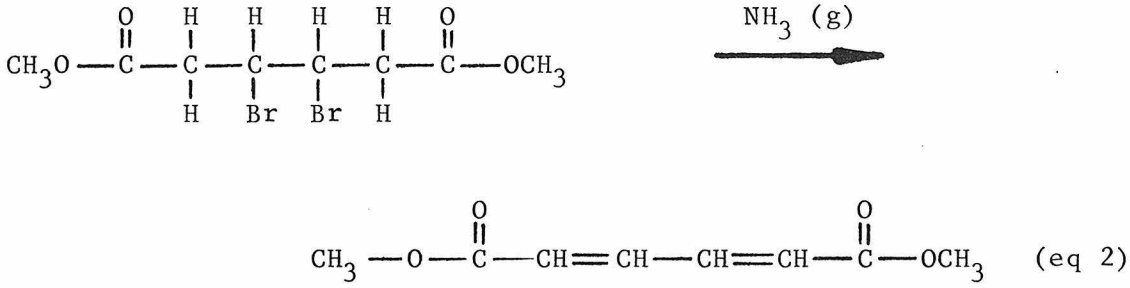
(eq 1)

was observed (5) that varying R could result in situations where crystallinity either enhanced or retarded the observed isomerization. It was further shown that the reaction was a chain process and the authors speculated that the orientation of molecules with respect to their nearest neighbor in the crystal could either enhance or retard the propogation of the radical chain.

A classic case of topochemical control in bimolecular processes is the work of Schmidt and coworkers (6) on the photodimerization of a variety of cinnamic acid derivatives. They were able to show that the relative orientation of starting material monomers could precisely predict the stereochemistry of the dimeric product.

The effect of crystal structure on molecular conformation has also been treated in a variety of systems. A good example of this effect

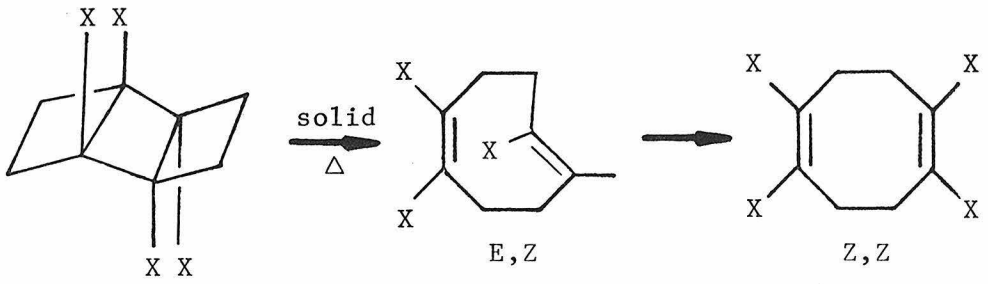
is the base catalyzed elimination of HBr from dimethyl meso-ββ' dibromo-adipate (7) (eq 2). In solution one obtains a mixture of cis-trans,



(eq 2)

trans-trans, and cis-cis dienes as well as a variety of side products. However, if the reaction is allowed to proceed in the conformationally fixed crystal one isolates only the trans-trans diene, the product expected by inspection of the crystal structure of the starting material.

A different kind of system that may demonstrate the constraints a crystal can impose on a unimolecular reaction is seen in the work of Bellus et al. (8) on the following reaction sequence (eq 3):



(eq 3)

X = H, $COOCH_3$, CN

When X = H or $COOCH_3$, only the ZZ isomer is isolated. However, when X = CN the reaction can be cleanly stopped at the relatively unstable E,Z isomer. The authors speculate that the crystal structure of the tetracyano starting material is such that only minimal motion is needed to go to the E,Z isomer. The reaction is stopped at that point by constraints imposed on it by the crystal lattice which forbid the more severe motion needed to go to the final product.

Such considerations raise the rather ironic possibility that when trying to use the solid state as an orienting medium for chemical reactions a problem that is the very opposite of that faced in solution may arise. Is the medium so rigid as to inhibit those molecular motions necessary for product formation? This very general question of the mobility of organic molecules within a crystal has been treated in a number of very elegant studies. McBride and coworkers have obtained considerable information on discrete atomic and molecular motions of very reactive intermediates (free radicals) in the decomposition of various peroxides and azo compounds (9). Gougoutas (10) has looked at some rare examples of topotactic reactions in which a crystalline starting material goes to a crystalline product whose structure can be analyzed and correlated, by postulated molecular motions, to the structure of the starting material.

B. Statement of Problem

In the course of our work on the solvolysis of a variety of alkyl benzensulfonate esters (11) we noticed a report by Kuhn and Ruelius (12), later confirmed by Brand and Rutherford (13), of the following reaction (eq 4). They indicated that gradually, on standing at room temperature,

(eq 4)

MSE ZWT

or more rapidly at higher temperatures, solid methyl-p-dimethylamino-benzenesulfonate (Methyl Sulfonate Ester - MSE) was cleanly converted to the p-trimethylammoniumbenzenesulfonate zwitterion (ZWT).

A few years later a report appeared by Valyashko and co-workers (14) in which they claimed that this apparent chemical transformation was in fact only a reorientation of MSE molecules from one crystalline modification to another. They based their conclusions primarily on UV data and the ability to recrystalize the "reaction product" and regenerate starting material.

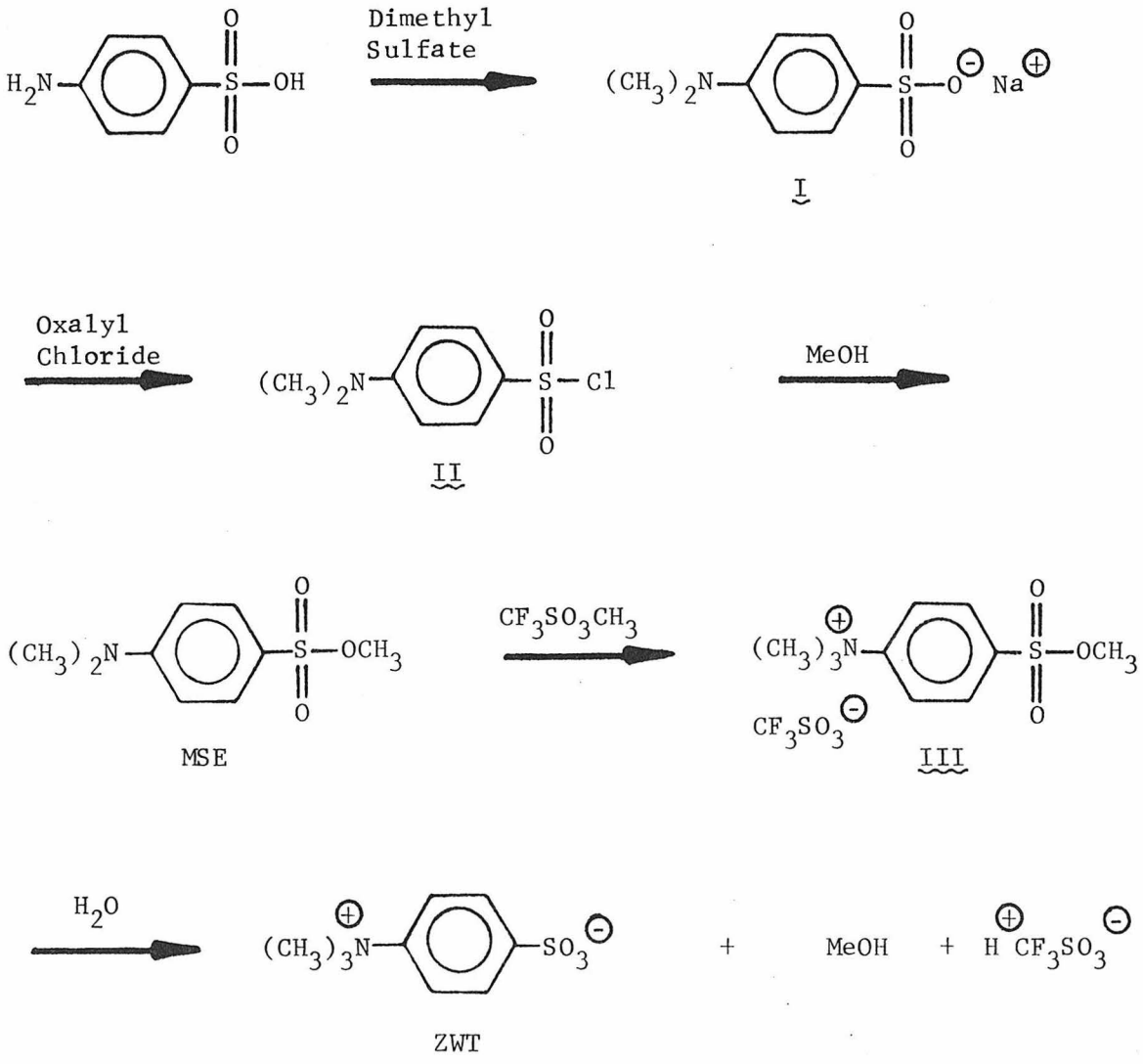
This controversy was of interest to us not only because modern spectroscopic techniques should easily determine whether the MSE → ZWT conversion was a real chemical transformation, but also because it

presented an interesting opportunity for a study of molecular motion in a solid state reaction. We therefore embarked on a detailed investigation of this reaction in the hope of answering the following questions: 1) Is the reaction a real chemical transformation and if so what is the mechanism of methyl transfer? 2) How does the structure of the starting MSE relate to the structure of the product and could we say anything about the kinds of molecular motion the crystal would allow? and 3) What role, if any, does the nature of the crystal lattice play in promoting the observed transformation?

II. Results and Discussion

We independently synthesized both MSE and ZWT by the route outlined in Scheme I (15). It should be noted that ZWT could also be obtained

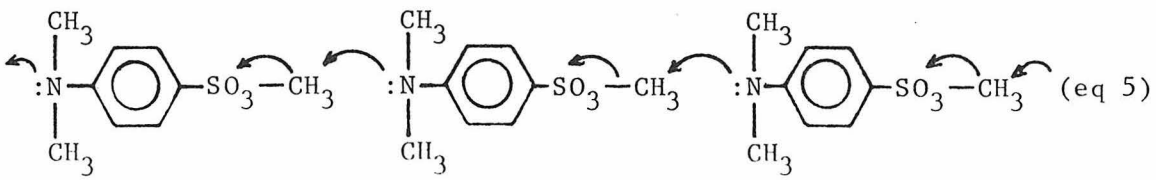
Scheme I



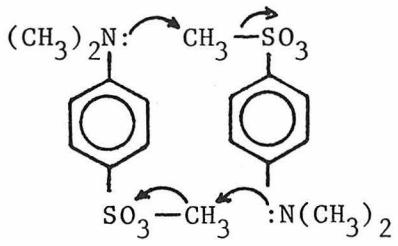
from the solvolysis of other alkylated sulfonate esters [see experimental section and ref. (11)].

Even the most concentrated solutions of MSE in a variety of organic solvents were unchanged over long periods of time (months or more). However, solid MSE, on standing at room temperature, was cleanly converted to ZWT which was identical in every respect with material obtained by solvolysis. Furthermore, we were unable to regenerate any MSE by the reported (14) recrystalization of ZWT from aqueous ethanol. We thus concluded that the reaction was in fact proceeding as initially reported (12,13) and turned our attention to the mechanism of methyl migration.

There are two general mechanisms that might convert MSE to ZWT. One possibility would be a simple intramolecular shift of the ester methyl to the dimethyl amino group. While this is a straightforward process, it is difficult to believe that the transition state for such a transfer would not involve very severe molecular distortion. Alternatively one might suggest an intermolecular chain reaction as shown in (eq 5), or at least a dimeric process as in (eq 6), or some variation on this intermolecular theme.

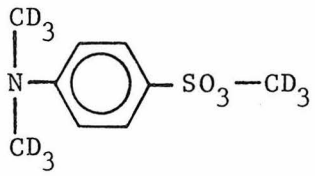


(eq 5)

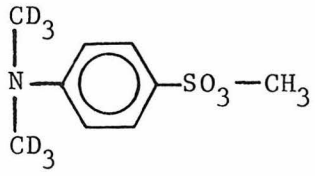


(eq 6)

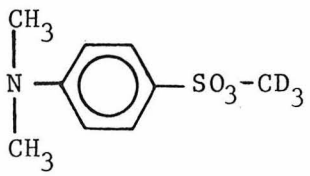
The basic question of inter- versus intramolecularity was amenable to solution by a simple "double label scrambling" experiment. Therefore, using commercial perdeuterated dimethyl sulfate and CD_3OD, we synthesized the following deuterated MSE isomers.



MSE-d_9



MSE-d_6



MSE-d_3

If the reaction were intramolecular, then a mixture of MSE-d_0 and MSE-d_9 would react to give only ZWT-d_0 and ZWT-d_9; while an intermolecular transfer of the ester methyl group should produce a 1:1:1:1 ratio of

ZWT-d_0:ZWT-d_3:ZWT-d_6:ZWT-d_9. While this seems relatively straightforward, the problem we initially encountered was that the only way to analyze for the ratio of deuterated ZWT isomers is by mass spectrometry. This was problematic since ZWT could not be volatilized in a conventional electron impact mass spectrometer even with the direct solid inlet probe at 500° and 10^{-8} Torr. Fortunately, a series of reports concerning the field desorption mass spectra (17) of a variety of organic salts (18) indicated that our zwitterion might be analyzable by this technique. After much searching for "the right man with the right machine", we developed a collaboration with Pui-Yan Lau and Gordon Wood of the University of Windsor, wherein we did the chemistry and they ran the spectra. [Interestingly our analysis was the first attempt ever to use FDMS as a tool for quantitative analysis and this aspect of our work has, independently, generated much interest (19).]

Authentic samples of ZWT-d_0 (m.w. = 215) and ZWT-d_9 (m.w. = 224), prepared from the appropriate MSE precursors, each gave a FDMS which showed essentially a parent molecular ion and little else. However, a complication arose when an equimolar mixture of separately generated ZWT-d_0 and ZWT-d_9, (a necessary control experiment), instead of giving two equal intensity peaks at 215 and 224, gave partially scrambled labeled methyl groups. In fact, any sample containing a mixture of CH_3 and CD_3 methyl groups gave results which approached a statistically random distribution of possible isomers. Fortunately, the randomization was not complete and the results were sensitive enough to variations in zwitterion ratios that we still were able to successfully analyze our data (Table 1).

Table 1. Results of Field Desorption Mass Spectrometry

entry	# scans	relative molar ZWT comp. d_0	d_3	d_6	d_9	observed peaks[a,b] 215	218	221	224
1	—	1	0	0	0	100	—	—	—
2	9	0	1	0	0	46	100	45	3
3	9	0	0	1	0	3	41	100	51
4	—	0	0	0	1	—	—	—	100
5	24	MSE-d_0 and MSE-d_9 Reaction Mix				44	100	101	46
6	9	1	1	1	1	44	100	98	46
7	14	1	0	0	1	61	100	94	65
8	8	2	1	1	2	49	100	101	54
9	12	1.74	1	1	1.74	47	100	98	52
10	18	1.6	1	1	1.6	46	100	99	47
11	10	0.7	1	1	0.7	44	100	96	39
12	12	0.3	1	1	0.3	37	100	98	34

[a] Intensities normalized so that peak at 218 = 100 (except entries 1,3,4).

[b] Average standard deviation = ± 5 units.

The actual experiment involved co-crystallizing a sample containing equal amounts of MSE-d_0 and MSE-d_9 from a homogeneous solution and allowing it to undergo solid state conversion to zwitterion. This mixed product was analyzed by FDMS (entry #5) and shown to be identical, within experimental error, with the expected intermolecular product, equal amounts of ZWT-d_0, d_3, d_6, d_9 (entry #6). Further controls were carried out (entries 7-12) to determine the limits of detection of an intramolecular reaction component. "Synthetic" potential product isomer mixtures with d_0:d_3:d_6:d_9 ratios of 1:0:0:1, 2:1:1:2, 1.74:1:1:1.74, and 1.6:1:1:1.6, which correlate to 0%, 67%, 73%, and 76% intermolecularity respectively, were analyzed. These data revealed that the observed reaction is $\geq$ 77% intermolecular (95% confidence limit).

Having established the intermolecularity of the rearrangement we now could view the role of the crystal in this reaction in two ways: either as a very concentrated reaction medium enhancing the reaction rate by allowing close (but isotropic) approach of the reacting molecules, or as a very specifically designed environment that aids the progress of the reaction by <u>orienting</u> reactive sites in such a way as to facilitate reaction. Either view would be consistent with the observed stability of MSE solutions relative to solid MSE. To test the importance of ordered crystallinity in this system, we decided to compare the rate of the reaction in the solid with the rate of the reaction in the pure melt, which is an unoriented medium of concentration equal to that in the solid. Since the melting point of MSE is 91° and plunging it into a 95° oil bath melts the entire sample within 15 seconds, we were able to

conveniently measure the rate of conversion of MSE to ZWT both as a crystal and a melt.

The data from this kinetic study are given in Table 2 and representative plots of percent conversion versus time at 81°, 88° and 95° are shown in Figure I. In all of the reactions MSE and ZWT were the only detectable species and the percent conversion of starting material to product was usually measured by partitioning the reaction mixture between $CDCl_3$ (dissolves only MSE) and D_2O (dissolves only ZWT) and integrating their respective NMR spectra.

As previously reported (12,13) the rate of rearrangement increases at higher temperatures (comparing ambient temperature, 81° and 88°) but our results indicate that this is only true for temperatures below the melting point of MSE. Melting the starting material introduces a sharp decrease in rate of conversion. Two striking examples of this comparison of crystal to melt are: in 10 min a crystal at 88° attains a higher degree of conversion to product than the 95° melt attains in over 4 hrs; a melt takes 500 min to achieve the same degree of conversion to product that a crystal at 81° (14° cooler than melt) attains in 20 min. This entire set of data seems to show that, at least in terms of initial rates of conversion, the crystal reacts between 25 and 40 times faster than the melt. This indicates that the solid state is providing more than just a high concentration medium for the intermolecular reaction.

In the hope of extending the scope of this rearrangement we prepared compounds IV, V and VI. However, none of these gave any indication of rearranging to the corresponding zwitterionic species even though one

Table 2. Kinetic Data for Conversion of MSE → ZWT[e]

Temperature	Rxn Time	Percent Product
Amb	1 day	3.3[a,d]
Amb	3 days	21.9[a,d]
Amb	8 days	49.3[a,d]
Amb	17 days	78.8[a,d]
81°	20 min	49[b]
81°	20 min	55[c]
81°	46 min	80
81°	46 min	87[c]
81°	80 min	88[b]
81°	120 min	90
88°	10 min	37[b]
88°	20 min	55[b]
95°	120 min	15[d]
95°	120 min	16
95°	180 min	26
95°	250 min	34
95°	500 min	53

[a]Data from ref (12). [b]All glassware EDTA and base washed. [c]MSE crystallized from MeOH before use. [d]Analyzed by weighing recovered MSE and ZWT. [e]Unless otherwise indicated all samples were powder obtained by rapid removal of solvent from a filtered solution of MSE in ether.

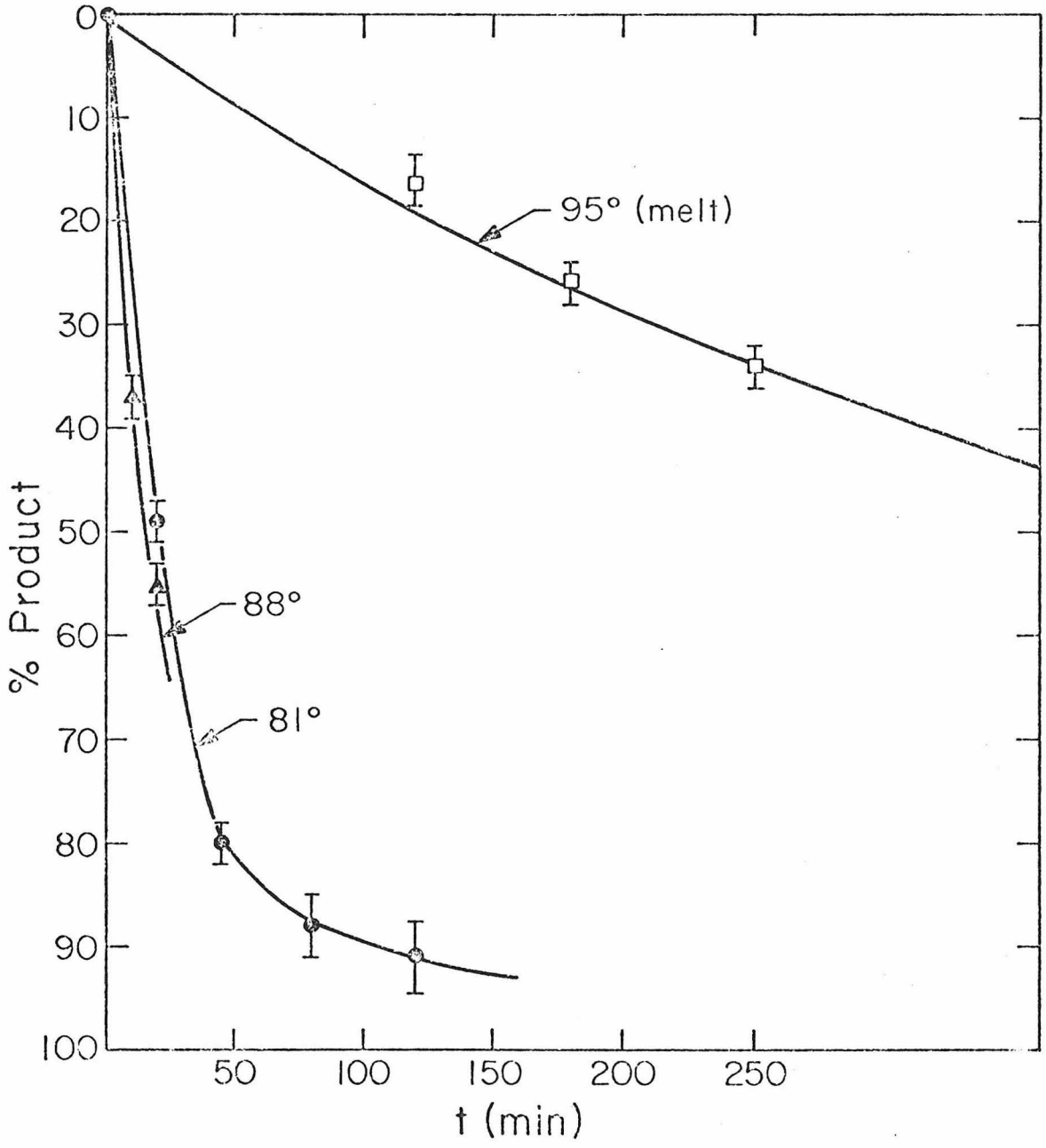
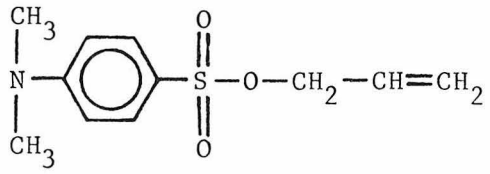
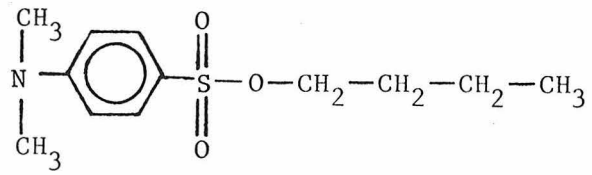


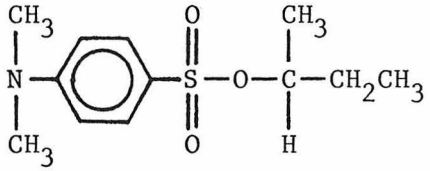
Figure I. Time dependence of the percent of product observed in the thermal conversion of methyl p-dimethylaminobenzenesulfonate (MSE) to p-trimethylammoniumbenzenesulfonate (ZWT) at three different temperatures. ○ = 81°, crystal; △ = 88°, crystal; □ = 95°, melt.



IV



V



VI

might have predicted that the kind of S_N2 process that we envisioned for MSE might be equally possible. Particularly disappointing was the lack of reaction in IV, where one might have predicted a relatively unhindered S_N2'-like process. Clearly the facility of the MSE→ZWT rearrangement goes beyond the normal reactivity of its functional groups.

All of the above evidence pointed towards the hypothesis that the crystal structure of MSE must play an important role in its reactivity. We therefore undertook, in collaboration with Jose Bonapace and Neil Mandel, to determine the single crystal structure of MSE using X-ray diffraction techniques.

Satisfactory crystals of MSE were obtained from methanol or from a methanol-water mixture. Because of the solid state decomposition, we could only obtain meaningful single crystal data for less than two days from any one given crystal. After two days of data collection at ambient temperature the intensities of three standard reflections

monitored at 30 reflection intervals decreased anisotropically 40, 45, and 60% respectively. Therefore, the data set used in this analysis consisted of three subsets individually corrected for decay, but collectively scaled together yielding 750 reflections whose intensities were greater than $3\sigma(I)$. The structure was solved by direct methods and refined by anisotropic full matrix least squares to a final $3\sigma R$ value of 0.098 and a goodness-of-fit of 4.13. The high residual is primarily due to the isotropic correction for the anisotropic intensity variation.

The lattice constants in the monoclinic space group $P2_{1/C}$, are $\underline{a}$ = 8.942(2) Å, $\underline{b}$ = 10.507(3) Å, $\underline{c}$ = 11.232(2) Å and $\underline{\beta}$ = 90.88(2) Å; with 4 molecules per unit cell the calculated density is 1.43 g cm^{-3}. The bond distances and angles listed in Table 3 are all within acceptable values. An ORTEP drawing of a single molecule is shown in Figure II. While the standard structural parameters of this molecule are quite unexceptional, a view of the stacking of the molecules within a chain in the crystal perpendicular to the [101] plane (Figure III) is very revealing mechanistically. The molecules stack with alternating dimethylamino and sulfonate groups, and with the aromatic rings inclined approximately 76° to each other. Each nitrogen is in alignment with a sulfonate ester methyl group only 3.54 Å away; the O(1)-C(9)---- N angle is 147° (sufficiently close to the linear alignment needed for the proposed S_N2-like transition state). The system can therefore readily transfer each ester methyl to its neighboring N atom and thus the <u>orientation in the crystal is directly implicated in lowering the entropy of activation of the reaction</u> by fixing the relative

Table 3. Interatomic distances and angles for methyl p-dimethylaminobenzenesulfonate (MSE)[a]

Distances (Å)		Angles (°)	
S - C(1)	1.74	C(9) - O(1) - S	118
S - O(1)	1.50	C(1) - S - O(1)	106
S - O(2)	1.41	C(1) - S - O(2)	109
S - O(3)	1.40	C(1) - S - O(3)	111
O(1) - C(9)	1.49	O(1) - S - O(2)	113
N - C(4)	1.37	O(1) - S - O(3)	101
N - C(7)	1.42	O(2) - S - O(3)	106
N - C(8)	1.47	S - C(1) - C(2)	119
C(1) - C(2)	1.40	S - C(1) - C(6)	121
C(2) - C(3)	1.36	C(1) - C(2) - C(3)	120
C(3) - C(4)	1.39	C(2) - C(3) - C(4)	121
C(4) - C(5)	1.41	C(3) - C(4) - C(5)	118
C(5) - C(6)	1.35	C(4) - C(5) - C(6)	121
C(6) - C(1)	1.37	C(5) - C(6) - C(1)	121
		C(6) - C(1) - C(2)	120
		C(3) - C(4) - N	119
		C(5) - C(4) - N	123
		(c)4) - N - C(7)	122
		C(4) - N- C(8)	123
		C(7) - N - C(8)	114

[a]The estimated standard deviations for distances involving sulfur are 0.01 Å; they are 0.02 Å for all other distances. For all of the angles esd's are 1°.

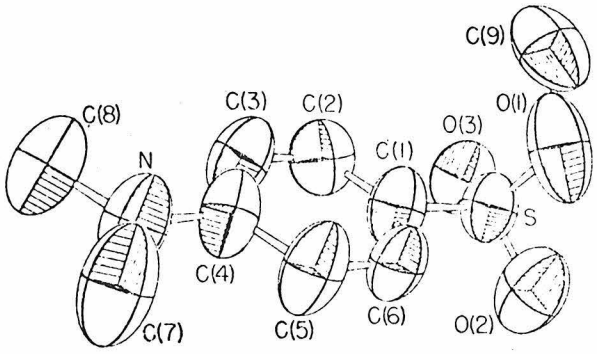


Figure II. ORTEP drawing of a single molecule of crystalline p-dimethyl-aminobenzenesulfonate (MSE).

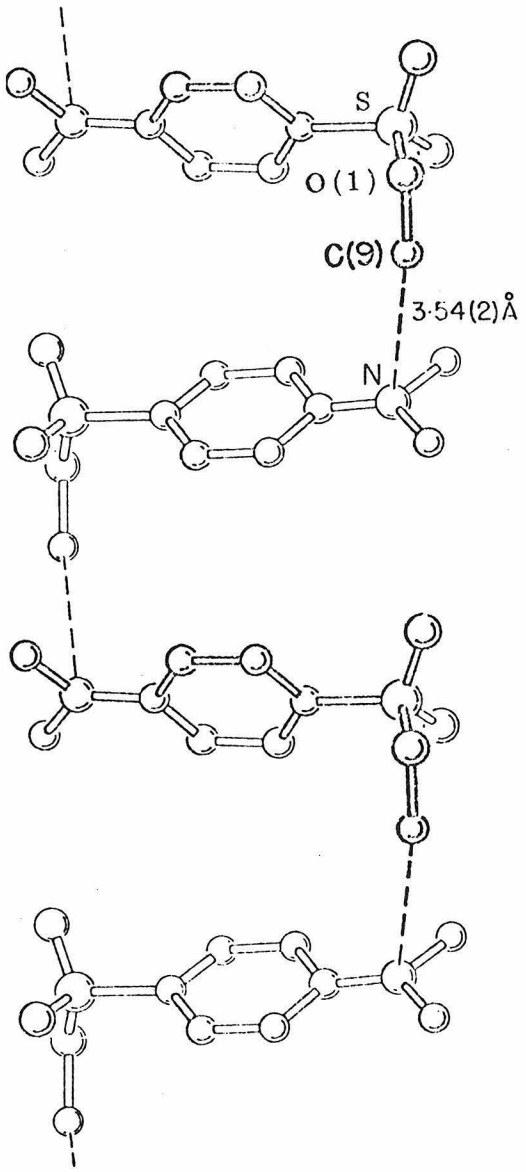


Figure III. A veiw of the stacking along one chain of molecules in crystals of methyl p-dimethylaminobenzenesulfonate (MSE), as seen perpendicular to the [101] plane. Distance indicated is that between the carbon atom of the methyl group which undergoes transfer in the solid state reaction, and the nitrogen atom to which it moves.

orientation of the reactive sites and facilitating the proposed (eq 5) chain reaction sequence.

A simple formulation of this proposed chain process led us to suspect that it might be possible to actually "see" the propagation of a "reaction front" on a macroscopic scale as has, for example, been observed in some heterogeneous gas-solid reactions by Lin, Curtin and Paul (20). We therefore attempted to follow the reaction by recording sequential pictures of a crystal of MSE "reacting" on the stage of a polarizing microscope. Pictures were taken at one day intervals for two weeks, and though there was an overall change in crystal appearance, consistent with the presence of an ongoing chemical reaction, there was no distinguishable uniform shift in crystal morphology. One might therefore speculate that our proposed reaction is initiated at random points throughout the crystal, akin to random thermal activation in other chemical processes. It is then propagated over microscopically short chains which can be interupted by random molecular dislocations that are present throughout the crystal in ever increasing numbers as the reaction progresses.

Having demonstrated the absence of uniform long range molecular motions, we were left with the question of how much molecular motion does go on within the confines of the initial crystal. From our single crystal X-ray work and by simple inspection of the gross crystal morphology of the reaction product, it was obvious that we did not have a clean single crystal→single crystal transformation of the sort that Gougoutas has reported (10). However, we wondered whether the original

MSE structure a) forces the product molecules into some meta-stable crystalline state, b) keeps them relatively amorphous, or c) allows them enough mobility to reorient themselves into their most stable crystal packing (i.e., the structure they naturally attain when crystallized from solution). We were able to answer this question by inspection of the X-ray powder patterns of MSE as it was transformed to ZWT.

An ether solution of MSE was evaporated to dryness and its X-ray powder pattern recorded. This sample was allowed to react and its powder pattern was recorded after 6 and 33 days. The d-values obtained from these photographs, as well as the powder pattern calculated for MSE from single crystal atomic coordinates, are listed in Table 4.

We then grew single crystals of ZWT by recrystallization from an H_2O solution. By oscillation and Weissenberg photographs these crystals were found to be orthorombic with $\underline{a}$ = 10.15 Å, $\underline{b}$ = 20.55 Å, and $\underline{c}$ = 9.69 Å, and a calculated density of 1.25 gm/cc for eight molecules per unit cell. Possible space groups are P_{ca2_1}, P_{ba2}, P_{bam}. The powder pattern of a finely ground sample of these crystals is listed in Table 4.

There are two significant points to be extracted from these data. 1) It must be noted that the experimental and calculated d-values for MSE show excellent agreement. This is a good check for the validity of our experimental technique (21). 2) The zwitterion obtained <u>in situ</u> in the rearrangement has a microcrystalline structure that is <u>identical</u> to its thermodynamically most stable single crystal packing, despite the constraints of the starting material lattice.

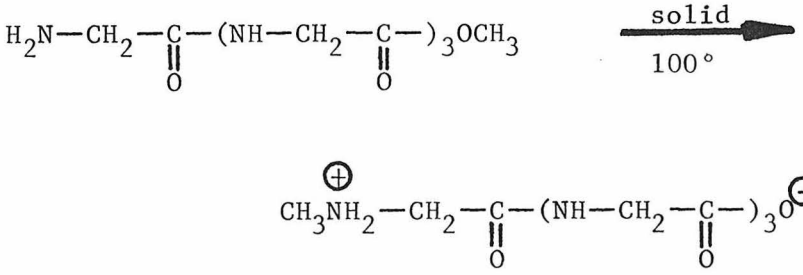
With the analysis of our system now complete we have found that

Table 4. Observed d-Values from Powder Diffraction Study (21)

Calc. MSE[a]	Observed MSE[a]	MSE + 6 days	MSE + 33 days (in situ ZWT)[b]	Recryst. ZWT[b]
7.67	7.74	7.64	5.82	5.81
6.81	6.84	6.77	5.24	5.23
5.79	5.82	5.77	5.12	5.10
5.25	5.27	5.74	4.81	4.80
4.79	4.81	5.21	4.51	4.51
4.76	4.78	5.14	4.20	—
4.74	4.74	4.77	3.65	—
4.47	4.49	4.65	3.50	3.53
4.31	4.33	4.41	3.49	3.49
4.20	4.21	4.26	3.12	3.12
3.88	3.90	4.18	2.90	—
3.52	3.53	3.85	—	2.71
3.34	3.35	3.52	2.00	2.01
3.30	3.31	3.50	—	—
3.13	3.14	—	—	—
2.90	2.90	—	—	—

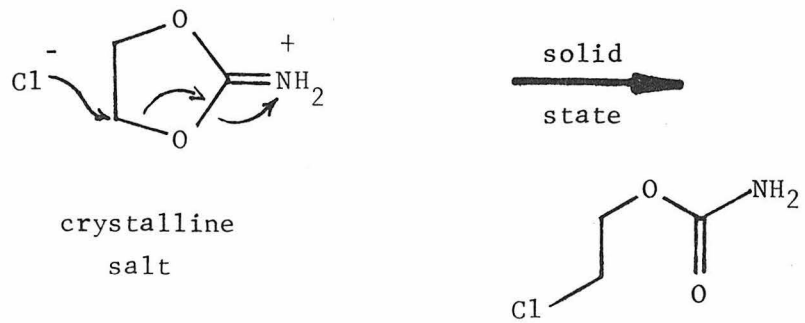
[a]Most intense lines for MSE = 5.82, 4.78, 4.21, 3.53. [b]Most intense lines for ZWT = 5.23, 5.10, 4.80.

there are in fact many transformations in the literature that may display the same kind of solid state acceleration that we have observed. An interesting reaction (22) analogous to ours is shown in (eq 7).



(eq 7)

Here, too, transfer of a methyl group in a crystalline system results in a stable zwitterionic product. The authors speculate (22) that the rigidity of the crystal lattice is in part responsible for the behavior of their system, but indicate no attempt to determine the details of the reaction mechanism. There are also many reports in the literature of compounds that are stable in solution but decompose either to known products or intractable tars when isolated as a solid. We suspect that in many cases [for example (23) (eq 8)] what they are observing may also be examples of nucleophillic attack (or some other process) facilitated by proper crystal orientation. These systems merit further investigation.



crystalline salt

(eq 8)

III. Experimental

A. General

NMR spectra were obtained on a Varian A60A or T-60 spectrometer. They are reported as: NMR: (solvent) chemical shift in units τ (multiplicity, number of protons); etc.. IR spectra were recorded either on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer or on a Perkin-Elmer Model 137 Spectrophotometer and are reported in cm^{-1}. Melting points were determined on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. Analytical electron impact mass spectra were obtained on a DuPont 21-492B high resolution mass spectrometer. All analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

B. Synthesis

Sodium p-Dimethylaminobenzenesulfonate (I). Using a modification of the procedure of Fierz-David and Blangey (24), a 1500 ml 24/40 round bottom flask was charged with 153.8 gms sulfanilic acid monohydrate and 69.9 gm sodium hydroxide pellets. 700 ml of water were added and the flask was stoppered. While shaking the flask to dissolve all the solid, it became very hot. 113 grams of dimethyl sulfate were added to this hot solution in one portion and the flask was again shaken (the reaction was very exothermic) until the solution was homogeneous. The reaction mixture was allowed to come to room temperature and then placed in the refrigerator overnight. The next day approx. 22 gms of wet solid was

filtered from the reaction. 45 gms of NaOH was dissolved in the supernatent and another 113 grams of dimethyl sulfate were added with shaking. A second crop of 34.5 gms of product was recovered the next day.

The products were combined, recrystallized once from water and dried under reduced pressure at 80° C to obtain 37 gms (21% yield) of clean dry white powder. A similar run using 121.2 gms sulfanilic acid at the start gave 43.5 gms (31% yield) of recrystallized material. NMR (D_2O): 7.08 (s, 6H), 2.74 (AB quart, 4H).

Sodium p-Dimethylaminobenzenesulfonate-d_6 (I-d_6). The procedure was basically the same as for the non-deuterated material except that we used dimethyl sulfate-d_6 (99% deuterated) obtained from Stohler Isotopes incorporated. 8.26 gms sulfanilic acid monohydrate were reacted with 3.8 gms NaOH pellets and 6 gms DMS-d_6. A second crop was obtained by addition of another 3 gms NaOH and 3 gms DMS-d_6. The total product of 4.4 gms crude damp material was recrystallized from H_2O and dried to yield 1.1 gms clean product.

p-Dimethylaminobenzenesulfonylchloride (II). A 1000 ml 3-neck 24/40 r.b. flask equipped with N_2 inlet, reflux condensor, mechanical stirrer and 25 ml addition funnel, was charged with 38 gms I (freshly dried at 80° under high vacuum) and 410 ml freshly distilled dry benzene. 17.1 ml of oxalyl chloride were added dropwise over 10 min at room temperature. The reaction mixture was refluxed for 3 hrs at which time the reflux condensor was replaced with a short path distilling head and the benzene

was distilled out (to dryness). Another 100 ml of dry benzene were added to redissolve the product and the reaction was again distilled to dryness. CH_2Cl_2 was added to dissolve the organic material and the inorganic salts were filtered off. The CH_2Cl_2 layer was washed with saturated aq $NaHCO_3$, then H_2O and saturated aq NaCl solution, dried over Na_2SO_4 and then evaporated to dryness. The crude product was recrystallized from ether or an ether pet-ether mixture to give 33.8 gms of product ranging in color from yellow to emerald green. Yield: 90% M.P. = 109.5°- 111.0° (lit (25) = 110.5°- 111.5°); NMR ($CDCl_3$): 6.9 (s, 6H), 2.77 (AB quart, 4H); IR ($CHCl_3$) = 1375, 1165, 1090, 810 cm^{-1}. Anal. Cald. for $C_8H_{10}ClNO_2S$: C = 43.74%, H = 4.55%, N = 6.38%, Cl = 16.18%; Found: C = 43.81%, H = 4.42%, N = 6.41%, Cl = 16.23%.

p-Dimethylaminobenzenesulfonylchloride-d_6 (II-d_6). The procedure was the same as used for the non-deuterated material, but here 1.1 gms of freshly dried sodium sulfonate d_6 (I-d_6) was reacted with 500 µl oxallyl chloride to give 1.0 gm (93% yield) of d_6 chloride (IV-d_6) whose NMR showed no signal at 6.9 τ (< 2%).

Methyl p-Dimethylaminobenzenesulfonate (MSE). Using a modification of the Organic Synthesis procedure for methyl tosylate (26), 6.45 gms of II were dissolved (with vigorous shaking) in 180 ml of reagent grade methanol in a 300 ml r.b. flask. Sufficient concentrated aqueous NaOH (≈4 ml) was added to make the solution strongly basic and the reaction was allowed to stand, first at room temperature and then a -10°, for 24 hrs. The

first crop of crystals ($\approx$ 2 gms) was collected and washed with water. The water washes and supernatent were combined to yield, after 1 day in the cold, a second crop of 3.3 gms of crystals. The combined product of 5.3 gms (84% yield) was stored as a solution in ether over Na_2SO_4 and K_2CO_3. NMR ($CDCl_3$): 6.93 (s, 6H), 6.30 (s, 3H), 2.78 (AB quart, 4H); IR (KBr): 1590, 1330, 1210, 1150, 1080, 985, 780, 740 cm^{-1}; M.P. = 90°-91° [lit. M.P. = 90°-91° (12), 91° (13,14).]

Anal. Cald. for $C_9H_{13}NO_3S$: C = 50.22%, H = 6.09%, N = 6.51%, S = 14.89%;

Found: C = 50.23%, H = 6.16%, N = 6.50%, S = 14.91%.

The analytical mass spectrum at 70 ev showed a base peak which was also the parent peak at m/e = 215, as well as minor peaks at 214, 216, 217.

MSE-d_3, MSE-d_6, MSE-d_9. The procedure used was basically the same as for the non-deuterated MSE. MSE-d_3 was made from 444 mgs of sulfonyl chloride (II-d_0) that were reacted with 14 ml of CD_3OD (99% obtained from Stohler Isotopes Inc.) using NaOD and D_2O. [The CD_3OD can be recovered (> 90%) by vacuum transfer at the end of the reaction.] The MSE-d_6 was prepared from 292 mgs of sulfonyl chloride (II-d_6) and 15 ml CH_3OH using NaOH and H_2O. The NMR's of MSE-d_3 and MSE-d_6 each indicate > 98% deuteration in the appropriate methyl groups.

MSE-d_9 was prepared by reacting 309 mgs of sulfonyl chloride (II-d_6) with NaOD and D_2O in 10 ml CD_3OD. The product was a white powder with M.P. = 89.0° - 90.0°. The NMR showed protons on the aromatic ring only. The mass spec at 70 ev showed a base peak which was also the parent peak at m/e = 224. To verify the percentage deuterium incorporation we

noted that for MSE-d_0, parent/(parent - H) = 1.93 and for MSE-d_9, parent/(parent - H) + (parent - D) = 1.94. This combined with the NMR spectrum indicated overall deuterium incorporation > 98%.

All of the MSE isomers were stored as dilute solutions in ether over anhydrous K_2CO_3 in refrigeration.

Methyl-p-Trimethylammoniumbenzenesulfonate Triflate. Approximately 1 gm of crude MSE-d_0 was dissolved in CH_2Cl_2 and dried over $MgSO_4$. This solution was filtered and solvent was removed under reduced pressure. The solid residue was redissolved in 10 ml spec grade $CHCl_3$ in a 50 ml r.b. flask equipped with a magnetic stirrer and an N_2 inlet. 400 µl commercial methyl triflate (Cationics Inc.) were added in one portion and the reaction was allowed to stir under N_2 at room temperature for 4-1/2 hrs. The reaction was cooled to $\approx 0°$ in an ice bath and 20 ml dry, distilled, pentane was added to precipitate out the product. The product was filtered under an N_2 atmosphere in a glove bag and exhaustively triturated with fresh pentane to give a clean white powder with the following spectra. IR (KBr): 1485, 1365, 1261, 1193, 1032, 990, 845, 800 cm^{-1}; NMR (D_2O): 6.33 (s, 9H), 6.20 (s, 3H), 1.86 (s, 4H).

Anal. Cald. for $C_{11}H_{16}F_3NO_6S_2$: C = 34.83%, H = 4.22%, N = 3.69%;

Found: C = 34.54%, H = 4.09%, N = 3.69%.

Allyl-p-Trimethylammoniumbenzenesulfonate Triflate. The dimethylaminobenzenesulfonate ester was prepared as above for MSE using 1.11 gms of sulfonyl chloride (II) dissolved in 25 ml commercial allyl alcohol

and aq NaOH, to give 1 gm wet product (IV) which was dissolved in ether and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual solid was recrystallized at low temperature from ether giving clean white crystals. M.P. = 41°; NMR ($CDCl_3$): 6.96 (s, 6H), 5.52 (d, J = 5, 2H), 4.72 (m, 2H), 4.29 (m, 1H), 2.79 (AB quart, 4H). Anal. Cald. for $C_{11}H_{15}NO_3S$: C = 54.77%, H = 6.22%, N = 5.81%;

Found: C = 54.76%, H = 6.17%, N = 5.79%.

The alkylation of the dimethylamino ester was done as above for MSE using 298 mgs allyl sulfonate ester dissolved in 2 ml dry distilled benzene and 145 µl methyl triflate. The product was a white powder that did not dissolve in $CDCl_3$. NMR (CD_2Cl_2): 6.12 (s, 9H), 5.33 (d, J = 5 cps, 2H), 4.52 (m, 3H), 1.86 (Broad s, 4H). Note: This material, in D_2O, goes to ZWT and allyl alcohol at room temperature with $T_{\frac{1}{2}} \approx 30$ sec. Due to its reactivity no analysis was obtained for this compound.

n-Butyl-p-Dimethylaminobenzenesulfonate (V) and sec-Butyl-p-Dimethylaminobenzenesulfonate (VI). 1.97 gms of sulfonyl chloride (II) were dissolved in 20 ml dry (distilled from KOH) pyridine in a 50 ml r.b. flask. 0.9 ml (.7 gms) n-butanol were added and the reaction was covered with a drying tube and stored in the refrigerator for 3 days. The reaction mixture was poured onto a mixture of 30 ml concentrated HCl and 100 gms ice. After the ice melted, 2.2 gms of crude reaction product were filtered off and washed with H_2O. The product was twice recrystallized from ether. M.P. = 35.5° - 37.0°; NMR ($CDCl_3$): 9.33 - 8.04 (multiplets, 7H), 6.95 (s, 6H), 6.02 (t, J = 6 cps, 2H), 2.82

(ABq, 4H).

Anal. Cald. for $C_{12}H_{19}NO_3S$: C = 56.01%, H = 7.44%, N = 5.44%, S = 12.46%;
Found: C = 55.89%, H = 7.28%, N = 5.38%, S = 12.43%.

The same procedure, using 1.65 gms sulfonyl chloride and 0.7 ml (.56 gms) sec-butanol, gave 1.5 gms of crude sec-butyl sulfonate ester. Recrystallization gave 0.8 gms of clean white needles. M.P. = 46.5° - 47.5°; NMR ($CDCl_3$): 9.18 (t, J = 6.5, 3H), 8.79 (d, J = 6.0, 3H), 8.49 (q, J = 6.5, 2H), 6.96 (s, 6H), 5.53 (q, J = 6, 1H), 2.82 (ABq, 4H).
Anal. Cald. for $C_{12}H_{19}NO_3S$: C = 56.01%, H = 7.44%, N = 5.44%, S = 12.46%;
Found: C = 56.22%, H = 7.11%, N = 5.44%, S = 12.51%.

The above esterification procedure gave no detectable product when used to make either the allyl or methyl esters.

p-Trimethylammoniumbenzenesulfonate (ZWT). This compound was prepared by 3 independent routes: 1) the thermal rearrangement of MSE at room temp, 81°, 88°, and 95°; 2) the H_2O solvolysis of alkylated MSE (III); 3) the H_2O solvolysis of alkylated allyl sulfonate ester (alkylated IV). The material isolated from each of these reactions could be recrystallized from water and had the following properties: M.P. >> 350 (no decomposition evident under vacuum); NMR (D_2O): 6.38 (s, 9H), 2.05 (s, 4H); IR (KBr): 1500, 1200, 1130, 1100, 1035, 1000, 840, 755 cm^{-1}; Field Desorption Mass Spec = 215.

Deuterated ZWT isomers were prepared by heating the corresponding MSE isomer at 81° under vacuum and analyzing the resulting powder by FDMS. ZWT-d_9 gave FDMS = 224 while ZWT-d_3 and ZWT-d_6 gave scrambling

(see text) but with the main peak for d_3 = 218 and d_6 = 221.

C. Field Desorption Mass Spectroscopy

I would like to gratefully acknowledge that the FDMS data was obtained by Pui-Yan Lau under the supervision of Professor Gordon Wood at the University of Windsor. The instrument used was a Varian MAT Model CH5 DF. The basic procedure can be summarized as follows: A powdered sample of zwitterion was dissolved in H_2O and filtered to remove any water insoluble impurities (i.e., MSE). This solution was spread on the tungestun wire anode by dipping and excess solvent was evaporated. The emitter was heated with a 23-27 mA heating current and maintained at pressures less than 10^{-6} Torr. The high voltage field was applied (typically + 3 kilovolts to anode and -8 kilovolts to cathode) and the spectra recorded on an oscillographic recorder. After each run the anode was cleaned by raising the current through it to 50 mA.

D. Kinetics of the Solid State Reaction

A sample of 29 - 37 mgs of MSE were placed in a 5 ml pear shaped flask topped with a ground joint and a stopcock. The flask was evacuated and the stopcock closed. The flask was then immersed in an oil bath that had previously been equilibrated to a temperature of 81°, 88°, or 95°. After a known amount of time the sample was removed from the oil bath and plunged into ice water. The vacuum was released and 1 - 2 ml each of D_2O and $CDCl_3$ were added using a glass stirring rod to help dissolve all of the sample material in one solvent or the other. After the

phases separated they were each pipetted into separate NMR tubes. The NMR of each solution was recorded and integrated using the Varian A-60A Spectrometer and the relative amount of MSE and ZWT was determined by comparing their integration (average of 3 - 5 scans) and correcting for the difference in volume of D_2O and $CDCl_3$ used in that run.

Two large scale (70 - 80 mgs) runs were performed in which MSE and ZWT were isolated and weighed. These results were within 3% of the NMR results.

E. X-Ray Single Crystal Structure Determination for MSE

Suitable crystals for X-ray diffraction work could be isolated either directly out of the reaction mixture in which MSE was synthesized, or by recrystallization from methanol or a methanol-water mixture. Clean single crystals of sufficient size for the structural work were selected and mounted on the goniometer head in a capillary tube. The data were collected and analyzed by Jose Bonapace and the details of this work as well as a listing of the computer programs used can be found in the thesis that he submitted (1975) to the Instituto de Quimica da Universidae Federal de Rio de Janiero, Brazil. His work was done under the supervision of Dr. N. S. Mandel at Caltech.

F. Preliminary Single Crystal Work on ZWT

Crystals of ZWT were very easily grown by cooling a saturated aqueous solution. A suitable crystal was chosen and used for oscillation and Weissenberg pictures using a Charles Supper Weissenberg

camera. The data from these pictures have been summarized in the above text (Results and Discussion).

G. Photography of the Reaction Through a Polarizing Microscope

A thin, clear single crystal of MSE was placed on the stage of a Bausch and Lomb polarizing microscope. A 35 mm camera was adapted to fit the eyepiece of the microscope and it was bolted onto the microscope. A remote trigger was used for the camera shutter and pictures were taken at fixed intervals. The entire apparatus (camera and microscope) was left undisturbed for the two-week duration of the experiment. The resulting slides gave a clear view of the sequence of changes in the way that the light was refracted by the crystal.

H. Powder Diffraction Patterns of MSE and ZWT

The powder pattern (d-values and relative intensities) of MSE was calculated using the atomic coordinates determined from our single crystal work and the program "Powder" written by Evon and Parthe (program available on request).

The experimental powder patterns were determined using CuK_{α} radiation with a circular powder sample holder and a Guinier camera. Exposure times ranged from 6.5 to 10 hrs. Films were measured using a comparator, and d-values were calculated using the distance in mm of each line from the midpoint between the α_1 and α_2 lines on that film.

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Part II: Micellar Effects on the Stereochemistry and Rate of Aqueous Solvolysis Reactions

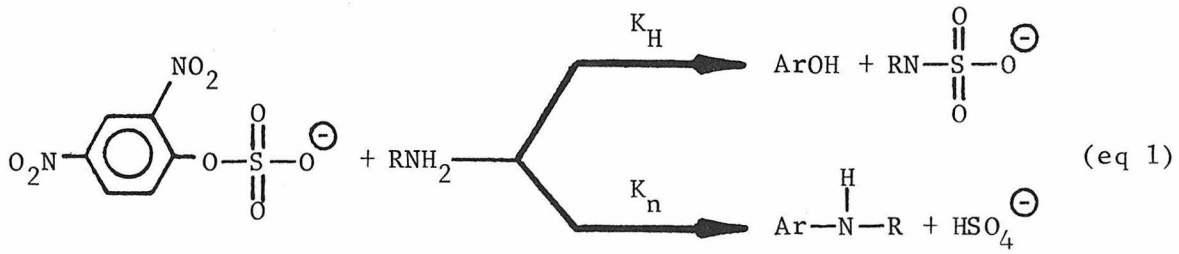
Introduction

Though the first record of catalysis by surfactants dates back to 1906 (1), the first recognition of micelles as the catalytically active species was not until 1942 (2) and detailed investigations of micellar catalysis did not emerge until the late 1950's. Thus, the rapid growth of micelle related research in less than twenty years has been quite spectacular. Fortunately, the field has been the subject of numerous review articles (3) and books (4) over the last six years, which greatly facilitate familiarizing one's self with the field.

It must be pointed out, however, that despite the abundance of recent studies on both the structure and catalytic properties of micelles, there are still many virgin areas in this field. In particular, most chemical studies have concentrated on the effect micelles have on reaction rates and very few attempts have been made to look at the effect micelles might have in altering reaction products. The synthetic chemist has shown limited interest (5), despite the recent impressive developments in phase transfer catalysis (6). The mechanistic organic chemist has to date found only a few systems where he has been able to use a micellar medium to effect the partitioning of an organic reaction. As models for the following work a few of these systems merit further discussion.

In studying the competitive hydrolysis and aminolysis of aryl sulfates, Fendler et al. (7) were able to use cationic micelles of hexadecyl trimethylammonium bromide (CETAB) to alter the balance between

K_n and K_H (eq 1). Under non-micellar conditions C-O bond cleavage (K_n)

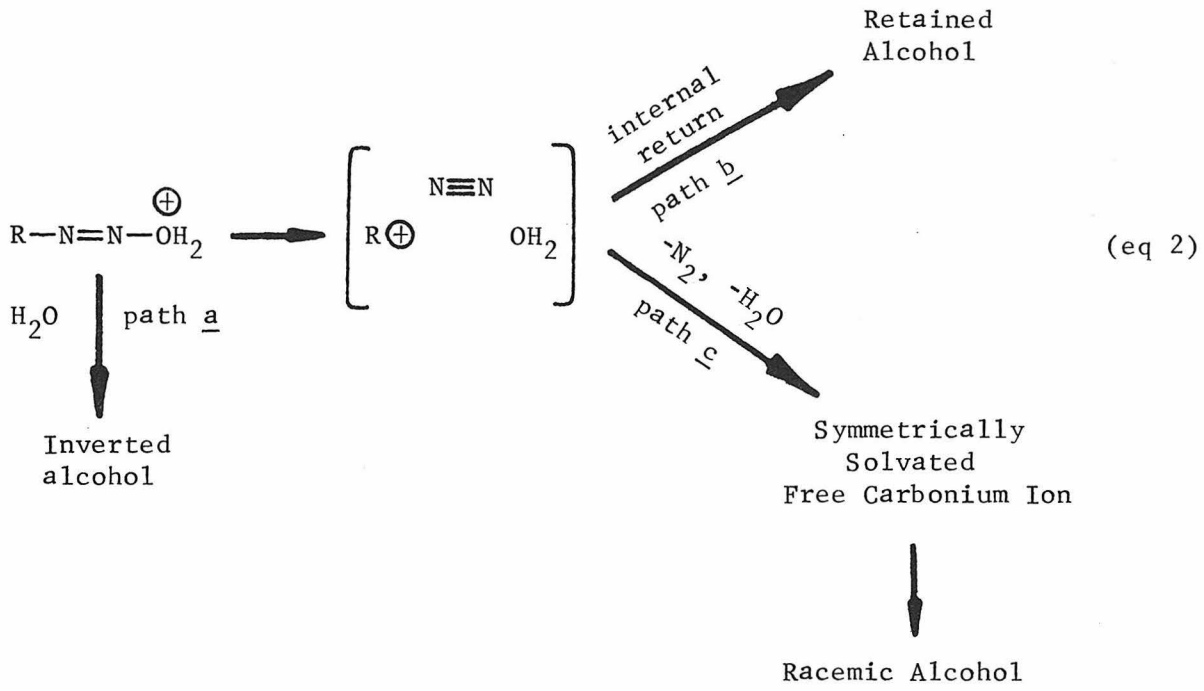


(eq 1)

accounts for 75% to 98% of the observed reactions. They found that cationic micelles can induce "complete suppression of aniline formation" (7). The authors acknowledge the micelle's ability to alter the relative extent of competing reactions but, disappointingly, only offer the following explanation:

> "[The above effects] may be primarily due to changes in the micro-environment of both the substrates and of the transition states by a contribution of electrostatic and hydrophobic interactions (7)."

A better example of the use of micelles to alter a delicate balance among reaction pathways is found in the effect of micellization on the stereochemistry of alkyl amine deamination reactions (8)(9). It is argued (8) that the diazotic acid reaction intermediate can partition itself among three stereochemically distinct pathways as shown in (eq 2). The contention is made that whereas normal stereochemistry (for the conversion of 2-octylamine to 2-octanol) is net 24% <u>inversion</u>, micellization generates a water poor environment which enhances path <u>b</u>



(eq 2)

and results in 6% net retention. This same argument has been adapted to a study of micellar control of 1,2-hydride shifts in deaminations (9) and these studies still stand as the best examples of a micellar partitioning of a reactive intermediate.

Our interest in micelle chemistry has been primarily directed towards studying chemistry that takes place in the rather unique micro environment of the micelle Stern layer (10). It has been amply demonstrated that the most unique and probably most interesting region in a micelle is that highly charged interface between the hydrophobic core and the bulk aqueous solution. It is in this region in particular that certain unique solvent properties may develop. Since a wide variety of organic

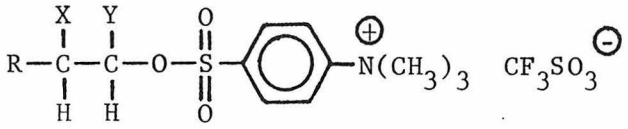
reactions have shown profound solvent dependence and since it has been amply demonstrated that most micellar reactions occur in the Stern layer (11), we felt that this rather unique "micro-solvent" deserved further investigation.

Much of the work that has been done to date on micellar systems can be fairly well explained in the following terms. The reaction substrate is partitioned between micellar and bulk aqueous phases by hydrophobic binding of a substrate to a micelle. Then, by simple electrostatics, this complex either attracts (rate acceleration) or repels (rate retardation) an incoming ionic reagent. We felt that a better probe of the nature of the Stern layer itself might result from generating a charged reactive species (e.g., $C^{\oplus}$ or $C^{\ominus}$) inside that environment, and comparing its reactions (i.e., unimolecular, bimolecular with a charged reagent, and bimolecular with a neutral reagent) with the analogous processes in bulk aqueous solution.

Our interest in such systems was further stimulated by a statement made by E. H. Cordes in a discussion of carbonium ion reactions taking place in a micelle (4a). While a variety of carbonium ion systems had been studied, in most cases the results were consistent with the above simple understanding of micellar behavior. He noted, however, that a simple disassociation of R-X to $R^{\oplus}$ and $X^{\ominus}$ in a micellar medium had never been investigated. Furthermore, he contended that it was impossible to predict the effect that micellization would have on such a process. We therefore began our research with the goal of designing a system that would a) generate carbonium ions by a disassociative process taking

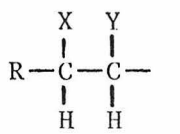
place in the micellar Stern layer, b) allow the carbonium ion to partition itself among a variety of both unimolecular and bimolecular reaction pathways and c) allow us to compare the reactions of this carbonium ion or carbonium ion-like transition state, in terms of kinetics, product distribution, and stereochemistry in simple aqueous solution to those in both homogeneous and mixed micellar environments.

In order to achieve as many of these goals as possible, we chose to study the solvolysis of I in aqueous solution. We chose I as the



I

	R	X	Y
Ia	C_5H_{11}	H	H
Ib	C_5H_{11}	CH_3	H
Ic	C_5H_{11}	H	CH_3
Id	C_6H_{13}	H	H
Ie	C_2H_5	H	H
If	CH_3	H	H
Ig	CH_2	void	H

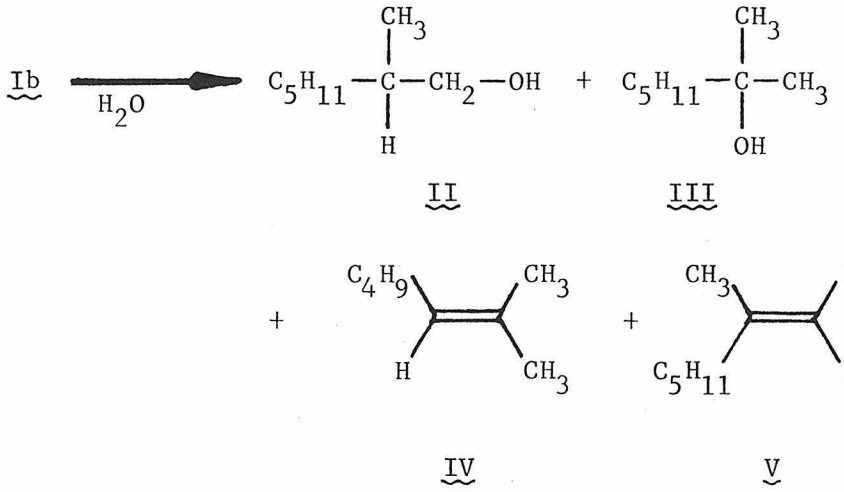
Ih  = CH_3

system for study because we expected that these compounds would be water soluble and thus allow us to study their behavior alone in dilute aqueous solution (12). They are also structurally similar to the water insoluble sulfonates more traditionally used in solvolytic studies. Since simple solvolysis reactions have been so extensively studied, their behavior would be a good probe for the specific effects of the micellar environment. Furthermore, the electron withdrawing power of $\overset{\oplus}{N}(CH_3)_3$ [σ_p = .86 (13)] would make this system very reactive even under mild conditions (25° in aqueous solution) and probably impart a lot of carbonium ion character to the solvolysis transition state. Also, varying the R group in $\underset{\sim}{I}$ allows us to control the ability of a given substrate to self-micellize or to hydrophobically bind to micelles composed of other surfactants.

Results - I

We were able to readily synthesize I by the alkylation of the corresponding dimethylaminobenzenesulfonate esters with methyl trifluoromethanesulfonate (methyl triflate). These esters in turn were prepared from the appropriate alcohols and p-dimethylaminobenzenesulfonyl chloride. The use of the triflate alkylating agent is notable for two reasons. We found that less reactive reagents [i.e., CH_3I, $(CH_3)_3SO^{\oplus}\ I^{\ominus}$, $Et_3O^{\oplus}\ BF_4^{\ominus}$] did not react with the dimethylamino nitrogen, presumably due to deactivation by the SO_3R unit. Furthermore, the triflate anion is extremely non-nucleophillic and presumably cannot interfere in our solvolysis reactions. The resulting alkylated sulfonates were all readily purified white powders. They were easily handled and could be stored indefinitely in a desiccator at room temperature or below.

The simple non-micellar behavior of I is consistent with the properties suggested above. They were water soluble and hydrolyzed in aqueous solution at room temperature to give the kinds of mixtures of alcohols and olefins that one might expect from the solvolysis of a sulfonate in water. Ia, Id, Ie, If, Ig, and Ih gave good yields ($\geq$ 70%) of their unrearranged precursor alcohols and traces of the 1-olefin were detected for Ia and Id. No effort was made to find the volatile butenes expected from Ie and If. Ib gave a mixture of the products indicated in equation (3) and Ic gave mostly 2-octanol with significant amounts of 1-octene, cis-2-octene, trans-2-octene, and 3-octanol.



(eq 3)

A summary of the effects of cationic micelles, of the compounds themselves (14) or of added CETAB, on the distribution of solvolysis products of Id, Ib, and Ic, i.e., alcohol vs. olefin, and rearranged vs. unrearranged alcohol, is listed in Table 1. We found that these effects, although apparently real, were not very large and were very difficult to reproduce with good accuracy.

A better characterization of system I, as well as a better probe of the effects of micelles on the hydrolysis of I, resulted from a study of the reaction kinetics. The results of this study are summarized in Table 2. These results indicate that trimethylammoniumbenzenesulfonate ("Amsylate") is a very reactive leaving group (15). The relative order of reactivity of alkyl amsylates is allyl $\geq$ 2° $\gg$ 1° and the observed secondary:primary rate ratio of $> 3.5 \times 10^2$ is among the largest known (16). These results suggest a substantial degree of carbonium ion character in the transition state of the solvolysis reaction. The effect of micelles on the rate of solvolysis of I is that

Table 1. Effect of Cationic Micelles on Solvolysis Product Distribution of I in Water at 25°.

Substrate	Concentration Relative to Its Own CMC	$\frac{[\text{Alcohol}]}{[\text{Olefin}]}$[b]	$\frac{\text{Rearranged Alcohol}}{\text{Unrearranged Alcohol}}$[b]
Id	below	92/1	<< .01
	above	92/1	<< .01
Ic	below	5/1	.04
	above	2/1	.04
	below[a]	2/1	——
Ib	below	14/1	2.5
	above	8/1	2.5

[a] 2 x CMC CETAB added. [b] Product ratios determined VPC integration.

Table 2. Rates of Solvolysis of I in Water with and without Added Surfactant.

Substrate	Initial Conc.	Additive (Molar Conc.)	Temp.	K x 10^5 sec^{-1}	$T_{\frac{1}{2}}$
Ib	2.7×10^{-3} M	—	22°	3.8[b]	300 min
Ib	8.3×10^{-3} M	—	22°	4.0[b]	290 min
Ib	1.3×10^{-3} M	CETAB (1.4×10^{-3})	22°	4.4[b]	270 min
Ib	3.8×10^{-3} M	SLS (1.97×10^{-2})	22°	(a)	(a)
Ic	$.2 \times 10^{-3}$ M	—	25°	1600[c]	.7 min
Ic	4.3×10^{-3} M	SLS (1.97×10^{-2})	22°	22.4[b]	52 min
Ic	2.5×10^{-3}	SLS (2.1×10^{-2})	22°	16.8[b]	69 min
Ic	5.45×10^{-3} M	NaDd (5.2×10^{-2})	22°	28.5[b]	41 min
Ia	1.0×10^{-3} M	—	40°	29.0[c]	40 min
Ie	—	—	25°	7.7[b]	150 min
Ie	1.7×10^{-2} M	—	40°	19.3[b]	60 min
If	3.4×10^{-2} M	—	25°	1600[b,d]	.7 min
Ig	—	—	25°	1900[b,d]	.6 min
Ih	—	—	25°	13.8[b]	84 min
Ih	3.8×10^{-2}	—	40°	22.2[b]	52 min

[a]Less than 5% reaction in 17 hours in NMR probe. [b]Rate measured by NMR. [c]Rate measured titrimetrically. [d]Values are approximate due to rapidity of reaction. Note: rate constants were measured for reactions run to $\geq$ 80% completion. Error < 10%.

cationic micelles (either of the reactant itself (14) or CETAB) do not significantly change the rate of reaction, while anionic micelles (sodium lauryl sulfate-SLS, sodium dodecanoate-NaDd) strongly inhibit the solvolysis reaction.

A further probe of the behavior of our system in the presence of a micellar medium is the study of the stereochemistry of the solvolysis of these sulfonates. We therefore synthesized optically active Ic using optically active 2-octanol. As might have been expected (17), the production of 2-octanol from this solvolysis proceeded with complete inversion of configuration at the secondary carbon. The observed 100% inversion persisted regardless of the starting concentration of Ic and in spite of the presence of an added cationic surfactant (micellar CETAB) or an added anionic carboxylate surfactant (micellar NaDd). However, in the presence of micellar SLS, the observed stereochemistry could be modified to a value as low as 54% net inversion. The effect of SLS on the reaction stereochemistry was investigated as a function of the concentration of SLS and the concentration of Ic. These results, as well as the results of other stereochemical experiments, are summarized in Table 3.

Table 3. Dependence of Stereochemistry of Solvolytic Displacement of Ic on Concentration of Ic and on Concentration and Nature of Added Surfactant.

Qualitative Conditions	Additive x 10^2	Ic x 10^2	Stereochemistry (% net inversion)
High [SLS]; low to moderate [Ic] (CMC SLS = .8 x 10^{-2} M)	2.8	1.1	56
	2.8	1.5	57
	2.1	.6	55
	1.7	1.0	54
Moderate [SLS]; moderate [Ic]	1.6	1.6	63
Moderate [SLS]; high [Ic]	1.7	2.1	81
	1.7	2.8	85
Low [SLS]; low to moderate [Ic]	.7	1.0	88
	.7	1.6	93
No additive; moderate [Ic]	—	1.7	101
	—	1.4	100
No additive; low [Ic]	—	.6	99
	—	.6	101
2.2 x CMC [NaDd]; low [Ic]	3.0	1.4	100
2 x CMC [CETAB]; low [Ic]	.14	.6	99
	.14	.6	101

Discussion - I

The most readily understandable result within the above data seems to be the general observation that amsylate solvolysis is strongly inhibited by anionic micelles. This requires a very strong binding of I to the anionic micelle, presumably by both hydrophobic and electrostatic forces. Thus, while homogeneously charged cationic micelles, with our cationic substrates, undoubtedly have several molecules of water incorporated between surfactant head groups that would otherwise repel each other, the anionic micelles use the tightly bound cationic substrate to help neutralize their effective charge and squeeze out water from the microscopic environment. This effect is quite comparable to the effect postulated by Moss et al. (8) in micelle-mediated deamination systems; they surmised that tightly bound anions were squeezing out water from the surface of a cationic micelle. Our system thus presents some insight into the behavior of a mixed cationic-anionic micellar catalyst and makes a rather clear prediction that the micellar Stern layer in these systems will not be as "wet" as the Stern layer of a homogeneous micelle (18). This is particularly important since in nearly all cases of catalysis by mixed micelles investigated to date, the components have been either similarly charged or charged and uncharged surfactants (19).

The above picture of the nature of the interaction of I with anionic micelles is consistent with the observed effect of SLS on the reaction stereochemistry. As can be seen from Table 3, the results with added SLS are surprisingly regular. These results allow us

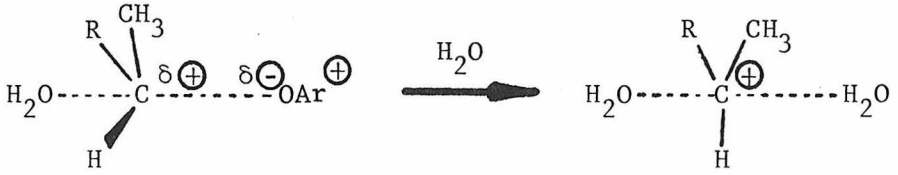
to contend that the actual solvolysis in the micellar SLS-Ic system is taking place on the micelle, rather than by combination of a highly inverting, fast solvolysis of a small instantaneous concentration of unbound monomeric Ic along with a highly retaining, but slower, micellar reaction. If this latter combination were in effect, the total observed stereochemistry would depend directly on the total concentration of SLS above some critical level for this system (an operational CMC). The results show it does not; a plateau at 55% inversion is observed.

The results show that with respect to the SLS-Ic interaction there is a simple relationship of catalytic significance. As long as the absolute concentration of SLS is relatively high and [SLS]$\geq$[Ic], our postulated tight binding of Ib to SLS micelles by both electrostatic and hydrophobic forces persists. As the relative concentration of Ic rises, presumably the substrate molecules become surrounded by an ever increasing fraction of solvent molecules instead of anionic surfactant head groups. Thus the reaction approaches the situation found with the cationic micelles alone, a return to aqueous rate and stereochemistry.

It must be pointed out, however, that while the above explanation treats the results of I with SLS rather well, it leaves two very difficult questions: 1) Why do anionic SLS micelles change both reaction rate and stereochemistry while anionic NaDd micelles change only the rate? 2) What is the precise mechanism whereby SLS surfactant molecules induce less than complete inversion in this

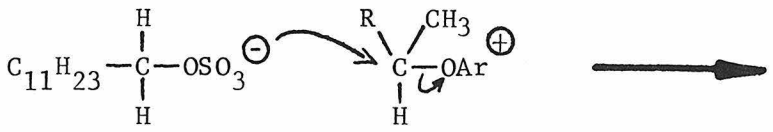
seemingly straightforward solvolysis reaction? Clearly these questions are related. They both require a better understanding of the microscopic details of the reaction going on in the micelle Stern layer.

It would seem that a good starting point for the analysis of these questions is the realization that there are at least three reasonable mechanistic possibilities that could explain the effect of SLS on the stereochemistry of the solvolysis of Ic. They are the following: 1) The highly charged environment at the surface of the mixed cationic-anionic micelle stabilizes the ion pair initially formed in the solvolysis of I and allows for internal return of the tight ion pair back to starting material. It has been amply demonstrated (20) that internal return in a solvolysis reaction can racemize the starting material either partially or completely. Thus our results would be consistent with a simple backside displacement by water competing with internal return. In total this would account for a product of reduced stereochemical integrity. 2) The incipient carbonium ion or ion pair is sufficiently stabilized by the ionic medium present in the Stern layer to allow water to replace the leaving group on the front side of the reactive species, as shown in eq (4). This process would also lead to increased

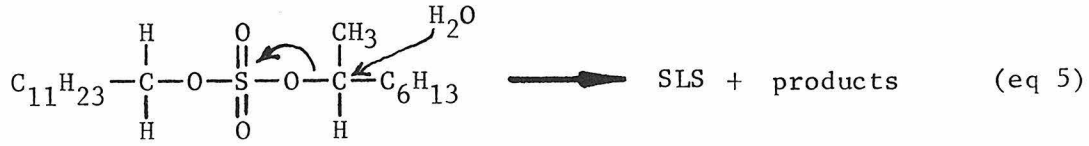


(eq 4)

racemization of the observed displacement product. [The reader is asked to note that this postulate would be a corollary to the more intuitive statement that the micelle should protect the backside of the ionizing species and thus retard backside attack by H_2O.] 3) The alkyl sulfate anion of SLS actually attacks Ic and forms a dialkyl sulfate (VI) as shown in eq (5). This species is hydrolyzed by water in what is



SLS Ic



VI

formally a second displacement step, thus regenerating the SLS along with doubly inverted 2-octanol. Our observed reduction in net inverted product would thus be the result of a catalytic displacement by SLS competing with a direct displacement by H_2O.

In most reaction systems these possibilities might be relatively simple to distinguish. For example, a simple reisolation of starting material at partial conversion would easily prove or rule out hypothesis #1. However, the extreme reactivity of Ic in the absence of SLS and the difficulty of recovering it pure (but unfractionated) from the reaction

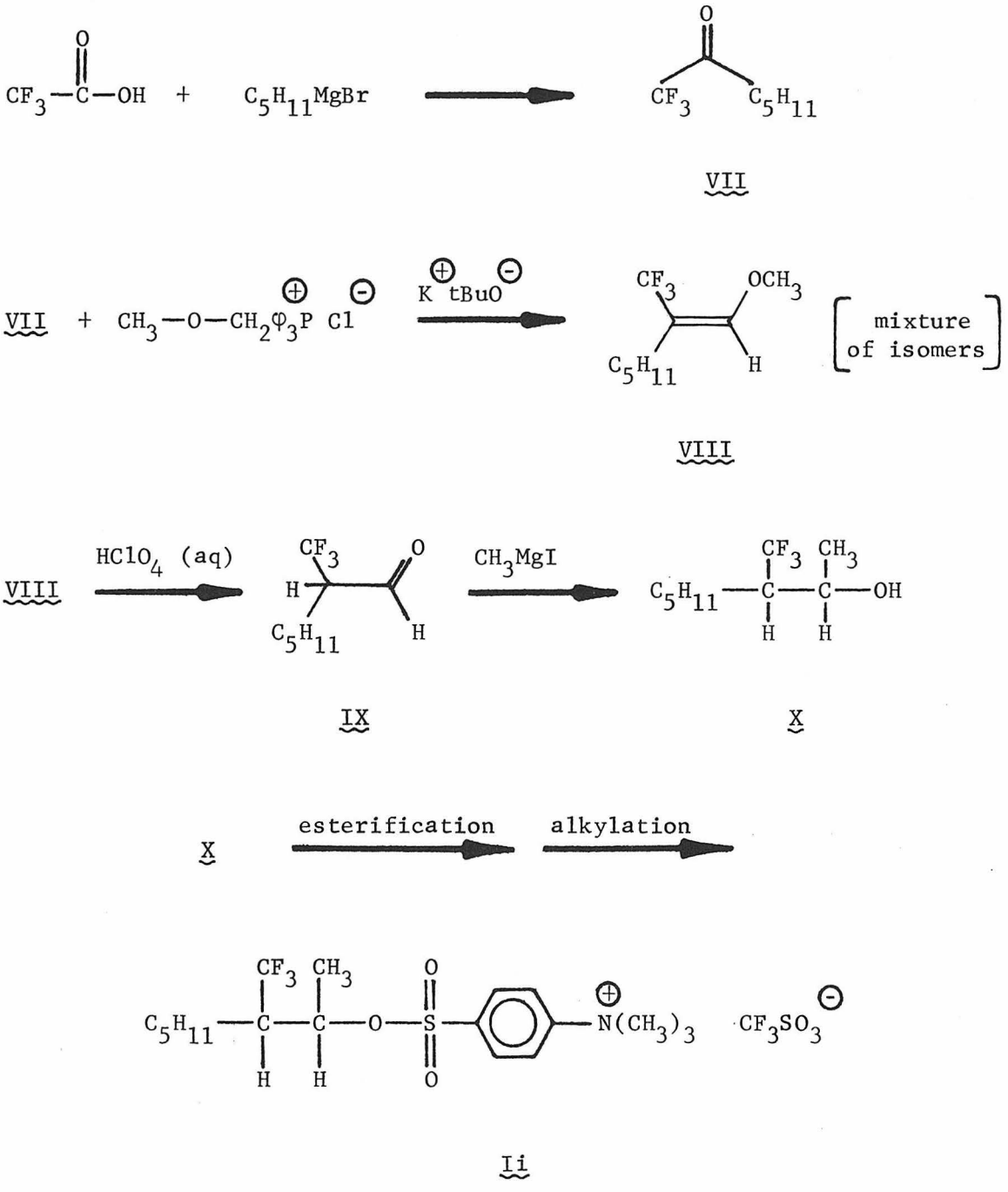
mixture, made this approach unworkable. Similarly, the common probe of measuring an *in situ* k_{α} *vs.* k_{t} was impossible due to the rather unpredictable extrinsic effects that micellar environments have on optical rotation (21), as well as the relatively low observed rotations of our reaction solutions. We therefore devised a series of experiments that would attempt to indirectly resolve the above mechanistic question as well as explain the apparent anomaly between SLS and NaDd.

Results - II

The primary difficulty in probing the source of the stereochemical effect of SLS was the lack of a convenient way to monitor the stereochemical fate of our starting material as the reaction progressed. The ability to do this might allow us to make some decision about hypothesis #1 -- the partial racemization of the starting material. We therefore synthesized Ii by the route indicated in Scheme I. We were able to separate the diastereomeric alcohols X by VPC and further enhance the stereochemical purity of this system by recrystallization of the p-dimethylaminobenzenesulfonate esters. By identification of the elimination products of each diastereomer of Ii we were able to correlate their absolute configurations. The major diastereomer was a mixture of RS and SR and the minor diastereomer was RR and SS (see the experimental section for details of this correlation). The presence of the diastereomeric CF_3 groups and the fact that their F^{19} NMR signals were easily distinguishable would allow us to observe any racemization of starting material. Racemization of diastereomerically pure starting material would manifest itself in the transient appearance of the F^{19} signals due to the other diastereomer as one observed the progress of the solvolysis in the NMR probe.

The solvolytic behavior of Ii can best be summarized as follows. In aqueous solution it reacted very slowly to give alcohol X as its primary product (along with some olefin and no rearranged alcohol). Ii was so unreactive, relative to all other compounds I, that while

Scheme I


CF3—C(=O)—OH + C5H11MgBr
VII
VII + CH3—O—CH2Φ3P Cl
K tBuO
mixture of isomers
VIII
VIII
HClO4 (aq)
IX
CH3MgI
X
X
esterification
alkylation
Ii

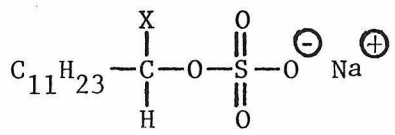
their rates could be monitored conveniently near ambient temperatures, Ii required ≥ 70° (22). As indicated in Table 4 the solvolysis of Ii is still significantly inhibited by the addition of micellar SLS even at this relatively high temperature (23). However, as is also indicated in Table 4, micellar SLS did not alter the stereochemistry of the solvolysis of Ii. Both in absence and presence of SLS the observed stereochemistry of the alcohol X produced is ≥ 98% inversion of configuration (This was determined by VPC analysis, since the two diastereomers of X are easily separated.). This maintainance of stereochemical integrity precluded

Table 4. Solvolysis of Ii.

Additive	Temperature	k x 10^5 sec^{-1}	Stereochemistry
None	74°	79.5	≥ 98% inversion
SLS (2 to 3 x CMC)	74°	5.1	≥ 98% inversion

any possible starting material racemization for this substrate and thus obviated the possibility of looking for diastereomer interconversion.

As a different approach to the above mechanistic questions we synthesized sodium 2-tridecyl sulfate (XI) and determined its effect on



SLS, X = H; XI, X = CH_3

the reactions of Ic. The advantages of such a system are: (a) it would allow us to better define the uniqueness of the stereochemical effect in the SLS-Ic system, and (b) if there were a nucleophilic displacement by $R—O—SO_3^{\ominus}$ occurring (hypothesis #3) the XI-Ic system would yield a new mechanistic probe. Whereas, in the case of the 1°-2° dialkyl sulfate (VI) generated from SLS-Ic, decomposition would always occur at the more reactive site and regenerate SLS and doubly inverted 2-octanol, in the XI-Ic system, the dialkyl sulfate intermediate would be chemically symmetric (2°-2°) and should decompose equally well from either side.

We observed the following effects when Ic was solvolyzed in the presence of micellar XI (24). The rate of reaction of Ic was inhibited to approximately the same extent as it was inhibited by SLS and NaDd; the observed rate constant at 22° was 18×10^{-5} sec^{-1} (compare with Table 2). The stereochemistry of the 2-octanol isolated from this reaction was only 86% inverted (as compared to 56% inversion for SLS but 100% inversion for NaDd and for no surfactant). We also noted in the VPC analyses of the reaction mixture of XI-Ic the presence of a variety of new products. These were shown by comparison to the solvolysis products of Ij (R = $C_{10}H_{21}$, X = H, Y = CH_3), to be 1-tridecene, cis and trans 2-tridecene and 2-tridecanol (25). Depending on the relative concentrations of XI and Ic in the starting reaction mixture, each mole of 2-octanol could be accompanied by, for example, .09 moles 2-tridecyl olefins and .28 moles of 2-tridecanol.

Further verification of a micelle dependent stereochemical effect resulted from the solvolysis of Ic in the presence of $NaClO_4$ and $NaEtSO_4$.

In both cases the isolated 2-octanol was completely inverted.

Because of its possible implication in our mechanistic schemes, we attempted to directly probe the nucleophilic behavior of our surfactants. While this was not readily done with the alkyl sulfates due to the inherent instability of dialkyl sulfates, we were able to directly measure the nucleophilicity of carboxylate towards I. To help quantify this nucleophilicity, we solvolyzed a variety of substrates I in water, in the presence of a known concentration of $Na^{\oplus}$ $OAc^{\ominus}$ and analyzed for the ratio of acetate to alcohol product. The results of this study are shown in Table 5.

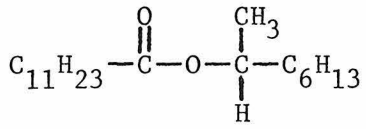
Table 5. Solvolyses of I in the Presence of Added Sodium Acetate.

Substrate Type	Substrate	(Molar Conc.)	Conc. NaOAc	Observed [OAc]/[OH] Products[a]	Corrected[b] Product Ratios
Me	Ih	(.07)	1.0 N	5.4[c]	300
1°	Ie	(.02)	1.0 N	1.9[c]	104
1°	Id	(.01)	0.1 N	.16[d]	90
1°	Id	(.01)	1.0 N	1.33[d]	74
2°	If	(.03)	1.0 N	$\leq$ .1[c]	$\leq$ 5.4
2°	Ic	(.01)	0.1 N	.01[d]	4.2
2°	Ic	(.01)	1.0 N	.11[d]	5.9

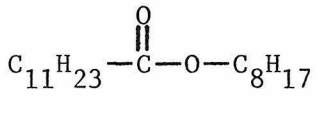
[a]Products identified by comparison with independently synthesized material. [b]Corrected for 55.4 M water vs. $[OAc^{\ominus}]$. [c]Measured by NMR integration in D_2O. [d]Measured by integration of VPC analysis of reaction mixture.

They indicate that as the carbonium ion character of the reaction transition state increases trapping of nucleophiles from solution becomes less selective. Thus, as the amsylate substrate is changed from methyl to primary to secondary, the enhanced effective nucleophilicity of $OAc^{\ominus}$ over water drops from a factor of 300 to 90 to 5.1 (26).

Based on the behavior of $OAc^{\ominus}$ we would expect that the amount of ester product resulting from trapping by carboxylate in the NaDd-I systems would be very small, since the concentration of NaDd used is only about .05 M. In fact, when Ic and Id were reacted in the presence of NaDd and the products analyzed by VPC, we found the expected esters in both cases, XII for Ic and XIII for Id. (The stability of these compounds to our reaction conditions was independently demonstrated.)



XII



XIII

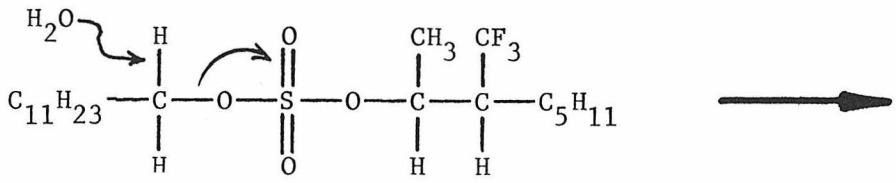
More importantly the amount of ester found in each case correlated well with the acetate system. Ic and NaDd gave $0 < XII < 1\%$ and Id and NaDd gave $XIII = 9 \pm 3\%$. Based on the concentration of NaDd used and on the acetate model we would have predicted a .48% yield of XII and a 8.2% yield of XIII.

Discussion - II

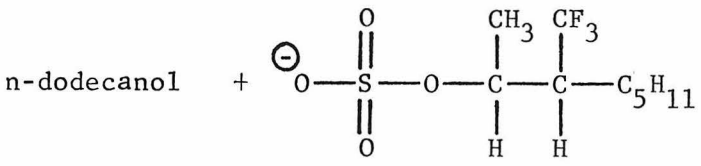
Any attempt to provide a mechanism consistent with all of the above data will have to consider the following apparent anomalies. 1) Why do we observe (in the reaction of XI and Ic) 2-tridecyl solvolysis products, when XI itself seems to be stable to our reaction conditions? 2) Why is XI just as effective as SLS at inhibiting the rate of hydrolysis of Ic but significantly less effective at perturbing its stereochemistry? 3) How does SLS inhibit the rates of solvolysis of both Ic and Ii while only changing the stereochemistry of Ic? 4) Why does NaDd effect only the rate but not the stereochemistry of the solvolysis of Ic?

The observation that all anionic micelles strongly inhibit amsylate solvolyses, whereas stereochemical effects seem to be both surfactant and substrate specific, seems to indicate that while our "water exclusion medium effect" may be adequate to account for the reaction kinetics, it is insufficient in accounting for the observed stereochemical effects. It is, however, reasonable to contend that the stereochemical effect of SLS on Ic and the decomposition of XI along with its lessened stereochemical effect on Ic, are all consistent with, and even suggestive of, the intermediacy of a dialkyl sulfate. Trapping of the reactive 2-octyl center by monalkyl sulfate anion would result in a dialkyl sulfate that itself is capable of hydrolysis, either to doubly inverted 2-octanol or to surfactant decomposition products. This hypothesis nicely handles questions #1 and #2 (above) and leaves open two possible answers to

question #3. Either, 1) the SLS-Ii dialkyl sulfate (XIV) never forms, or 2) it forms, but always cleaves on the SLS side to give dodecanol and XV, but not doubly inverted alcohol X (27) (eq 6). Since we could find



XIV



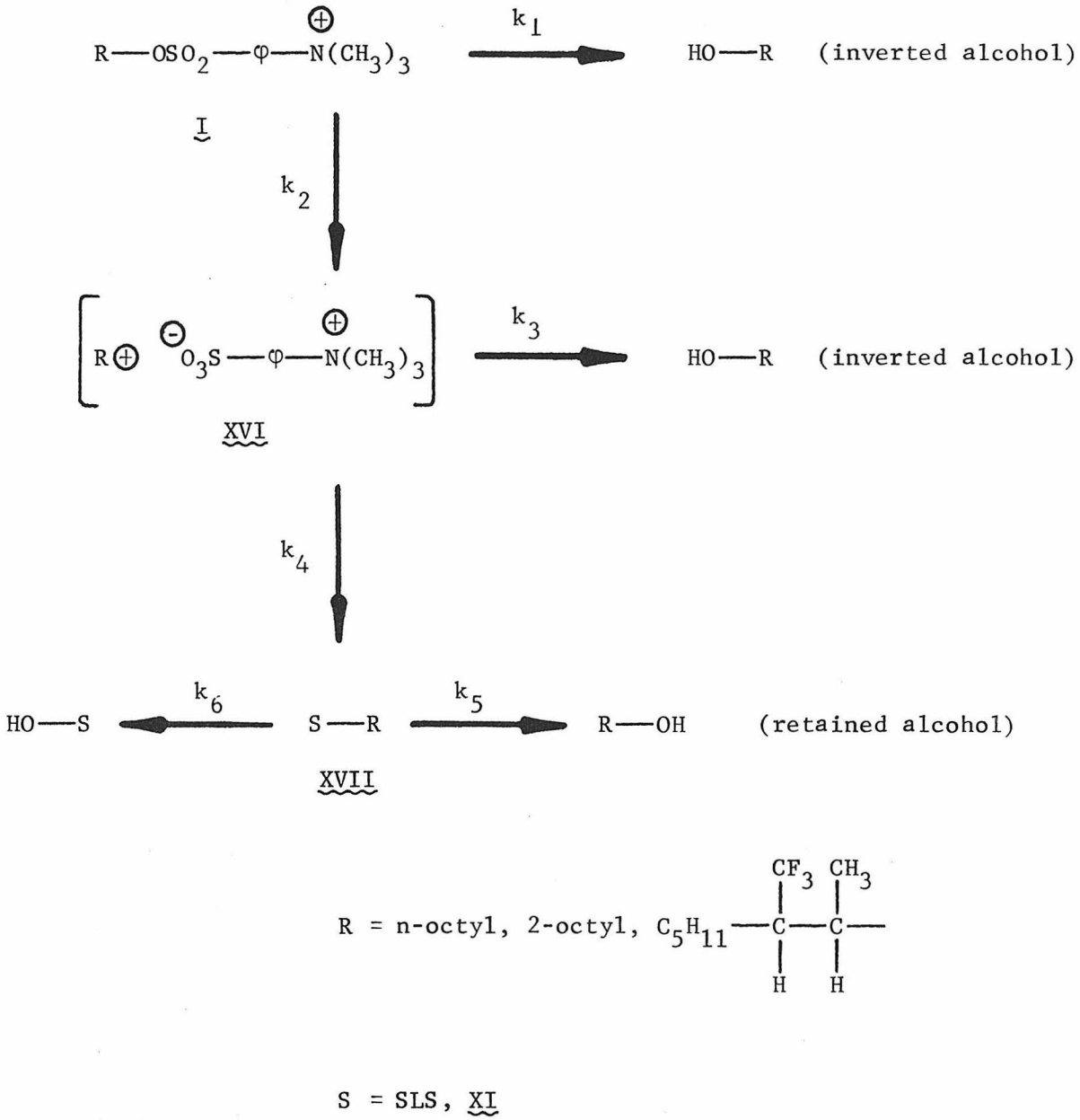
XV

(eq 6)

no evidence for increased dodecanol formation in the reaction of SLS-Ii and any attempts to locate XV by F^{19} NMR were at best ambiguous (28), we believe that XIV is never formed. Furthermore, in a reaction of SLS-Id where the hypothetical dialkyl sulfate would be 1°-1° (and should thus cleave on both sides), we could find no evidence for increased SLS decomposition. We contend that an overall mechanistic picture as depicted in Scheme II may be operative.

When R is such that R⊕ would be a very unstable species (i.e., 1° or CF_3 substituted), $k_1 \gg k_2$, and all that is ever observed is inverted alcohol regardless of the medium or the presence of surfactants. When R⊕ is energetically accessible, the intimate ion pair XVI is generated.

Scheme II



R = n-octyl, 2-octyl, C_5H_{11}—C(CF_3)H—C(CH_3)H—

S = SLS, XI

This species will be of very high energy relative to I and will thus be a much less selective nucleophile trap (Note analogy to the above reduced selectivity in trapping $OAC^{\ominus}$ over H_2O as R was changed from methyl to 1° to 2°.). Therefore, XVI will now react with any nucleophilic species that is in its immediate proximity. Since we have already postulated, based on the reaction kinetics, that the anionic micelle Stern layer around our cationic species (I) is relatively water free with strongly interacting ionic species, this forced intimacy of $RSO_4^{\ominus}$ and XVI makes k_4 a reasonable process despite the relatively poor "normal" nucleophilicity of $RSO_4^{\ominus}$. It must also be noted that the intermediacy of intimate ion pairs in solvolysis reactions is firmly precedented (29). Furthermore, the distinction made here between reaction pathways based on the relative stabilities of $R^{\oplus}$ as R loses a reactive leaving group is identical to the mechanistic treatment of the deamination of 1° *vs.* 2° alkylamines (30).

We believe that the above scheme is consistent with all the data herein reported. There remains only one unanswered question. Since the micellar Stern layer is able to impose unusual nucleophilic properties on alkyl sulfates, why does it not do the same for alkyl carboxylates? Why was the observed amount of XVII (S = RCOO) in the reactions of I with NaDd only that which could be explained by the normal nucleophilic behavior of carboxylates? This contrasting behavior, of carboxylate and sulfate head groups in our system, can best be understood by reference to a number of independent physical studies.

A wide range of properties of ions and their ability to interact

with hydrophobic species in water have been correlated in what is known as a lyotropic series. The most extensive such series, for monovalent anions, based on their interaction with a variety of gels and proteins in water and on their "salting out" ability, was compiled by Voet (31) and is indicated below in Sequence 1. A more specific

Sequence 1

$$F^{\ominus} < IO_3^{\ominus} < H_2PO_4^{\ominus} < HCO_3^{\ominus} < CH_3CO_2^{\ominus} < BrO_3^{\ominus} < NO_2^{\ominus} \quad Cl^{\ominus} <$$

$$ClO_3^{\ominus} < Br^{\ominus} < NO_3^{\ominus} < ClO_4^{\ominus} < I^{\ominus} < CNS^{\ominus}$$

example of sequencing of anions with respect to only one property was compiled by Reiman (32). He ordered monovalent anions in terms of their affinity for an ammonium resin (Sequence 2). Similar to this, Larsen and Magid (33) measured, by calorimetry as well as by competition studies, the relative affinities of a series of anions for the surface of CETAB micelles (Sequence 3). Interestingly, these sequences, to a

Sequence 2

$$OH^{\ominus} < F^{\ominus} < CH_3CO_2^{\ominus} < H_2PO_4^{\ominus} < Cl^{\ominus} < NO_2^{\ominus} < HSO_3^{\ominus} < CN^{\ominus} < Br^{\ominus}$$

$$< NO_3^{\ominus} < HSO_4^{\ominus} < I^{\ominus} < ClO_4^{\ominus}$$

Sequence 3

$$CH_3COO^{\ominus} < F^{\ominus} < OH^{\ominus} < HCO_2^{\ominus} < Cl^{\ominus} < NO_3^{\ominus} < Br^{\ominus} < Tos^{\ominus}$$

large extent, seem to parallel the hydration energies of the ions, a few values of which are indicated in Table 7.

Table 7. Enthalpies and Free Energies of Hydration at 25° (34). (Kcal/mole)

	F^-	OH^-	Cl^-	Br^-	I^-	BF_4^-	ClO_4^-	I_3^-
$-\Delta H_{298}$	121.9	110	87.6	79.8	69.7	71.2	57.1	43.8
$-\Delta G_{298}$	112.5	—	82.3	75.2	67.1	65.8	—	—

An obvious corollary to the above sequences is the statement that the more interaction there is between a particular ion and water the less interaction there will be between that ion and other ions. We would thus contend that while carboxylate at the surface of the micelle is tightly bound to its hydration sphere as it would be in bulk solution, the sulfate head group is interacting much more strongly with the cations present in the Stern layer. In view of the observation by Larsen and Magid (33) that SLS binds $NH_4^{\oplus}$ much more tightly than it binds $Na^{\oplus}$, it is furthermore reasonable that both SLS and XI would be very tightly associated with the $N(CH_3)_3^{\oplus}$ group of I. This situation would serve to generate an alkyl sulfate anion which is unsually well disposed

to react with our incipient carbonium ion center, thus accounting for the "uncharacteristically high" observed nucleophilicity of SLS and XI.

This analysis is corroborated by an NMR study of Gustavsson and Lindman (35) which directly compares physical properties of micellar sodium octanoate and sodium octyl sulfate. By looking at changes in relaxation times for Na^{23} counterions, they concluded that "the mode of counterion binding may be different for octanoate and octyl sulfate micelles (35)". They propose that "for carboxylate head groups, hydrogen bonding between the surfactant end group and the water of counterion hydration should be important, whereas [it] should not be significant for alkyl sulfates (35)". They further demonstrate this difference by showing that the weakly hydrated $Rb^{\oplus}$ ion is bound more tightly to sulfate head groups than to carboxylate head groups. Thus, our ability to distinguish between the chemical behavior of carboxylate and sulfate surfactants seems to be quite consistent with the wide variety of physical studies cited above.

In conclusion, it is interesting to speculate as to the relevance of our results to related systems. In particular, it may be possible to re-evaluate the results in Moss' deamination system (8) in light of our findings. The stereochemical perturbation of both amsylate solvolyses and aqueous deamination reactions is anion dependent. In both cases, hydrophobic poorly hydrated anions are more effective at changing the overall reaction stereochemistry. Since in both systems the reaction centers are at secondary carbons, the possibility of trapping available

nucleophiles should be comparable. Moreover, the carbonium ion generated under deamination conditions should be more reactive and a less selective electrophile. We therefore suggest that it is possible that the increased retention observed in the deamination systems may also be due to a double displacement process. Since the explanation proposed by Moss et al. (8) seems to be based on a "medium effect" which promotes increased retention by increasing internal return of OH (see discussion in introduction above), a simple O^{18} labeling experiment would distinguish these two mechanistic possibilities.

Experimental

A. General

Proton NMR spectra were obtained on a Varian A-60A or T-60 spectrometer (unless otherwise specified). They are reported as NMR: (solvent); chemical shift in units τ (multiplicity, number of protons), etc.. When higher field proton NMR was required the spectra at 100 MHz were recorded on a Varian XL-100-15 spectrometer, and at 220 MHz on a Varian HR-220 spectrometer. F^{19} NMR were obtained at 94.7 MHz on the Varian XL-100-15. IR spectra were recorded on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer and are reported in cm^{-1}. All boiling points are uncorrected. Melting points were determined on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. Mass spectra were obtained on a Dupont 21-492B high resolution mass spectrometer. Analyses were performed either by Spang Microanalytical Laboratory, Ann Arbor, Michigan or by the Caltech analytical laboratory (as indicated). Preparative vapor phase chromatography was performed on a Varian Aerograph 90-P3 gas chromatograph using 3/8" O.D. stainless steel columns, a helium carrier gas, and a thermal conductivity detector. Analytical VPC was performed on a HP-5750 Research Chromatograph using 1/8" O.D. stainless steel columns, a helium carrier gas and a flame ionization detector. Integration of analytical VPC output was accomplished by use of an Autolabs System I Computing Integrator. Optical rotations were recorded at five wavelengths on a Perkin-Elmer Model 141 Polarimeter using a water jacketed cell with a volume of 0.95 ml and a path length

of 10.001 cm. Surface tensions of micellar solutions (for CMC determinations) were measured by use of a Fisher Automatic Surface Tensiomat equipped with a 6 cm platinum-iridium ring and a thermostated cell. All surfactants (CETAB, SLS, NaDd, XI) were purified by recrystallization from acetone or ethanol. The H_2O used for all reactions was first distilled, then deionized, then distilled again.

B. Synthesis

Alkyl Trimethylammoniumbenzenesulfonate Triflate (I). The syntheses of sodium p-dimethylaminobenzenesulfonate and its conversion to the sulfonyl chloride have already been described in part I of this thesis. There, too, is described the special esterification procedure used to make Ig and Ih as well as their physical and chemical characterization. The procedure used to esterify all the remaining compounds, to make the dimethylamino esters, is the "alcohol + chloride in pyridine" procedure already explicitly described for the synthesis of the precursors to Ie and If. In all cases except Ii, the starting alcohols were obtained commercially and used as is. The procedure for alkylation of these dimethylaminobenzenesulfonates to the compounds I using methyl triflate (Cationics Inc.) has been described in detail for Ig and Ih and will therefore not be repeated here.

It should be noted that the yields for these esterifications were all 70-90% and the yields for the alkylations were all > 90%. Both of these steps may be performed on a scale ranging from 10 mgs to 10 gms of material. The only useful modification to be noted is that the

esterification of unreactive alcohols (i.e., X) can be aided by heating the reaction mixture to approximately 55° for two days after a day at ambient temperature. This resulted in yields > 80%.

The following is a listing of characteristic data for compounds Ia-Ij and their dimethylamino precursors.

Ia Dimethylamino Ester: M.P. = 42° (recrystallized from pet-ether); NMR (CCl_4): 2.90 (ABq, 4H), 6.15 (t, J = 6 cps, 2H), 6.97 (s, 6H), 8.8 (m, 13H).

Anal. Cald. for $C_{15}H_{25}NO_3S$: C = 60.0, H = 8.66, N = 4.66, S = 10.66;
Found (Spang): C = 60.23, H = 8.61, N = 4.57, S = 10.63.

Trimethyl Ammonium Ester: NMR ($CDCl_3$): 1.91 (s, 4H), 5.90 (t, J = 6 cps, 2H), 6.27 (s, 9H), 8.75 (m, 13H).

Ib Dimethylamino Ester: M.P. = 54.5°-56.0° (recrystallized from ether); NMR ($CDCl_3$): 2.8 (ABq, 4H), 6.19 (d, J = 5.5 cps, 2H), 6.94 (s, 6H), 8.9 (m, 15H).

Anal. Cald. for $C_{16}H_{27}NO_3S$: C = 61.34, H = 8.63, N = 4.47;
Found (Caltech): C = 61.35, H = 8.37, N = 4.55.

Trimethyl Ammonium Ester: NMR ($CDCl_3$): 1.91 (s, 4H), 6.06 (d, J = 5.5 cps, 2H), 6.27 (s, 9H), 8.8 (m, 15H).

Anal. Cald. for $C_{18}H_{30}NF_3O_6S_2$: C = 45.28, H = 6.29, N = 2.94;
Found (Caltech): C = 45.13, H = 6.25, N = 2.82.

Ic Dimethylamino Ester: racemic M.P. = 90.5°-92.0°, opt active M.P =

76.0°-77.5°; NMR ($CDCl_3$): 2.82 (ABq, 4H), 5.47 (m, J = 6 cps, 1H), 6.95 (s, 6H), 8.8 (m, 16H).

Anal. Cald. for $C_{16}H_{27}NO_3S$: C = 61.34, H = 8.63, N = 4.47, S = 10.2;

Found (Spang): C = 61.41, H - 8.59, N = 4.56, S = 10.14.

Trimethyl Ammonium Ester: NMR ($CDCl_3$): 1.90 (s, 4H), 5.28 (m, J = 6.5 cps, 1H), 6.27 (s, 9H), 8.8 (m, 16H). No analysis was obtained because it is too reactive.

Id Dimethylamino Ester: M.P. = 33.0°-34.5° (recrystallized from ether); NMR ($CDCl_3$): 2.81 (ABq, 4H), 6.03 (t, J = 6 cps, 2H), 6.96 (s, 6H), 8.8 (m, 15H).

Anal. Cald. for $C_{16}H_{27}NO_3S$: C = 61.34, H = 8.63, N = 4.47;

Found (Caltech): C = 61.54, H = 8.49, N = 4.42.

Trimethyl Ammonium Ester: NMR (CD_2Cl_2): 1.89 (s, 4H), 5.87 (t, J = 6.3 cps, 2H), 6.24 (s, 9H), 8.78 (m, 15H).

Anal. Cald. for $C_{18}H_{30}NF_3O_6S_2$: C = 45.28, H = 6.29, N = 2.94;

Found (Caltech): C = 45.41, H = 6.22, N = 2.88.

Ie Dimethylamino Ester: Described in Part I of thesis.

Trimethyl Ammonium Ester: NMR (D_2O): 1.90 (s, 4H), 5.80 (t, J = 6.0 cps, 2H), 6.32 (s, 9H), 8.6 and 9.2 (m, 7H) [Note: On standing, this NMR sample solvolyzed to butanol].

Anal. Cald. for $C_{14}H_{22}F_3NO_6S_2$: C = 39.91, H = 5.23, N = 3.33;

Found (Caltech): C = 39.85, H = 5.18, N = 3.19.

If Dimethylamino Ester: Described in Part I of thesis.

Trimethyl Ammonium Ester: NMR (CD_2Cl_2): 1.96 (s, 4H), 6.36 (q, J = 6.0 cps, 1H), 6.27 (s, 9H), 8.44 (q, J = 7.0 cps, 2H), 8.75 (d, J = 6.0 cps, 3H), 9.20 (t, J = 7.0 cps, 3H). Compound was too reactive for analysis.

Ig and Ih were previously described.

Ii Dimethylamino Esters: minor diastereomer: M.P. = 5.40-55.5 (recrystallized from ether); major diastereomer: oil; NMR ($CDCl_3$): 2.84 (ABq, 4H), 5.25 (m, 1H), 6.97 (s, 6H), 7.22 (m, 1H), 8.70 (m, 14H).

Anal. (minor) Cald. for $C_{17}H_{26}F_3NO_3S$: C = 53.54, H = 6.82, N = 3.68;

Found (Caltech): C = 53.52, H = 6.77, N = 3.59.

Trimethyl Ammonium Esters: NMR ($CDCl_3$): 1.88 (s, 4H), 5.02 (m, 1H), 6.23 (s, 9H), 7.79 (m, 1H), 8.67 (m, 14H).

Anal. Cald. for $C_{19}H_{29}F_6NO_6S_2$: C = 41.84, H = 5.32, N = 2.57;

major - Found (Caltech): C = 41.44, H = 5.13, N = 2.50;

minor - Found (Caltech): C = 41.41, H = 5.15, N = 2.44.

F^{19} NMR of Ii: The dimethylamino esters in $CDCl_3$ each showed a doublet with J = 10 cps with the major diastereomer being 30 Hz downfield of the minor.

Trimethyl ammonium esters in D_2O each showed a singlet for $CF_3SO_3^{\ominus}$ and doublets for each diastereomer J = 9.5 cps. The relative positions of these signals in Hz downfield from a sample of HCF_3SO_3 in D_2O were as follows: $CF_3SO_3^{\ominus}$ = 10 Hz, major diastereomer = 1087 Hz, minor

diastereomer = 1209 Hz.

Ij Dimethylamino Ester: Solid at low temperature (0°), melts to oil at room temperature. NMR ($CDCl_3$): 2.80 (ABq, 4H), 5.5 (m, 1H), 6.97 (s, 6H), 8.78 (m, 26H).

Trimethyl Ammonium Ester: NMR ($CDCl_3$): 1.89 (s, 4H), 5.27 (m, 1H), 6.24 (s, 9H), 8.75 (m, 26H).

Trifluoromethyl 2-Heptanone (VII). Using the procedure of Dishart and Levine (36), a 1 liter 3-neck flask equipped with a reflux condensor, addition funnel, N_2 inlet, and magnetic stirrer was flame dried and charged with 14.6 gms of oven dried magnesium metal and 400 ml dry ether. 75 ml (91 gms) of n-pentyl bromide (Aldrich) were added dropwise at a rate sufficient to maintain a gentle ether reflux. After the addition was complete the reaction was allowed to stir for 1 hr. at room temperature to guarantee complete reaction. 14.9 ml (22.8 gms) of trifluroacetic acid (MCB) were mixed with 50 ml dry ether and this solution was added dropwise to the Grignard reagent over a period of 1 hr. The reaction was refluxed an additional 2 hrs after the acid addition was complete and it was then poured onto a mixture of ice and 100 ml conc. HCl. This mixture was extracted exhaustively with ether and the combined ether fraction was washed with saturated aq $NaHCO_3$, H_2O, and saturated aq NaCl. The ether solution was dried over Na_2SO_4, then filtered and the ether was removed under reduced pressure at room temperature. The remaining liquid was distilled through a 10" vigreaux column. The

desired ketone (VII) distilled over at 100° at atmospheric pressure [L.t. (37): B.P. = 112°] and continued distillation at reduced pressure gave significant amounts of the alcohol corresponding to the reduction of VII. Yield VII = 17 gms (51% yield). Yield of alcohol was between 20% and 25%. NMR ($CDCl_3$): 7.28 (t, j = 6.5 cps, 2H), 8.65 (m, 9H); IR (neat): 1770 ($\geq C=O$), 1150, 1250 (CF_3) cm^{-1}.

Methoxy Methylene Triphenyl Phosphonium Chloride (38). Caution: The chloromethyl methyl ether used in this preparation is a very volatile, very potent carcinogen. It should therefore be used with extreme care, in a well ventilated hood and all glassware should be thoroughly base-washed after use.

A 1-neck 500 ml 24/40 r.b. flask equipped with a magnetic stirrer and an N_2 inlet was charged with 100 gms φ_3P and 225 ml CH_2Cl_2 (distilled from $CaCl_2$ and stored over molecular sieves). 30.5 ml (32.4 gms) of chloromethyl methyl ether (Aldrich) were added in one portion and the flask was fitted with a reflux condensor, under N_2, and allowed to reflux overnight. The next day 100 ml of dry (distilled from LAH) benzene were added and all of the CH_2Cl_2 and unreacted chloromethyl methyl ether were distilled off at atmospheric pressure. Using a make-shift Schlenk-like apparatus, consisting of a metal tube with filter paper on the end and a rubber septum, the white solid was repeatedly slurried in fresh benzene which was then filtered off. This process was repeated four times with 100 ml portions of benzene and after the last solvent removal the flask containing the white solid pro-

duct (the original reaction flask) was attached to a vacuum line and dried for 10 hrs. The resulting white powder (122.5 gms - 92.6% yield) was stored in a desiccator. NMR ($CDCl_3$): 2.2 (m, 15H), 4.16 (d, J = 4 cps, 2H), 6.29 (s, 3H).

1-Methoxy-2-Triflouromethyl-1-Heptene (VIII) - Mixture of E and Z.

A 3-neck 2 liter flask, equipped with an N_2 inlet, magnetic stirrer, and an addition funnel was flame dried and charged with 47.2 gms methoxy methylene triphenyl phosphonium chloride and 750 ml dry ether. While this slurry was being vigorously stirred, 15.5 gms K^+tBuO^- (Ventron) were added in 3 or 4 portions. Within 15 min a red solution resulted and it was allowed to stir for another 1.5 hrs. 11 gms of triflouro-methyl ketone (VII) (92% pure by VPC) were diluted to 450 ml with dry ether and this solution was added over 2.5 hrs to the reaction mixture. The reaction was then allowed to stir at room temperature for 26 hrs at which time 200 ml H_2O, followed by 100 ml pentane were added. The aqueous layer was separated and the organic layer was washed three times with 200 ml H_2O. The combined aqueous layers were backwashed once with 100 ml pentane which were added to the organic solution (volume = 1400 ml). The ether and pentane solvents were removed under reduced pressure. This solution (300 ml) was filtered to remove Φ_3PO and then dried over Na_2SO_4. After drying, removal of the rest of the solvent yielded 20 ml (18 gms) of black-red oil. This was distilled through a 6" vigreaux at 20 mm pressure to yield a main fraction (approx. 10 ml) at 92°-94° and approximately 1 ml of a higher boiling afterrun. By VPC analysis

(1/8" x 12', 15% Carbowax 20 M on Chrom W) the first fraction (9.42 gms) was shown to be a 2.6/1 ratio of isomer 1/isomer 2. Fraction #2 was .43 gms of pure isomer 2. Total yields of distilled material was therefore 9.85 gms (83% yield). This mixture of isomers was used as is for the next step in the reaction sequence. IR (neat mixture of isomers): 1680, 1455, 1350, 1295, 1250, 1215, 1110, 1050 cm^{-1}.

The mixture of isomers could be separated by preparative VPC (15' x 3/8", 10% DEGS on Chrom P). At 140° isomer #1 had a retention time of 8 mins and isomer #2 a retention time of 14 mins. Their ^{19}F NMR (Varian XL-100-15) show each CF_3 group to be a singlet. The two signals are separated by 366 cps ($\approx$3.9 ppm). Their proton NMR (60 MHz) with tentative assignments are indicated below. Isomer #1 (OCH_3 and CF_3 trans) NMR ($CDCl_3$): 3.4 (m, 1H), 6.30 (s, 3H), 7.85 (t, j = 7 cps, 2H), 8.7 (m, 9H); Isomer #2 (OCH_3 and CF_3 cis) NMR ($CDCl_3$): 3.9 (broad s, 1H), 6.30 (s, 3H), 7.96 (t, j$\approx$6.0 cps, 2H), 8.7 (m, 9H).

2-Trifluoromethylheptanal (IX). In a 1 liter separatory funnel with a teflon stopcock combine 550 ml dry ether and 150 ml of 60% perchloric acid. This very exothermic process evaporated about 50 ml of ether which were replaced. 9.85 gms of neat enol ether (VIII) were added and the funnel was shaken a few times to guarantee complete homogeneity. The hydrolysis proceeded slowly and it was necessary to let this mixture stand in the stoppered separatory funnel for at least three days. After three days a saturated aq Na_2CO_3 solution was added, slowly, in 100 ml portions. After each addition of base the aqueous

layer was drained off. This process was repeated until the resulting aqueous layer was of neutral pH. The ether solution was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure at room temperature. The aldehyde product was a clear liquid which could be used as is for the next step. IR (neat): 1740 (>C=O), 1255, 1175, 1145, 1100; NMR ($CDCl_3$): 0.34 δ (m, 1H), 7.08 (m, H), 8.8 (m, 11H).

3-Trifluoromethyl-2-Octanol (X). A flame dried 3-neck 14/20 100 ml round bottom flask was equipped with a reflux condensor, magnetic stirrer, septum, and N_2 inlet. It was charged with 1.1 gms magnesium metal and 20 ml dry ether. 2.8 ml CH_3I (distilled) were added by syringe at a rate sufficient to maintain a gentle reflux. The reaction was allowed to stir at room temperature for 2 hrs after the addition of CH_3I was complete. 4 gms of aldehyde IX were added as a 50% solution in ether over a period of 10 min. The reaction was then refluxed for 2 hrs after which it was quenched by pouring onto a mixture of ice and HCl. This mixture was repeatedly extracted with ether and the combined ether extracts were washed once with H_2O and once with saturated aq NaCl. The ether solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure at room temperature. The resulting 4.2 gms of light yellow liquid was about 81% product by VPC (27' x 1/8", 15% Carbowax 20 M at 141°), indicating a crude yield of 3.4 gms (79%). This material consisted of two species in the ratio of 55/45 which could be analyzed using the above VPC conditions (retention times: major = 17 min, minor = 20 min). Pure samples of each diastereomer

were obtained by preparative VPC (15' x 3/8", 10% DEGS on Chrom P; at 155° and flow of 100 ml/min). Each diastereomer had the following physical properties. Major diastereomer: NMR ($CDCl_3$): 5.82 (doublet of quartets, $J_{CH_3\text{-}H}$ = 6.5, $J_{H\text{-}H}$ = 3.0, 1H), 7.85 (m, 1H), 7.93 (s, 1H), 8.62 (m, 11H); IR (neat): 3390, 2960, 2870, 1463, 1375, 1260, 1168, 1140.

Anal. Cald. for $C_9H_{17}F_3O$: C = 54.55, H = 8.59;

Found (Caltech): C = 54.26, H = 8.39.

Minor diastereomer: NMR ($CDCl_3$): 5.86 (doublet of quartets, $J_{CH_3\text{-}H}$ = 6.5, $J_{H\text{-}H}$ = 4.5, 1H), 7.80 (m, 1H), 7.91 (s, 1H), 8.63 (m, 11H); IR (neat): 3390, 2960, 2875, 1465, 1376, 1255, 1170, 1095, 1058.

The F^{19} NMR of each of the above showed a doublet (J = 9.75 cps) and the signals for the minor diastereomer were 110 cps (1.17 ppm) downfield of those for the major diastereomer.

3-Trifluoromethyl-2-Octene (Mixture of E and Z Isomers). Ethyl triphenyl phosphonium bromide was prepared from ethyl bromide (Aldrich) and triphenyl phosphine (MCB) in dried distilled benzene, and was used as is for the next step. A 3-neck, 24/40 round bottom flask equipped with a magnetic stirrer, reflux condensor, N_2 inlet and a septum, was flame dried and charged with 46.2 gms of $Et\varphi_3P^{\oplus}\ Br^{\ominus}$ and 300 ml dry ether. While this slurry was being rapidly stirred, 52 ml of a 2.4 molar solution of nBuLi in hexane (Ventron) were added by syringe over 20 min. After stirring for 1 hr at room temperature the clear red solution was cooled

to 0° and 17 ml of ketone (VII) were added *via* syringe over 10 min. The reaction mixture was stirred at room temperature for 1 hr and then refluxed for 4 hrs, at which time it was diluted with pentane and quenched by the addition of H_2O. The organic solution was filtered and then washed with saturated aq sodium bisulfite, H_2O, and saturated aq NaCl. After drying over anhyd Na_2SO_4 the volume of the organic solution was reduced from 600 ml to 100 ml which were filtered and then distilled through a 15" vigreaux to give 15 ml of 80% pure product. This material was redistilled carefully to yield approximately 10 ml of 90% pure product. B.P. ≈ 118°-119°. VPC analysis of this material (50° on a 27' x 1/8", 15% Carbowax 20 M) indicated the presence of both isomers (ratio 1.5/1) with the earlier eluting olefin predominating. IR (mixture of olefins-neat): 2940, 2860, 1670, 1460, 1390, 1315, 1260, 1165, 1115; major product (early eluting), NMR ($CDCl_3$): 4.2 (q, J = 7.5 cps, 1H), 7.83 (m, 2H), 8.19 (m, 3H), 8.72 (m, 9H); minor product (later eluting), NMR ($CDCl_3$): 3.8 (q, J = 6.5 cps, 1H), remainder of spectrum assumed to be the same as above, but the isomers were *not* preparatively separated.

The above compounds were assigned based on the chemical shift difference of the vinyl protons. By analogy to other systems (39) it was assumed that a proton cis to the CF_3 group would be downfield. The major olefin product is the Z isomer (CF_3 and CH_3 on same side) and the minor, later eluting, olefin is the E isomer.

F^{19} NMR showed a singlet for each compound and they were separated by 709 Hz, approximately 7.5 ppm. These peaks were not assigned.

Carboxylate Esters. Methyl acetate was obtained commercially (MCB). n-Butyl, 2-butyl, n-octyl, and 2-octyl acetates were prepared by the following procedure. A 50 ml erlenmeyer flask was charged with 10 ml of acetic anhydride (reagent grade) and either 5 ml butanol or 8 ml octanol (reagent grade). After standing at room temperature for 24 hrs the reaction mixtures were each poured onto 50 gms of ice. The organic material was extracted into ether and the ether layer was washed successively with: dilute aq HCl, H_2O, saturated aq $NaHCO_3$, H_2O, and saturated aq NaCl. The resulting ether solution was further dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure to yield products which were pure by NMR and $\geq$ 98% pure by VPC (12' x 1/8", 15% Carbowax 20 M Chrom W). Yield = 7.2 gms n-octyl acetate, 7.4 gms 2-octyl acetate, 4.7 gms n-butyl acetate, and 3.5 gms 2-butyl acetate.

n-dodecyl esters XII and XIII were prepared by reaction of their respective alcohol precursors with n-dodecanoyl chloride which was prepared from NaDd and oxalyl chloride, all by standard procedures (40). The resulting esters were purified by chromatography on silica gel using pet-ether and ether elutents and were then distilled under reduced pressure (.2 mm) to yield clear liquid products. n-dodecanoyl chloride: B.P. = 84° at .2 mm; NMR ($CDCl_3$): 7.12 (t, J = 7 cps, 2H), 8.73 (m, 21H). n-octyl-n-dodecanoate: distilled on molecular still at .2 mm; NMR ($CDCl_3$): 5.96 (t, J = 6.5 cps, 2H), 7.72 (t, J = 6.5 cps, 2H), 8.73 (m, 36H). 2-octyl-n-dodecanoate: B.P. = 120° at .18 mm; NMR ($CDCl_3$): 5.12 (m, 1H), 7.72 (6, J - 7 cps, 2H), 8.75 (m, 37H).

Sodium Monoalkyl Sulfates XI and XV. This procedure is based on that of Dreger et al. (41). XI: A 50 ml round bottom flask cooled to 0° and equipped with an addition funnel topped by a drying tube, was charged with 9.6 ml glacial acetic acid and 3.3 ml chlorosulfonic acid. While stirring this mixture with a magnetic stir bar 12 ml of neat 2-tridecanol (K and K) was added dropwise over approximately 5 min. When the addition was complete the reaction was allowed to stir at 0° for 1 hr and then quenched by pouring onto 30 gms ice. 30 ml of n-butanol were then added followed by sufficient saturated aqueous Na_2CO_3 to neutralize the entire solution. The mixture was saturated with solid $NaHCO_3$ and extracted 5 times with 50 ml portions of n-butanol. The combined organic extracts were washed once with saturated aqueous NaCl solution and briefly dried over solid anhydrous Na_2SO_4. The solution was filtered and all of the solvent was removed under reduced pressure to yield 13 gms of white solid. This material was recrystallized twice from water and once from ethanol to yield 7.9 gms of pure material (55% yield). A repeat of this procedure using 7.3 ml alcohol yielded, after 5 recrystallizations, 5 gms material (81% yield). M.P. = 158°-161°; NMR (D_2O): 5.5 (m, 1H), 8.68 (m, 26H).

XV: A 10 ml round bottom flask was charged with 3 ml glacial acetic acid and .7 ml chlorosulfonic acid and let stir under N_2 at 0°. 2.47 gms (73% pure by VPC) of alcohol X (mix of diastereomers) was added in one portion and the reaction was allowed to stir at 0°-4° for 45 min. The reaction was warmed to 17° over 30 min and then quenched with ice and worked up as above to yield 2.35 gms of crude white solid (100% yield =

2.71 gms) which by NMR showed a significant NaOAc impurity. Attempts to purify this material by recryst from H_2O failed and a partial purification was achieved by oiling the product out of $\leq$ 2 ml H_2O, redissolving the oil in 5 ml H_2O and lyopholizing it to dryness. This powder shows $\leq$ 10% $OAc^{\ominus}$ impurity and was used as the "known" for purposes of characterizing XV. H'NMR (D_2O): 4.95 (m, 1H), 7.24 (m, 1H), 8.6 (m, 14H). The F^{19} NMR chemical shift values for the mixture of diastereomeric sulfates was very solvent dependent and very concentration dependent. Each diastereomer appeared as a doublet (J = 10 cps) but the chemical shift difference between them varied between 15 and 30 cps. Typically these peaks were approximately 1160 cps downfield from an external standard of CF_3SO_3H in D_2O.

C. Correlation of Configurations of Ii Diastereomers

During the course of the solvolyses of Ii it was observed that each diastereomer gave only one of the two possible trisubstituted olefinic products. Since we had previously assigned structures to the E and Z isomers of 3-trifluoromethyl-2-octene based on their NMR chemical shifts (vide supra), we were able to use the identity of these olefins to correlate the diastereomers of Ii. Since the major diastereomer of Ii only gave the E olefin it was assigned the R,S or S,R configuration (assuming that the elimination process prefers a trans elimination of proton and leaving group). Similarly since the minor diastereomer of Ii only gave the Z olefin isomer it was assigned R,R or S,S.

D. Procedure for Analytical Solvolyses Reactions

5-20 mgs of the appropriate substrate I were transfered into a 10 ml vial with a teflon lined cap. (Note: Secondary and allyl substrates were handled only in an N_2 atmosphere in a glove bag.) A known amount of solvent (either water or a freshly prepared stock solution of a surfactant) was added and the vial was capped and placed on a Burrell Wrist Action Shaker for the duration of the reaction. The organic products were then extracted with 1 ml portions of pentane. The problem of separating the organic solution from the aqueous surfactant solution was aggravated by the formation of emulsions. This was usually solved by centrifuging, in a desk top centrifuge, the vial with the solution being partitioned and then pipetting off the organic layer. If sulfate surfactants were being used, they could be precipitated by saturating the aqueous layer with BaCl during the first extraction. (Barium sulfates are insoluble in water.)

The products were analyzed by injecting the combined pentane solution directly onto the analytical VPC and integrating the resulting chromatogram. The problem of simultaneously separating isomeric olefins as well as isomeric and diastereomeric alcohols was solved most efficiently by the use of temperature programming and relatively long, heavily loaded, and tightly packed columns. The following two columns gave the best results:

Column #1: 27' x 1/8", 15% Carbowax 20 M on Chrom W-DMCS 100/120

Column #2: 20' x 1/8", 25% STAP on Chrom W-DMCS 100/120

For less demanding analyses or when analyzing for alcohols with 12 or

13 carbons a 12' or 15' version of column #1 was used. All products were identified by comparison with commercially available authentic samples except those of Ii. These products were independently synthesized and are described in this thesis.

E. Kinetic Measurements

1) By NMR. These runs were generally done using the Varian XL-100-15 operating in the FT mode. This was particularly crucial for those reactions where the concentration of I was 5×10^{-3} M or less. The rate of the reaction was measured by monitoring the appearance of either the $N^{\oplus}\text{-}(CH_3)_3$ peak (a very sharp singlet) or the peak attributable to the aromatic ring of the zwitterion being produced. These peaks were well resolved from those of the starting material and thus could be easily followed. Plots of $\ln(P_\infty - P_t)$ vs. time were linear for over 80% reaction and the average deviation from the least squares "best line" was < 6%.

2) By Autotitration. These experiments were done using a Radiometer Autoburette and Titrator with a jacketed cell that was thermostated using a Precision Scientific Constant Temperature Circulating System. The automatic burette was filled with a .01 N NaOH solution and was set to maintain a pH-Stat of 6.5. The rate of consumption of base was automatically recorded and was a direct measure of the rate of the reaction. Rate constants were obtained from plots of $\ln(V_\infty - V_t)$ vs. time where V_∞ is the infinity titer of the reaction. In these cases the plots were linear for > 90% reaction.

F. Stereochemistry Determinations

Resolved (+)-2-octanol was obtained (Norse) and used as is. The optical purity of the 2-octanol used in these studies as well as the 2-octanol obtained as a reaction product was determined by two independent means. The alcohol was purified by preparative VPC (22' x 3/8", 20% Carbowax 20 M on Chrom W). It was then weighed (5-20 mgs used) by pipetting directly into a 1 ml volumetric test tube. The sample was diluted to 1 ml with spectral quality chloroform and the observed rotation was measured. The value used for the optical purity of a given sample is the average of its purity compared to starting alcohol at all five wavelengths (three readings at each wavelength). This same sample was then subject to esterification with (+) methoxy phenyltrifluromethyl acetyl chloride using the procedure of Dale, Dull, and Mosher (42), with one simplification. The acid chloride (1 drop acid chloride per 5 mgs of alcohol) and pyridine were added directly to the 1 ml $CHCl_3$ polarimeter sample and this reaction was stored at room temperature for one day. After workup the resulting esters were dissolved in an 80% $CDCl_3$ + 20% TFA solvent and were subjected to analysis by F^{19} NMR. Broad band proton decoupling was very helpful in improving the signal resolution. The two singlets from the CF_3 groups of the diastereomeric 2-octyl esters were cleanly resolved and separated by 20 to 45 cps, depending on small changes in solvent. Peak areas were determined by both machine integration and by cutting and weighing three xerox copies of the peaks.

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14. The critical micelle concentrations for Ia and Ib have been determined at 25° by a plot of surface tension vs. concentration. Ia = 1.2×10^{-2}, Ib = 9×10^{-3} M.

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18. (a) A variety of probes of micellar structure would be useful in looking at this "special" Stern layer. In particular fluorescence (18b) and F^{19}NMR (18c) studies would be of great value. For example see, N.E. Schore and N.J. Turro, J. Amer. Chem. Soc., 97, 2488 (1975) and references therein. Reference (4a), Chapter 1, pp. 8-13. (b) It is interesting to note that while physical studies have been performed on micelles of surfactants with long chain anions and long chain cations [i.e., $R\text{-}N(CH_3)_3^+$: RSO_4^-], there are no reports of the catalytic behavior of these systems. Some leading references: A.B. Scott, H.V. Tartar, and E.C. Lingafelter, J. Amer. Chem. Soc., 65, 698 (1943); E.W. Anacher, J. Coll. Sci., 8, 402 (1953); H.W. Hoyer, A. Marmo, and M. Zoellner, J. Phys. Chem., 65, 1804 (1961); H.W. Hoyer and I.L. Doerr, ibid., 68, 3494 (1964); J.M. Corkill, J.F. Goodman, S.P. Harrold, and J.R. Tate, Trans. Faraday Soc., 62, 994 (1966).

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22. The large substitutent effect exerted by this CF_3 group in the β position is consistent with our contention that an alkyl amsylate ionizes via a transition state with significant carbonium ion character.

23. (a) CMC (23b) of SLS at 25° = 8.3×10^{-3} M, at 70° = 11.4×10^{-3} M; (b) P. Mukerjee and K.J. Mysels, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand., 38 (1971); (c) The temperature dependence of micellar catalyses has been repeatedly demonstrated (catalysis decreases with increased temperature). See refs 3 and 4.

24. Lit (23b) CMC of XI at 40° = 6.5×10^{-3} M. We measured the CMC at 25° = 4.5×10^{-3} M.

25. (a) Since the simple decomposition of monoalkyl sulfates is a well precedented process (25b), we did the following controls to show that we were not just observing simple surfactant decomposition. The rate of 2-tridecyl species production in our solvolysis was $\gg 10^2$ faster than that observed in water, .1 N HCL and 1 N HCL.

Mixing a solution of XI with a completed SLS-Ic reaction mixture resulted in no detectable decomposition of XI. Only when XI was present during an ongoing solvolysis of Ic could its decomposition be noted. Lastly, the ratio of alcohol to olefin products of XI we obtained resemble typical solvolysis products (Ij) and do not resemble the mixtures obtained from monoalkyl sulfate decomposition (25b); (b) see: J. Kurz, J. Phys. Chem., 66, 2239 (1962); V.A. Motsavage and H.B. Kostenbauder, J. Coll. Sci., 18, 603 (1963); R.L. Burwell, J. Amer. Chem. Soc., 74, 1462 (1952).

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27. The greater reactivity of Ia, Id, Ie over Ii indicates that the β CF_3 substitution makes that center even less reactive than a simple primary center, so it should always cleave as shown in (eq 6).

28. This ambiguity resulted from the large solvent and concentration dependence of the chemical shifts of XV and from the fact that Ii and X both also had F^{19} chemical shifts within 20 Hz of XV.

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PROPOSITIONS

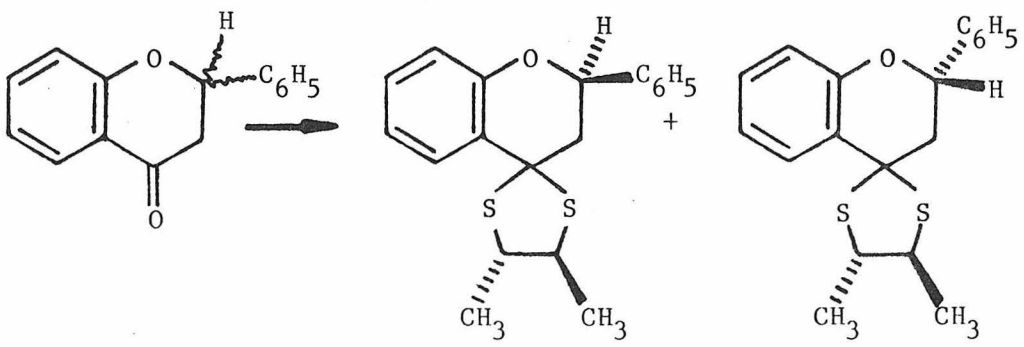
Abstracts of Propositions

1. The synthesis and use of chiral carbonyl cation and anion equivalents is described. Their projected utility for asymmetric induction and for simple resolution of otherwise difficult to resolve species is discussed.
2. Possible routes to potentially aromatic triene-diones are suggested and some speculation on their physical and chemical properties is presented.
3. A mechanistic study of mono-alkyl sulfate ester hydrolysis in both acid and base is described. Its primary purpose is to monitor the effects that cationic and anionic micelles would have on the partitioning of a reaction among four well established competitive pathways.
4. A new approach to stereospecific cyclopropane synthesis is proposed. A primary application is the synthesis of trans-fused small ring bicyclics which are of both physical and chemical interest.
5. The synthesis of a series of small ring heterocycles is described. The advantage of studying strained azabicyclic and tricyclic compounds over their carbocyclic analogs are pointed out and the use of an azatricyclic system as an entry to a $C_5H_5^{\oplus}$ analog is described.

Chiral Carbonyl Equivalents

The utility of the carbonyl functional group in synthetic organic chemistry has made it the focus of a great deal of research. Thus, the introduction of carbonyls or their equivalents both electrophilically (i.e., acylation) and nucleophilically (i.e., carbonyl anion equivalents) is a well developed area of chemistry. The reactivity of carbonyls often dictates that they be masked or protected at various points in a synthetic sequence. This is most commonly accomplished by conversion to the ketal or thioketal. An interesting, but relatively obscure extension of the use of these protecting groups is found in the use of optically active diols or dithiols to protect carbonyls in molecules that already possess one asymmetric center. The introduction of this new optical center makes what had previously been enantiomeric ketones (or aldehydes) into diastereomers. This new "stereo-relationship" allows physical separation of the optical isomers. Ultimate de-ketalization yields the two original enatiomers, now optically resolved. Two interesting applications of this concept are illustrated below (1,2).

ref (1)



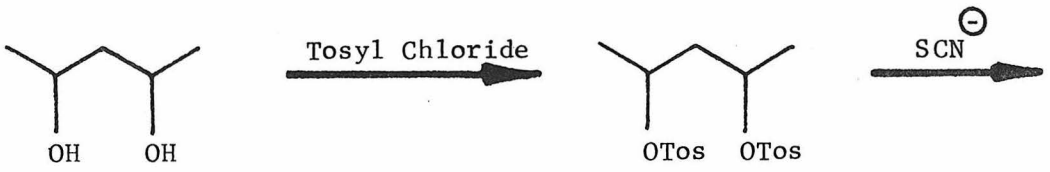
Alternatively, racemic IV could be made, without worrying about stereochemistry, from racemic III. By using it to make the thioketal of an optically active ketone (e.g., commercially available, optically pure camphor) one would obtain separable diastereomers, which upon resolution and cleavage back to IV would yield optically pure II.

The basic chemical reactvities of I and II are fairly predictable and well understood. I has been shown (4b) to cleanly trap anions such as $OEt^{\ominus}$ and $CN^{\ominus}$ and some neutral nucleophiles. When analogs of II are metalated by removal of a proton (to give $II^{\ominus}$), they are known to behave as excellent nucleophiles in a variety of displacement and addition processes (3). Therefore, the kind of chemistry one would like to initially accomplish would be electrophilic (with I) or nucleophilic (with $II^{\ominus}$) attack at a prochiral center. A few possible systems are suggested in Scheme II. In each of these cases the stereochemistry of the new chiral center is determined by the face of the sp^2 center from which the reagent enters.

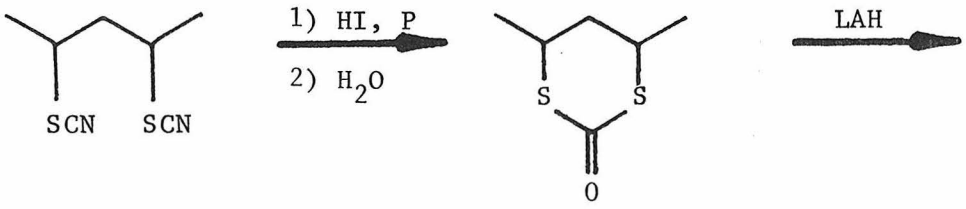
It must be noted that the possibility of significant asymmetric induction will directly depend on the ability of I and II to select between the two faces of a substrate, i.e., the energy difference between the two diasteromeric transition states for each addition. One could presumably enhance the "effective chirality" of these reagents by the use of asymmetric solvents (8) and/or bulkier groups than methyls at the chiral centers of the reagent. In particular the use of a chiral solvent which would presumably be well coordinated to these ionic species might be a very big asset.

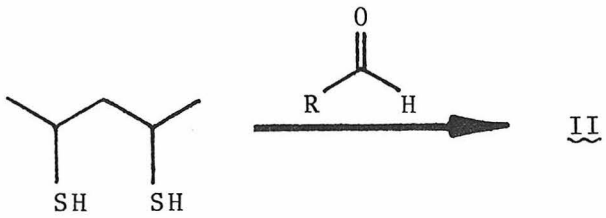
give I as a stable crystalline solid (5). Optically pure II could be prepared by one of two routes. Commercial dl-2,4-pentanediol (III) could be resolved by standard means (6) and then converted by the stereospecific sequence outlined in Scheme I to compound II (7).

Scheme I



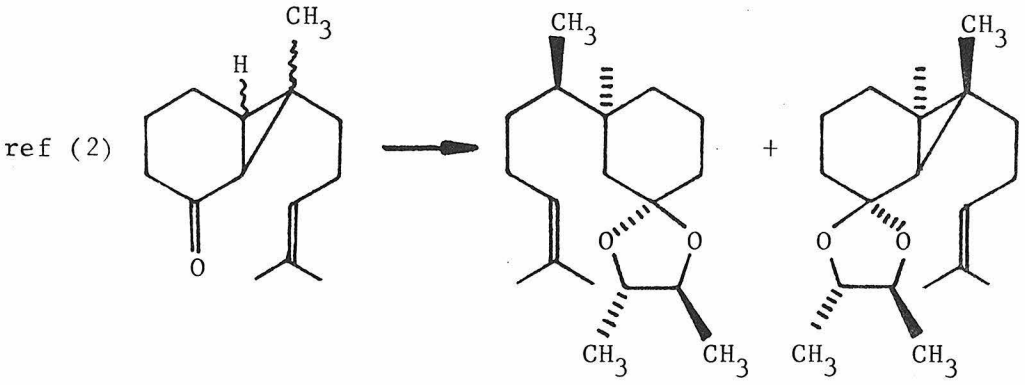
III



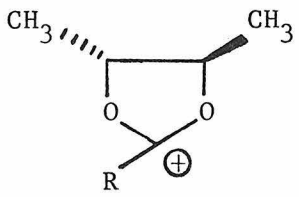


II

IV

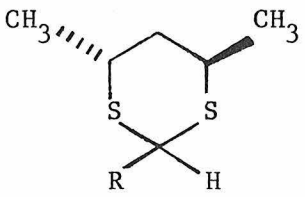


This elegant use of chiral ketals as well as a) the recent development of 1,3-dithianes as carbonyl anion equivalents (3) and b) the stability and ready availability of oxocarbonium ions (4), prompts the following suggestion. Chiral carbonyl equivalents I and II should be synthesized with the hope of using them for: 1) optical induction in the introduction of carbonyls at prochiral centers, 2) possible kinetic resolutions, and 3) simplifying the resolution of otherwise difficult to resolve optically active compounds.



R = H, CH_3, Φ

I

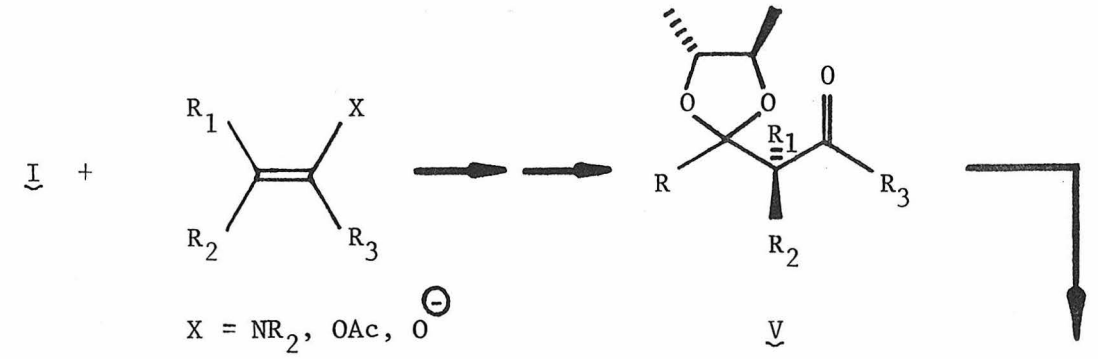


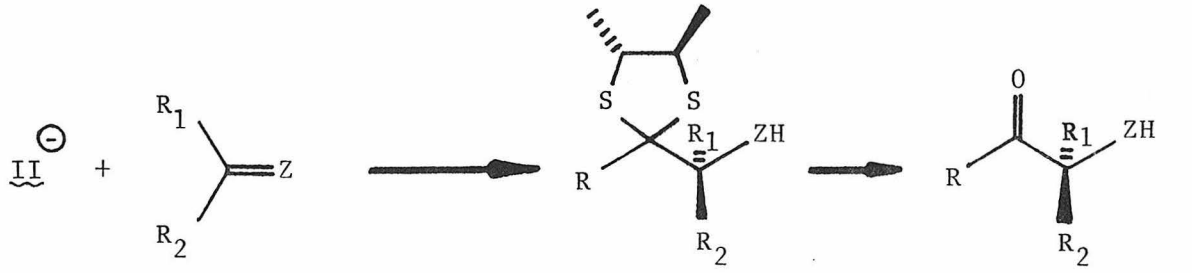
R = H, alkyl, acyl

II

The preparation of racemic I has already been reported (4a) and using commercially available, optically pure 2,3-butane diol should

Scheme II


I +
X = NR2, OAc, O⊖
V
chiral
1,3-diketone
VI


II⊖ +
Y = O, NR
VII
chiral α-hydroxy
or α-amino ketone
VIII

Another interesting aspect of these reagents is that by building in the resolving agent in the course of a synthesis one can sometimes avoid problems. For example, if VI ($R \neq R_1 \neq R_2 \neq R_3$, all alkyl or aryl) were synthesized directly, there would be no readily available means of resolving it since distinguishing between the two carbonyls, chemically, would be at best difficult. Thus, a further advantage in the proposed scheme is that even if the diastereomers of V and/or VII are produced in equal amounts (no optical induction), at least the diastereomers could be physically separated to still give chiral VI and VIII.

There are, of course, many additional applications of these systems. The use of II as a kinetic resolving agent might be possible. This would involve reacting, for example, a d,l mixture of a secondary halide with a deficiency of II in the hope of it reacting with one halide enantiomer faster than the other. It should also be noted that though alcohols are usually readily resolved by recrystallization of diastereomeric derivatives, this approach depends on the ability to obtain crystalline derivatives of the desired alcohols. This often leaves much to be desired with respect to chiral tertiary alcohols. Our system, in particular by the reductive removal of the dithiane from VII with Raney nickel, would be a direct entry to chiral tertiary alkyl and aryl alcohols and amines.

Last but not least, it should be pointed out that deprotection back to the carbony regenerates the initial optical reagent with little or no loss of optical purity (9). Thus one can effectively recover and recycle the chiral reagent.

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3. (a) This chemistry has largely been developed by the research groups of E.J. Corey and D. Seebach. A recent leading reference is: D. Seebach and E.J. Corey, J. Org. Chem., 40, 231 (1975) and references therein; (b) A review of this chemistry: D. Seebach, Synthesis, 17 (1969).

4. (a) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, Ann., 632, pp. 38-55 (1960); (b) H. Meerwein, V. Hederich, H. Morschel, and K. Wunderlich, Ann., 535, pp. 1-21 (1960). (Note: Meerwein was born in 1879 and was 81 and still active at the time this research was published.)

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6. S.H. Wilen, Tables of Resolving Agents and Optical Resolutions, Notre Dame Press, 1972.

7. This proposed sequence is parallel to the reactions used in ref 1.

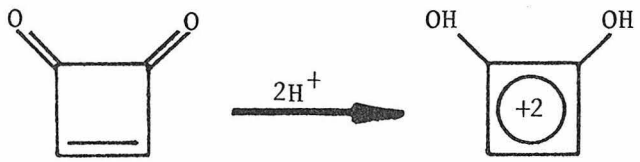
8. Asymmetric solvent used for alkyl lithium reagent: D. Seebach, H. Dorr, B. Bastani, and V. Ehrig, Ang. Chem. Int. Ed., 8, 982 (1969). They make secondary alcohols from aldehydes with 30% induction.

9. (a) Review on mechanism of acetal hydrolysis: E.H. Cordes, Prog. Phys. Org. Chem., 4, pp. 1-44; (b) Reference to mechanism of dithiane removal; D.S. Tarbell and D.P. Harnish, Chem. Rev., 49, 67 (1950); also a discussion in reference 3b, page 33.

The Synthesis and Properties of 6π Electron Cyclic Diketones

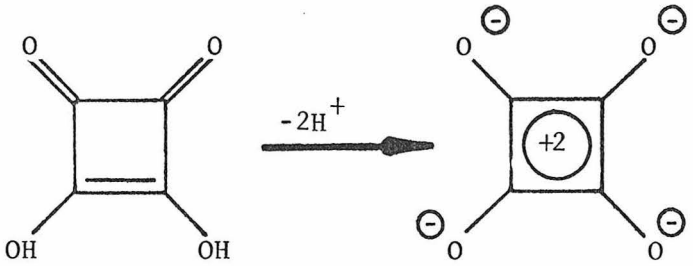
The concept of non-benzenoid aromaticity (1) has stimulated a great deal of research and has led to the construction of a wide range of systems (2). With the understanding that not only neutral $[4n + 2]\pi$ electron species could be aromatic, such stable systems as the cyclopentadienyl anion, cyclopropenyl cation, cycloheptatrienyl cation, and cyclooctatetraenyl dianion have been made and studied. It has been further noted that, particularly in the case of unsaturated cyclic carbonyl compounds, if significant resonance contributors of a molecule have a $[4n + 2]$ conjugated cycle of electrons, even at the expense of charge separation, these forms contribute more than might have otherwise been expected. Thus, cyclopropenone and tropone both have physical and chemical properties suggestive of a good deal of cyclopropenium and cycloheptatrienyl cation character.

This concept was extended by Roberts *et al.* (3) to the dicarbonyl system I, which in its protonated form is best represented by the conjugated 2π electron system II (eq 1). Similarly the relatively high acidity of squaric acid, III (4), is best accounted for by a delocalized structure, IV (eq 2). In recent years there have been many attempts to further extend this concept to the 6π electron analogs of I. However, the isomeric cyclooctatriene diones V and VI have proven to be most elusive. It is only very recently that the first synthesis of the 1,4-diketone V has been reported (5). It is therefore the object of



(eq 1)

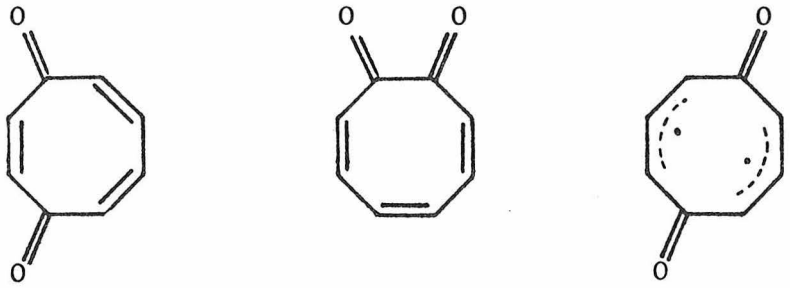
I II



(eq 2)

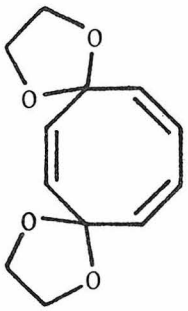
III IV

this proposal to present a number of as yet unexplored routes to all three isomers, V, VI, and VII and to consider their potential physical and chemical properties.

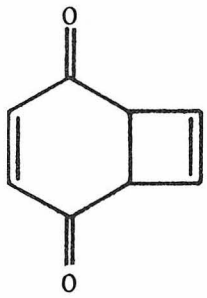


V VI VII

The two precursors to V that came closest without achieving their goal were the compounds VIII (6) and IX (7). The unexpected downfalls of these routes were that VIII could not be deprotected and the pyrolysis of IX resulted in a 50% yield of tropone (7c) (The mechanism of tropone



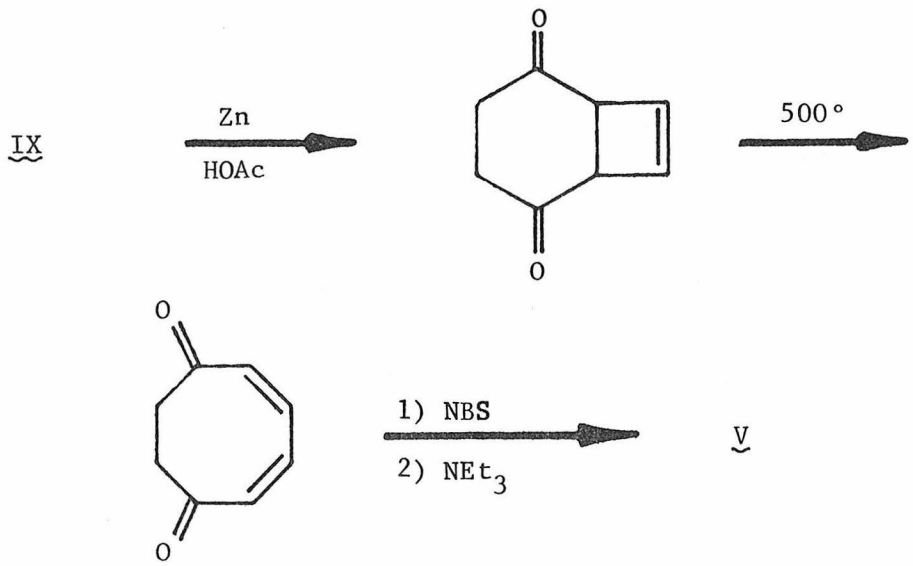
VIII



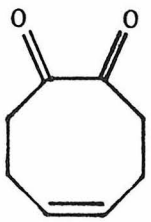
IX

formation is an interesting problem in itself.) Beyond possible speculation on how to successfully convert VIII to V (thioketal protecting group instead?), it is more important to note that Kitahara et al. (5) were able to elegantly salvage a synthesis of V from IX by the route outlined in Scheme I. In total, their approach was eleven steps from

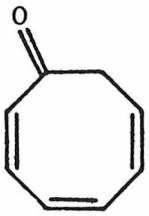
Scheme I



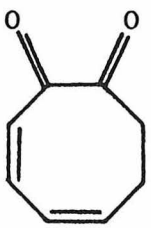
COT in 7% overall yield. Similarly some of the closest, but as yet unsuccessful approaches to VI, have been the preparation of X (8), XI (9), and XII (10). All attempts to introduce the remaining functionality in these systems have been fruitless.



X



XI

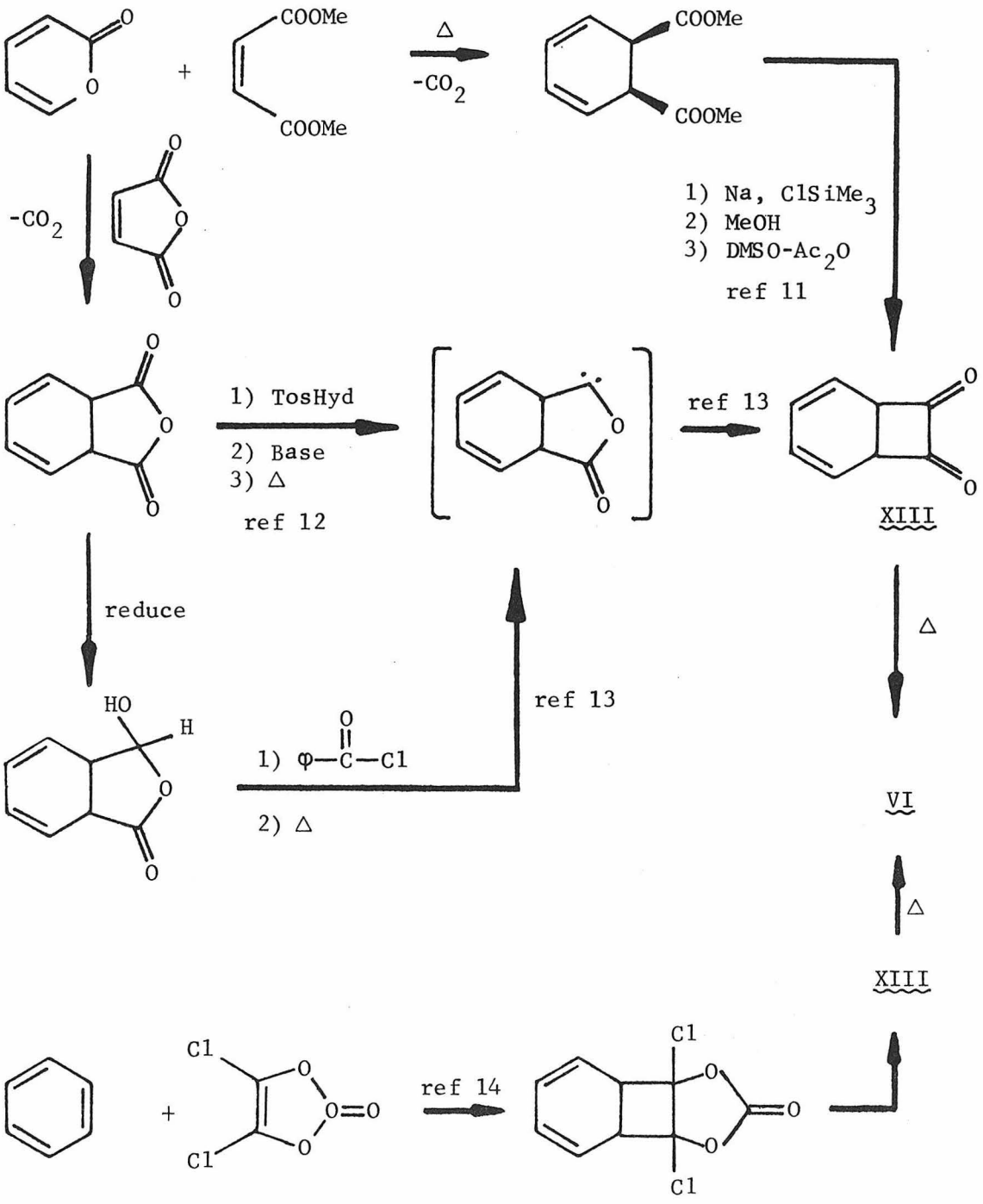


XII

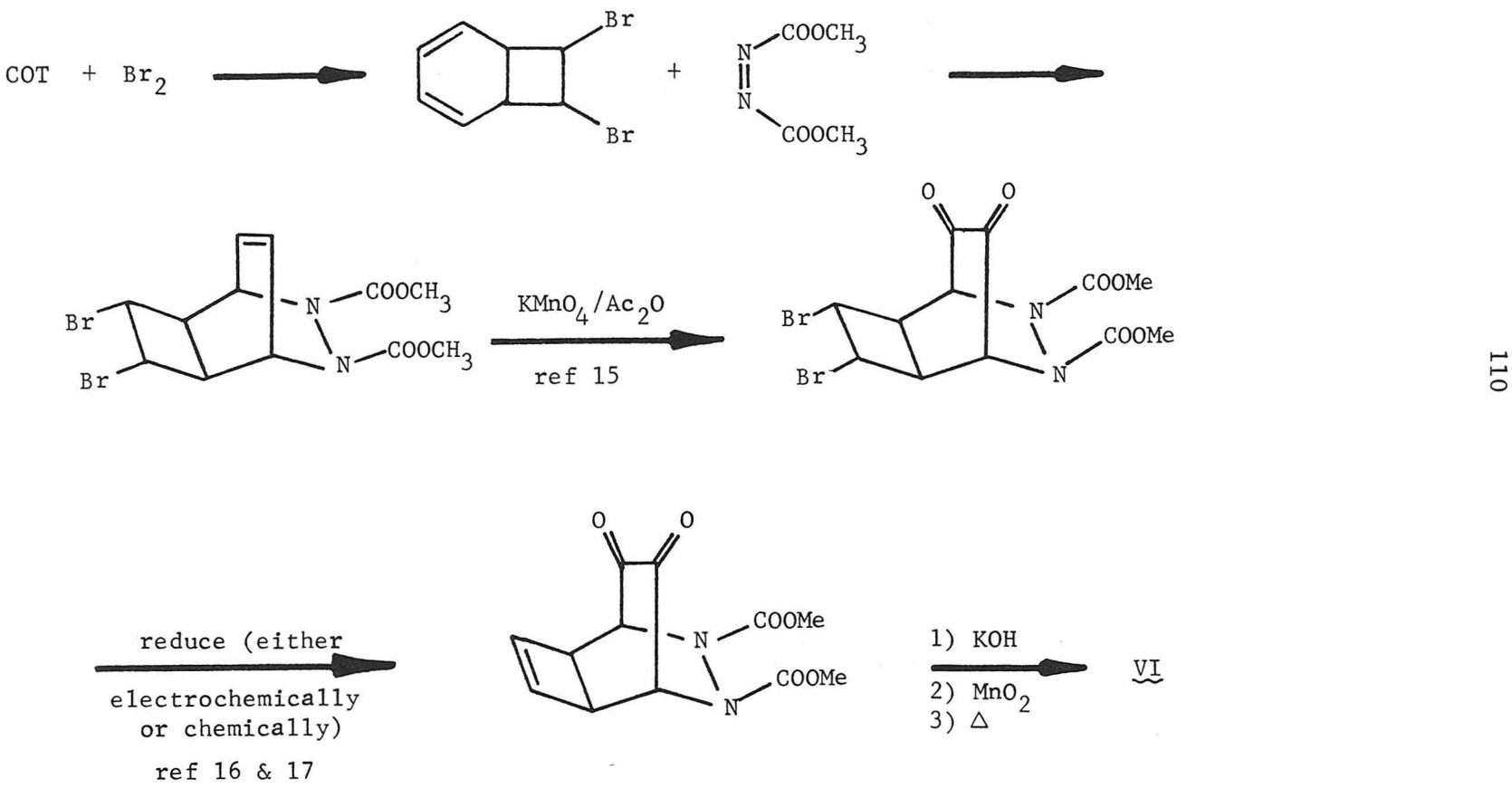
Schemes II and III outline a variety of approaches to VI; Scheme IV indicates an alternate synthesis of V; Scheme V provides a synthesis of VII; and Scheme VI demonstrates a common approach to V and VII by virtue of the symmetry of the eight-membered ring.

With the hope that the above routes would provide a reasonable chance of obtaining V, VI, XIV, and XV, we can now turn to an investigation of their properties. The reported properties of V (5) seem to indicate that V itself shows none of our desired "aromaticity". The question of whether or not its mono- or di-protonated derivatives would resemble the homo-tropylium cation or the cyclooctatetraenyl dication respectively, is still unanswered. Presumably an attempt to isolate these salts and obtain crystal structures (planarity?) would be very much in order. In particular the comparison between V and VI and their comparison to the aromatic behavior of I are of greatest interest. Significant differences between V and VI would be very informative and the comparison of VI to I

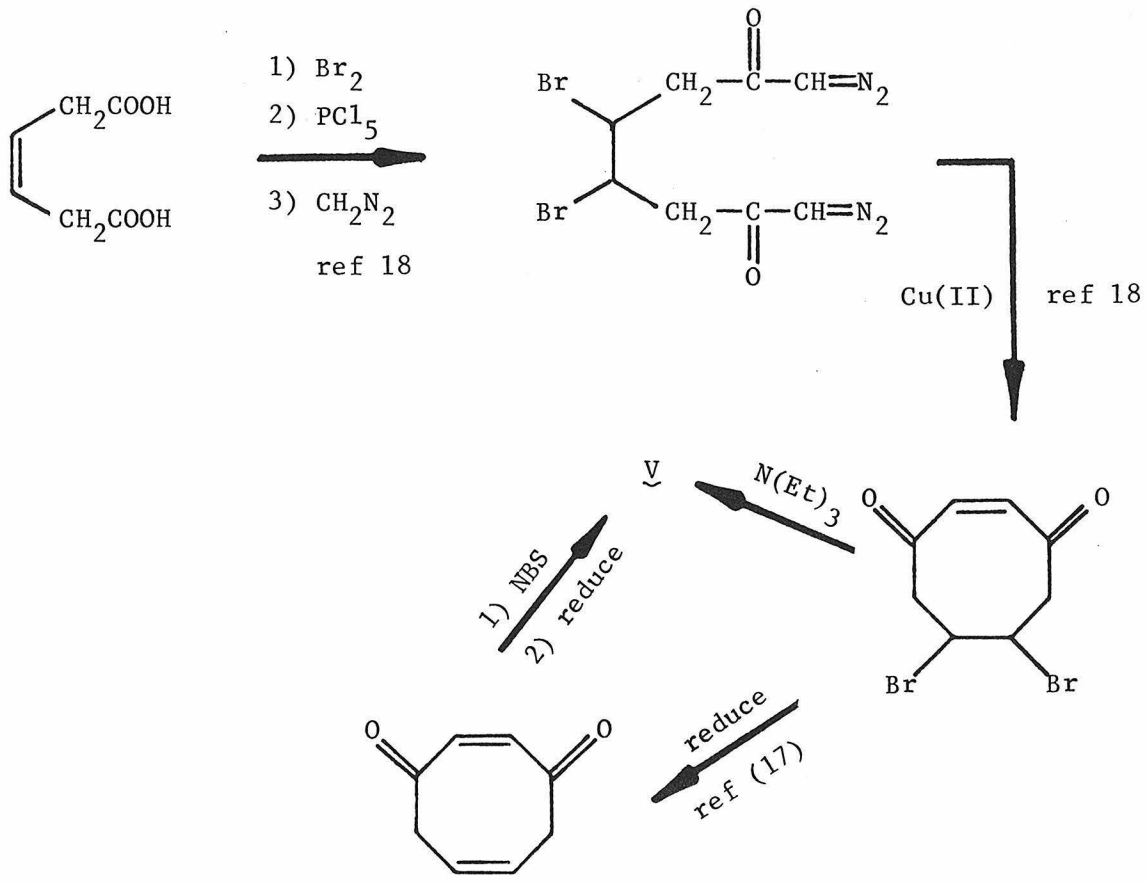
Scheme II


COOMe
COOMe
Δ
-CO2
COOMe
COOMe
1) Na, ClSiMe3
2) MeOH
3) DMSO-Ac2O
ref 11
-CO2
1) TosHyd
2) Base
3) Δ
ref 12
ref 13
XIII
reduce
Δ
HO
H
1) φ—C—Cl
2) Δ
ref 13
VI
Δ
XIII
Cl
Cl
ref 14
Cl
Cl

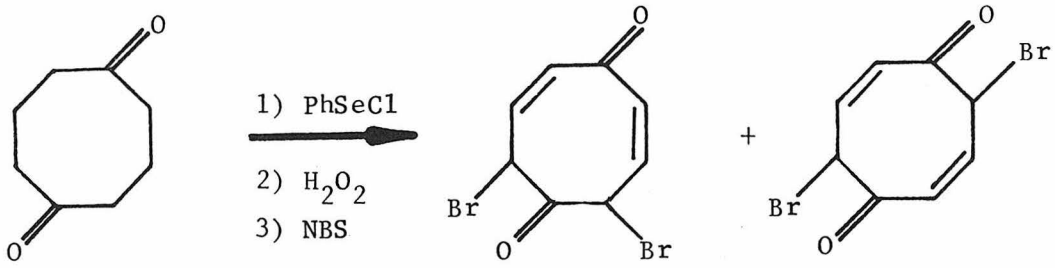
Scheme III


COT + Br_2
Br
Br
+
N
N
$COOCH_3$
$COOCH_3$
Br
Br
N
N
$COOCH_3$
$COOCH_3$
$KMnO_4/Ac_2O$
ref 15
O
O
Br
Br
N
N
COOMe
COOMe
reduce (either
electrochemically
or chemically)
ref 16 & 17
O
O
N
N
COOMe
COOMe
1) KOH
2) MnO_2
3) Δ
VI

Scheme IV

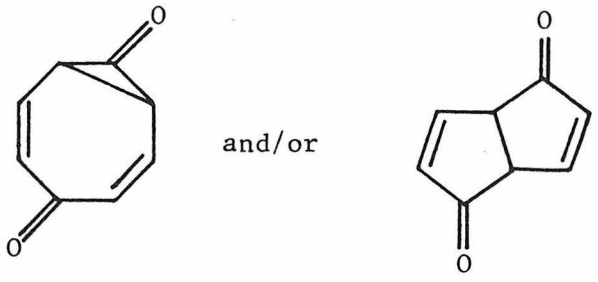

CH2COOH
CH2COOH
1) Br2
2) PCl5
3) CH2N2
ref 18
Br
CH2—C—CH=N2
O
Br
CH2—C—CH=N2
O
Cu(II)
ref 18
V
N(Et)3
1) NBS
2) reduce
O
O
Br
Br
reduce
ref (17)
O
O

Scheme V



ref 19

These compounds could be directly reduced (17) or converted to the pyrazolines and pyrolyzed. They should give:

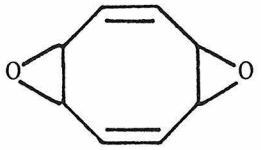


XIV

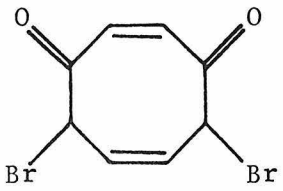
XV

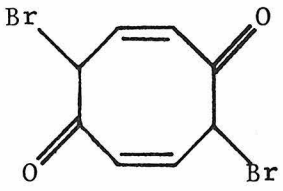
ref 20

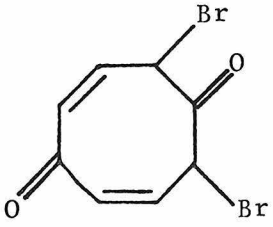
Scheme VI



1) HBr
2) CrO_3







reduction
ref (17)

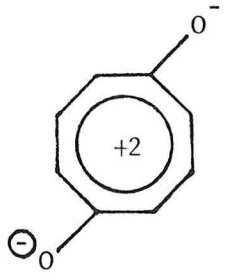
V

As per Scheme V

to give XIV and/or XV

should parallel a comparison between cyclopropenone and tropone. One would want to look for abnormally large dipole moments in V and VI or for significant C-O single bond character in the IR of these compounds. These properties would confirm the presence of the desired charge separated resonance forms. It is also very convenient that compounds like XI and XII are known and can serve as standards for possible non-aromatic behavior of VI.

An NMR study of V and VI and their protonated forms would be desirable but an even more interesting use of NMR would be an investigation of the behavior of VII. In principle compound XIV has three different kinds of protons. A slow warming of XIV in the NMR probe should providence evidence for a very facile degenerate Cope rearrangement by equilibrating all four protons α to the carbonyls. Moreover, continued warming should result in a pronounced downfield shift and in the approach of the remaining signals to each other due to a form best written as XVI. A similar study would be done for compound XV. It is



XVI

most interesting to note that the prediction has been made (21) that VII will exist as a ground state singlet biradical and should be a highly colored species. Thus VII could in fact be the most interesting

species among the above valence isomers.

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Micellar Effects on Sulfate Ester Hydrolysis

Due to their importance in a wide variety of biological systems, sulfate and phosphate esters have received a great deal of attention from both biologists and chemists (1). Since 1) the mechanisms of these hydrolyses have been studied in some detail (2), and 2) since they occur in water under relatively mild conditions, they have also been the subject of many studies centered on the ability of micelles to catalyze these processes. It is, however, distressing to note that particularly for sulfate esters, all of the studies to date have concentrated on the effects of micelles on the gross kinetics of these processes at a variety of pH's and are sorely lacking in a unified explanation of their results. This lack of detailed mechanistic understanding of these catalytic systems leads to the following proposal. The effects of micelles on the decomposition of mono-alkyl sulfates should be probed by use of optical and isotopic labels. Evidence is presented which suggests that such experiments may uncover a system in which a micellar medium may dictate the choice among competitive sites for a bimolecular attack and competitive sites for unimolecular bond cleavage.

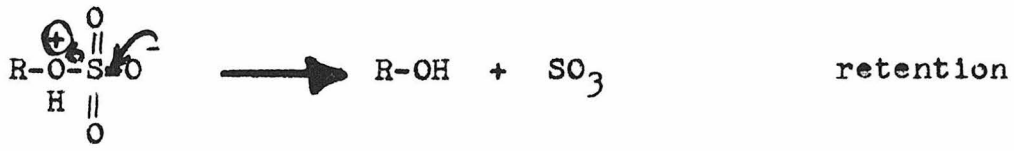
The general mechanism for hydrolysis of mono-alkyl sulfates can best be thought of as a competition between C-O and S-O bond cleavage (1a)(3,4). Each of these processes can

result from either a unimolecular or bimolecular process, which in turn can be either acid or base catalyzed. A summary of the possible competing pathways in acid medium is indicated in Scheme I. Similarly, in Scheme II the possibilities for neutral and basic medium are outlined. Each process is also identified as to its stereochemical result. For simplicity's sake decomposition leading to olefin formation (observed as a minor process) is not considered.

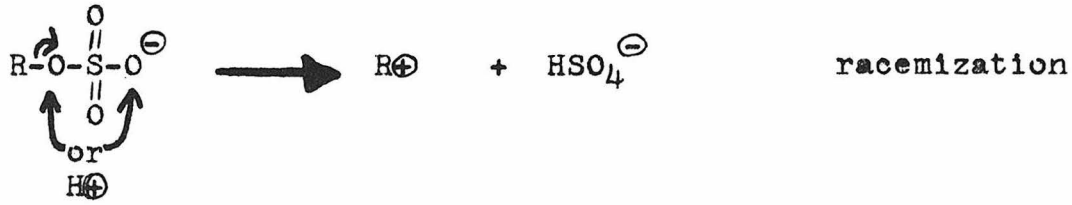
It should be noted that in both cases reactions 1 and 4 could be distinguished from 2 and 3 by the appropriate O^{18} label. Moreover, such a study in combination with a good kinetic and stereochemical analysis could easily disect each contributing pathway. Fortunately, this analysis has largely been done. Burwell and coworkers (4) have looked in some detail at systems where R is secondary and found the following. The basic hydrolysis of secondary mono-alkyl sulfates proceeds 87%-96% by bimolecular C-O bond cleavage (reaction #3). This conclusion is based on second order kinetics and on almost complete inversion of configuration in the hydrolysis. On the other hand, the situation under conditions of acid catalyzed hydrolysis is very different. The reaction stereochemistry is sensitive to both the identity and the concentration of acid used and varies between 10% and 70% net <u>retention</u> of configuration. This indicates that a) reactions 1 and 4 could account for as much as 85% of the total reaction path-

Scheme I

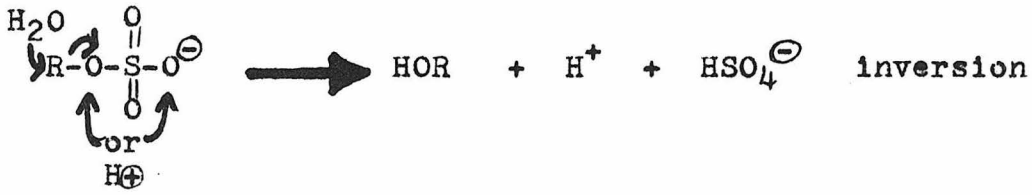
#1) unimolecular, S-O cleavage:



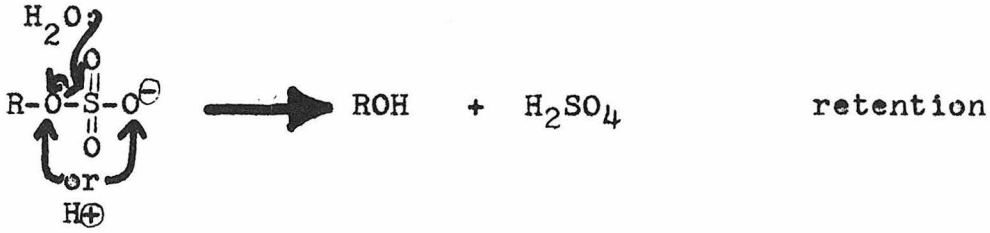
#2) unimolecular, C-O cleavage:



#3) bimolecular, C-O cleavage:

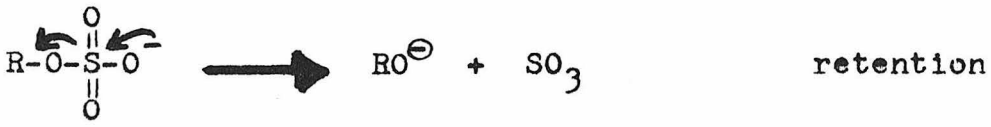


#4) bimolecular, S-O cleavage:



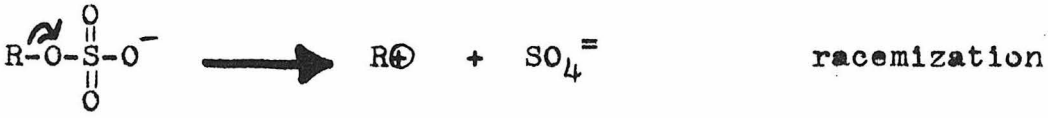
Scheme II

#1) unimolecular, S-O cleavage:



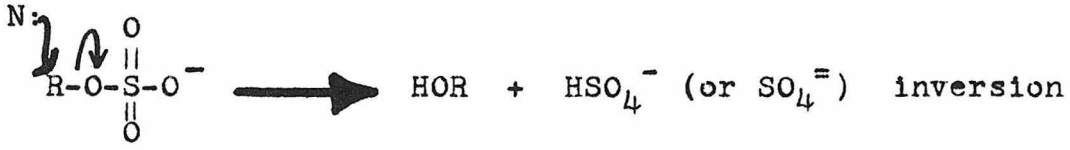
retention

#2) unimolecular, C-O cleavage:



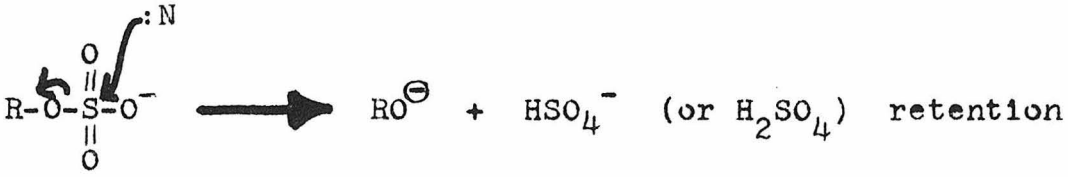
racemization

#3) bimolecular, C-O cleavage:



inversion

#4) bimolecular, S-O cleavage:



retention

where N=OH^- or H_2O

way, and b) it is quite possible that under these conditions all four pathways are now effectively competing. This pronounced mechanistic change with change in pH clearly indicates that mono-alkyl sulfate hydrolysis is a very delicately balanced combination of reaction pathways.

Most of the work done on micellar effects on sulfate hydrolysis has been done on the mono-aryl system (5). The kinetic effects observed are generally small (anywhere from 10% to a factor of 6) and their variation with the nature of the surfactant used is at best erratic (5,6). While the authors do not acknowledge it, it seems reasonable that since the predominant mechanism for aryl sulfate hydrolysis is just a mixture of bimolecular and unimolecular S-O bond cleavage (analogous to reactions #1 and #4), the ability of the micelle to perturb this system will be small. Consistant with this, the only really significant effect on the overall rate of the sulfate hydrolysis is in the alkyl systems. Studies done in this area (7) indicate that anionic micelles greatly (30x to 50x) enhance the rate of acid hydrolysis, and retard the rate of basic hydrolysis. These results are then rationalized on an electrostatic basis. The net negative charge of the anionic micelle increases the effective H^+ concentration and thus further catalyzes the reaction. Conversely, this anionic charge repels OH^- and retards the base catalyzed process (7a).

It is most distressing to note that despite the known diversity of mono-alkyl sulfate mechanism, the above micellar studies have been limited to a simple rate study of primary substrates. Even within these kinetic studies there are a few systems that should be looked at. As per the above electostatic explanation one would expect that cationic micelles should enhance the basic hydrolysis and retard the acid catalyzed hydrolysis of these esters. Suprisingly, this was <u>not</u> the case for the aryl sulfates (5,6), and thus the simple kinetic study in the alkyl cases should be extended to cationic and even non-ionic micelles to test this prediction.

More importantly, however, since we know that the acid catalyzed hydrolysis has been shown to be a balance of a variety of pathways, these simple rate studies do not tell us the whole story. Does the anionic micelle enhancement of acid catalyzed hydrolysis result in a preferential enhancement of any one of our four hydrolytic pathways? Can the micelle change the ratio of unimolecular to bimolecular processes or the ratio of S-O to C-O bond cleavage? It would seem from results of micellar effects on the aminolysis of aryl sulfates (6) that this interesting perturbation may be possible (8).

Thus it seems that the most interesting experiments to be done in these areas are the following. Using a substrate like optically active 2 decyl sulfate (9) a study of both the degree of O^{18} incorporation (reaction run in H_2O^{18}) and of

the stereochemistry of the alcohol produced as a function of micellar medium would be most informative. Moreover, the use of an optically active tertiary substrate (e.g. 3 methyl 3 undecanol) would introduce a component due to reaction #2 in the above schemes (10), and thus probably be an even more sensitively balanced substrate. The ability to identify clearly those processes that the micelle affects most significantly, would greatly increase our understanding of both the physical and chemical properties of the Stern layer and aid in the design of future research.

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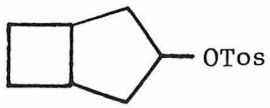
8. See discussion of reference 6 in the introduction to part II of this thesis.

9. a) The resolution of long chain secondary alcohols by standard means is well precedented. This alcohol was chosen as an example because it has a long enough hydrophobic chain to micellize but it is not crystalline either as the optically pure species or the racemate. (This avoids problems of fractionation during product isolation.) b) The preparation of alkyl sulfates (with no loss in optical purity from the alcohol) is readily achieved by the procedure of Dreger et al, Ind. and Eng. Chem., 36, 610 (1944). See part II of this thesis.

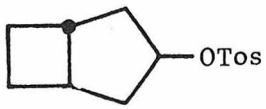
10. Based on the precedent of "normal" S_N1 and S_N2 processes for alkyl system, one would expect to see no free carbonium ion in either primary or secondary systems. However, this S_N1 process is competitive for tertiary substrates.

Trans-Fused Bicyclic Systems

Since the discovery of remote sigma bond participation in a solvolysis reaction by Winstein and coworkers (1), chemists have looked for ways of testing the limits of that phenomenon. This resulted in many attempts to design systems with strategically placed cyclopropane and cyclobutane rings (2). One interesting probe of the mode of sigma bond participation resulted from the attempted comparison of cis-fused to trans-fused bicyclic systems, in terms of their relative efficiency of sigma bond delocalization. One such study was designed by Meinwald et al (3) in which they compared the cis-fused and trans-fused [3:2:0] systems I and II. Another such study was conducted by Gassman et al (4) on the bicyclo [5:1:0] system (cis=III, trans=IV).



I



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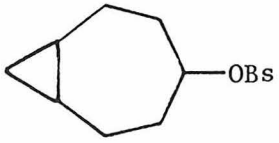
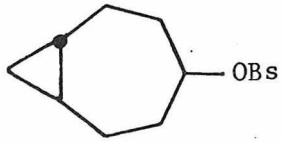


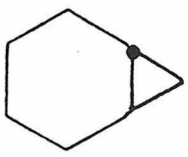
III



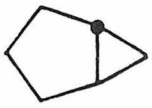
IV

The results of these studies seemed to show that the trans-fused rings couldn't participate very well, and in fact relative rate retardations were observed. However, since even the cis-fused cases of these systems do not show much sigma participation, it was not clear that these were the ideal systems for such an investigation.

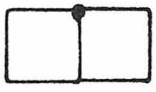
At the time that these ring systems were made it was noted that they were the smallest trans-fused cyclobutane and cycloprane systems known(5). It was observed (5c) however, that the remarkable thermal stability of the ring system IV (parent $<70\%$ rearranged in 40 hrs at 280°) seemed to bode well for chances of making even smaller fused homologs. Since these smaller homologs would further test the limits of strain incorporation in organic systems and since they might provide truly informative solvolysis substrates, it is most surprising that they still have not been made. It is therefore proposed that some of the same techniques that have been recently applied to strained unsaturated systems (i.e. trans cyclo-olefins and cycloalkynes) be applied to the synthesis of V, VI, and VII.



V



VI

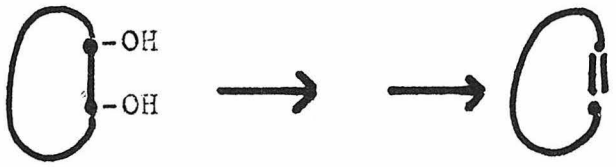


VII

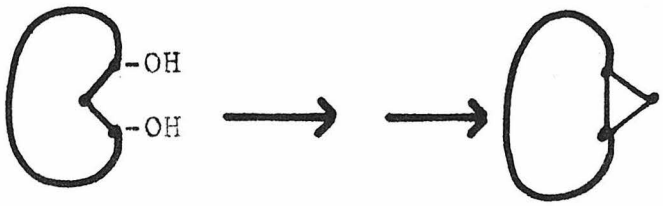
Generally, the proposed approach is based on the methods used successfully to convert 1,2 diols, stereospecifically to cis or trans-olefins. However, in our systems, instead of the new bond being a π bond it would be a sigma bond. Conceptually, this is illustrated in Scheme I. It is worth some notice

Scheme I

known



proposed

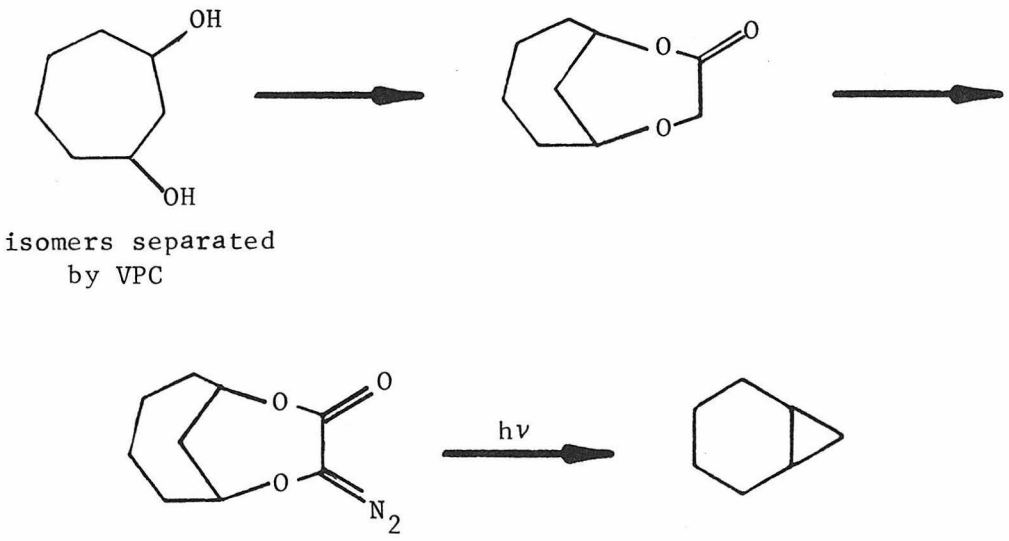


that our necessary precursors in this approach are also readily synthesized (e.g. aldol followed by reduction) and the isomers of these cyclic compounds (cis 1,3 diol vs. trans 1,3 diol) can be easily separated by VPC.

As to possible ways to convert the diols to cyclopropanes, a number of systems come to mind. Corey's thiocarbonate (6a) or trithiocarbonate (6b) might be one possibility, but in order to facilitate preparation of the more unstable compounds one might prefer an approach developed by Chapman et al (7)

for generation of trans cyclo-olefins in a low temperature matrix. It is applied in Scheme II to a possible synthesis of V. It should be noted that the ring contraction to a ketene

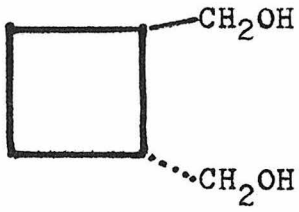
Scheme II



intermediate is well precedented and that photolysis of the ketene then yields the di-oxo-carbene. This species loses CO_2 in an allowed 6π electron thermal process to give stereospecific cyclopropane formation. Thus the original diol stereochemistry should dictate the fusion stereochemistry.

It should be noted in passing that optically active trans diol would give optically active fused cyclopropane. It should also be noted that this approach could develop into a useful general approach to cyclopropanes being stereo-

specifically made from diols of known stereochemistry. One last note on these synthetic approaches. While the precursors for V and VI are obvious, it seems ill-advised to try to make VII by closure of the trans 1,4 diol; the diol VIII would probably be a better precursor.



VIII

The physical properties of these compounds prompt the following speculation. Will V be isolable as predicted (5c)? Which will be more stable, VI or VII (note they are isomeric)? As to their chemical reactions, it would be most exciting if derivatives of VI, in particular, would be stable enough to be solvolyzed, since the cis-fused [3:1:0] system is the classic representative of cyclopropyl sigma participation (tris-homo-cyclopropenyl (8)). This would make an interesting contrast and be genuinely informative as to the question of the orientation of the cyclopropyl orbital needed for sigma participation (4). It would further be interesting to see if an appropriate derivative of VII (at any non-bridgehead position since all four outside positions are equivalent), would behave like a normal cyclobutyl system and enter into

the cyclopropyl-carbinyl manifold, or whether the trans-fusion would change the inherent reactivity of the cyclo-butyl ring.

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The Syntheses and Properties of Interesting Small Ring Hetrocyclic Compounds

Since the first synthesis of a bicyclobutane derivative in 1959 (1), much serious interest has been expressed in the properties of strained polycyclic compounds. A variety of these small ring hydrocarbons have been actively sought and a few have, to date, still defied all synthetic approaches. Even conceptually simple extension of this work to bridged bicyclics has met with varied success. Thus, while the "zero carbon" bridged species, tetrahedrane is yet to be made, shortly after Wiberg's initial work (2) both Masamune (3) and Doering (4) reported the synthesis of the one carbon bridged bicyclobutane (eq 1). Since then a

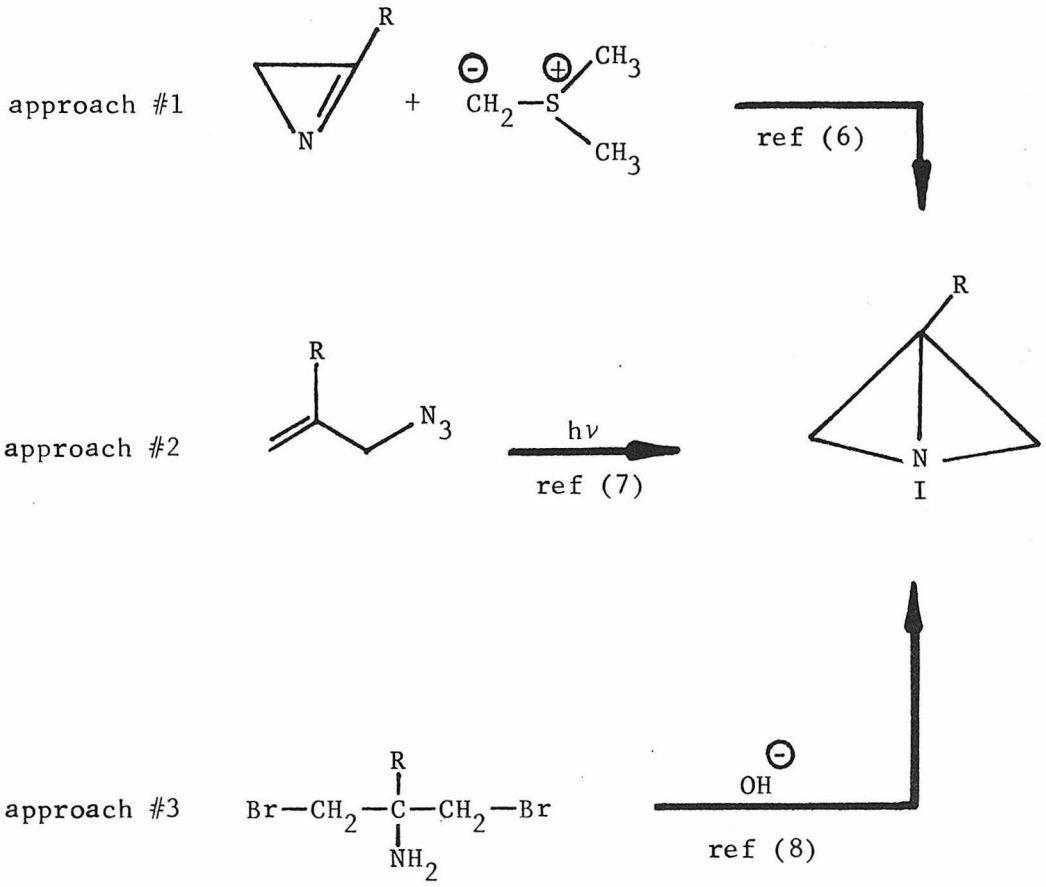
(eq 1)

R = Φ, CH_3

variety of strained polycyclic hydrocarbons have been made and studied (5).

Between 1967 and 1969 three successful approaches to the synthesis of azabicyclobutane appeared. They are summarized in Scheme I. Interestingly, however, there have to date appeared in the literature no examples of bridged azabicyclic systems. Furthermore, of the wide

Scheme I

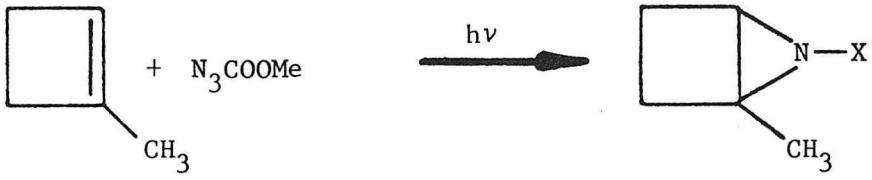


R = φ, CH_3, Et, H

variety of small ring heterocycles possible, many of the most interesting examples have yet to be reported. This is particularly disappointing since the presence of a single heteroatom in a molecule's skeleton can provide a variety of probes into the nature of the molecule that would be otherwise (in the carbocyclic cases) unavailable. Therefore an initial discussion of possible syntheses of some of these systems seem in order.

While the [1:1:0]-1-azabicyclobutane (I) is known, its one carbon bridged derivative is not. Three general routes to this compound (II) are outlined in Scheme II.

Another interesting azabicyclic system is the [2:1:0] system III (10). While IIIa is known (eq 2) (10a), the parent IIIb is as yet unreported. Two possible solutions to this can be suggested. The electrochemical



(eq 2)

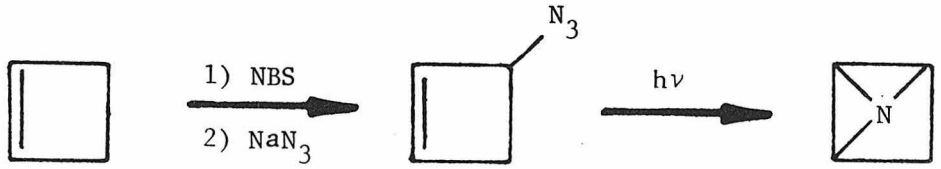
IIIa, X = COOMe

b, X = H

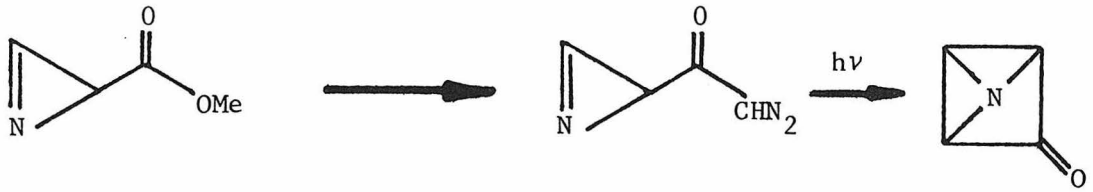
reduction of IIIa to IIIb at controlled potential should be attempted. The use of pyrrole in the Diels-Alder approach to II would result in IIIb directly.

The [2:1:0] system that is isomeric to III, that is the system with

Scheme II

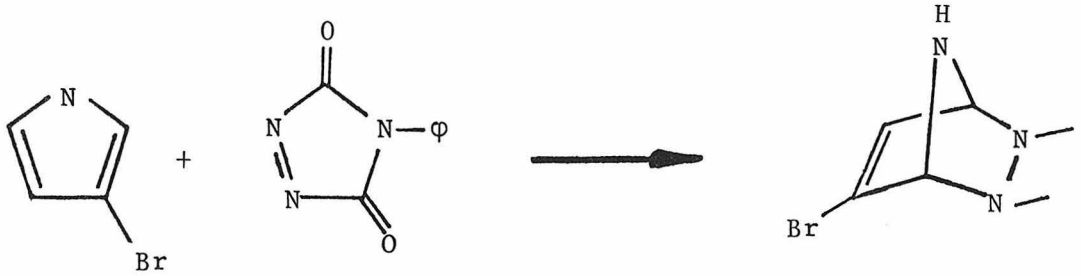


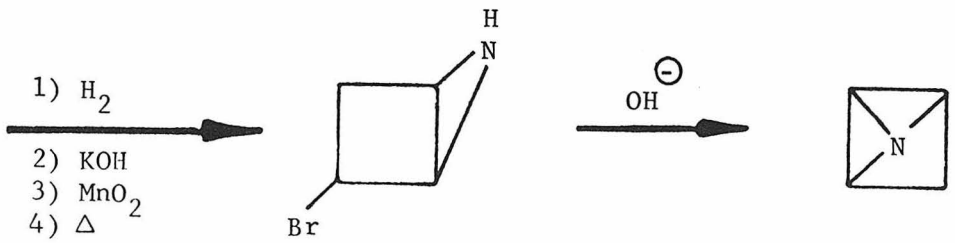
II



ref (9)

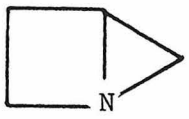
IIa



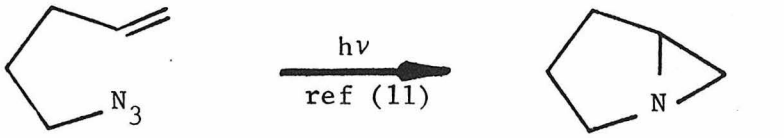


II

the nitrogen at the bridgedhead IV, should be readily attainable in either of two ways, analogous to the known preps of the [3:1:0] V (eqs 3 and 4). Particularly the combined analogy of (eq 3) and the

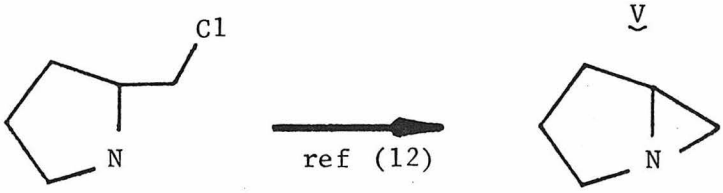


IV



(eq 3)

V

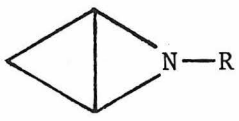


(eq 4)

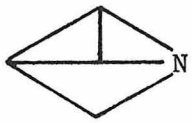
V

photochemical approach to I (7) leave little doubt that the nitrene approach to IV should work.

The last systems for present speculation are VI and VII, analogs of I and II. In particular, interest in VI is high because of its obvious



VI

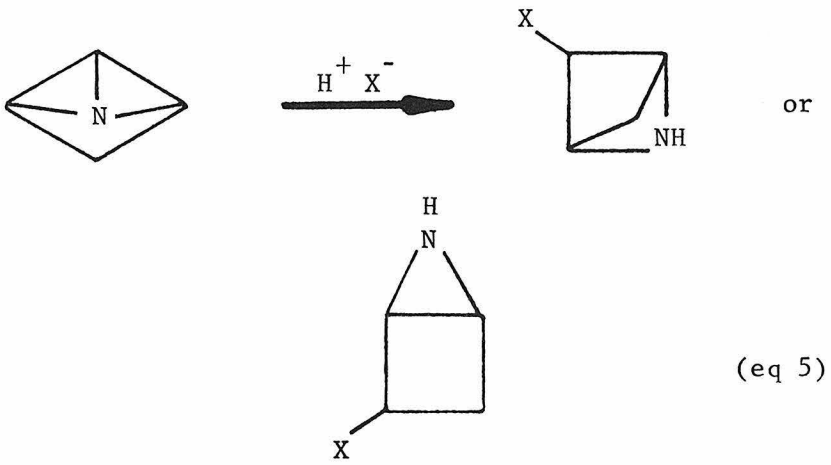


VII

analogy to the theoretically interesting 1H-azirene (13) (4π electron).

Possible approaches to these molecules could be as follows. By analogy to (eq 2) above, the addition of a nitrene to cyclopropene should result in VI; and the use of a cyclopropene in a photochemical syntheses analogous to ref (7) should result in VII.

A comparison of the properties of I-VII presents a number of interesting possibilities. The recent availability of natural abundance N^{15} NMR (14) and the elegant use of both carbon and hydrogen NMR data to develop models for the bonding in strained carbocyclics (15), makes I-VII interesting substrates for NMR study. Since it is well known that amine basicity can vary greatly as the hybridization of the nitrogen changes (16), a measure of the pK values of these compounds would be of great interest. There are also a variety of chemical studies that would be of interest. For example, besides comparing the reactivities of I-III one might ask questions like: would the protonation of II lead to VIII (a relatively unhappy [1:1:1] system) or to a derivative of III (eq 5)?



(eq 5)

Possibly the most interesting possibility that is made available by the above systems is the potential conversion of II to IX, the hetero

IIa, X = O
b, X = Br
c, X = OH

IX

analogue to the much studied (17) $C_5H_5^{\oplus}$ species. Synthesis of IX could possibly be achieved by modification of each of the three routes to II. One approach might be to make IIb by the use of 2-azido, 3-bromo cyclobutene (in approach #1 of Scheme II) or 3,4-dibromopyrrole (in approach #3 of Scheme II). Alternatively reduction of IIa would give IIc. Treatment of IIb with SbF_5, or of IIc with magic acid, should result in IX. One might also want to try simple abstraction of a hydride from the parent II.

The study of the properties of IX by low temperature NMR, in particular, should be most revealing. The primary question of whether it closes up to the truly pyrammidal system or instead prefers to exist in a less symmetric form should be readily answered by these experiments and should be most interesting.

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