The Synthesis and Solvolytic Investigations of 2-Hexanone-5-(p-N-methylpyridinium) ether and n-Hexyl-p-carboxybenzenesulfonate

Thesis by

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To my loving wife Judy,

a truly beautiful person.

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I wish to thank Professor Robert Bergman for the guidance and encouragement he has given me during the course of this work.

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My deepest love and thanks go to my wife Judy, who most certainly deserves a large share of this degree in return for her love, patience, and support.

ABSTRACT

The synthesis and purification of 2-hexanone-5-(p-N-methyl-pyridinium) ether was accomplished. The reaction of this compound with aqueous NaOH failed to produce the desired products, cis- and trans-2-methylcyclopropylmethyl ketone. It appears that the desired anionic ring closure of the starting material did not take place, but instead, a simple displacement reaction occurred to produce 5-hydroxyhexan-2-one.

In a second project, the synthesis of n-hexyl-p-carboxybenzene-sulfonate was attempted by two different routes. The first route involved esterification of p-carboxybenzenesulfonyl chloride and n-hexanol to form the desired sulfonate. This method proved unsuccessful, and was abandoned. The second route involved oxidation of n-hexyl-p-toluenesulfonate to the carboxy compound. This method was successful, producing n-hexyl-p-carboxybenzenesulfonate in about 7% yield. This molecule was found to have an approximate half-life of 14 hours when reacted with 1 N aqueous NaOD at room temperature.

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GENERAL INTRODUCTION

The formation of high molecular weight aggregates in aqueous solution by surface active molecules (surfactants) possessing distinct regions of hydrophobic and hydrophilic character is known as micellization.[1] Micellization occurs only when the concentration of the surfactant molecules exceeds a characteristic value known as the critical micelle concentration (CMC). At concentrations lower than the CMC, the surfactant molecules exist primarily in monomeric form. In forming micelles, typically 10 to 100 surfactant monomers are arranged in such a manner as to allow their hydrophobic portions, which generally consist of long hydrocarbon chains, to bury themselves in the interior of the micelle. At the same time, the hydrophilic regions, which are normally polar functional groups, become exposed to the aqueous environment on the exterior of the micelle. These polar functional groups may either be neutral in the case of non-ionic micelles, or may bear a charge in the case of ionic micelles. Thus, the surface of the micelle consists of a highly polar shell, known as the Stern layer, which is a region of higher charge density than the aqueous solvent.

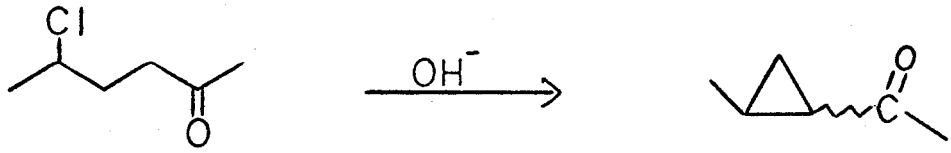
Much interest has been shown in the kinetics and mechanisms of organic reactions occurring in the presence of aqueous micelles. A number of investigators have reported significant rate enhancements or inhibitions exhibited by micelles on organic reactions.[1] However, few instances have been reported in which micelles have influenced the mechanism of a reaction or changed the nature (e.g., stereochemistry or product ratios) of the products.[2] It therefore seems worthwhile to attempt to devise a system which could exhibit a micellar effect on the nature of the reaction products. In devising such a system, one must keep in mind the fact that most organic reactions in micellar systems are known to take place at or near the Stern layer.[1,3] So it seems logical that a reaction involving a charged intermediate, such as a carbonium ion, a carbanion, or other charged species, would stand the best chance of exhibiting a micellar effect on the products.

The projects reported herein have involved the synthesis and investigations of molecules which would react in an aqueous environment, proceed via a familiar mechanism, preferably through a charged intermediate, and thus, possibly allow us to observe some micellar effects on the nature of the reaction products.

Chapter I: Synthesis and Investigation of the Solvolysis of 2-hexanone-5-(p-N-methylpyridinium) ether

INTRODUCTION

The aqueous sodium hydroxide induced ring closure of 5-chlorohexan-2-one (1) to 2-methylcyclopropylmethyl ketone (2) was investigated by Bergman and Napierski,[4] in hopes of observing a



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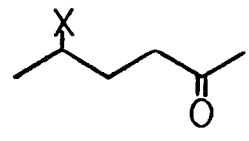
micellar effect on the cis/trans product ratio. The reaction was run in the presence of cationic hexadecyltrimethylammonium bromide (CTAB), in the presence of sodium lauryl sulfate (NaLS), and in the absence of micelles. No micellar effect was observed on either the product ratio or the rate, and they concluded that 1 was not sufficiently bound to the micelle. After investigating a series of molecules (3) with different leaving groups x, it was concluded that 2-hexanone-5-



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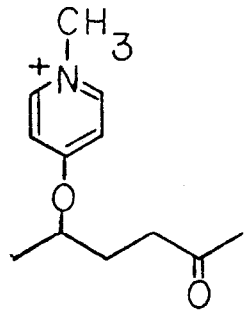

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(p-N-methylpyridinium) ether (4) had a good chance of meeting all the necessary criteria of the desired molecule, i.e., it should be sufficiently stable to work with, water soluble, and able to undergo ring closure via an anionic intermediate. Thus, this project involved the preparation and purification of 2-hexanone-5-(p-N-methylpyridinium) ether and the investigation of the ability of this compound to undergo anionic ring closure. The ultimate goal was to study the micellar effects, if any, exhibited by various surfactant systems upon the product ratio obtained from the ring closure reaction.

EXPERIMENTAL

General

All NMR spectra were recorded on Varian A-60A and T-60 model spectrometers, at normal probe temperature. NMR data is reported in this form: NMR (solvent) chemical shift in units δ ppm downfield from TMS internal standard (multiplicity, number of protons), etc. A Perkin-Elmer 257 Grating Infrared Spectrometer was used to record all infrared spectra. For gas chromatographic analysis, a Hewlett-Packard 5750 Research Chromatograph was used.

Preparation of 2-hexanol-5-(4-pyridine) ether (5)

The procedure of Bergman and Napierski[4] was modified as follows: A mixture of 4.72 g of 2, 5-hexanediol (Aldrich) in 12 ml of freshly distilled (from CaH_2) DMSO was stirred under an N_2 atmosphere. To this solution was added 1.68 g of a 57% dispersion of NaH in mineral oil (Alfa), and the mixture allowed to stir under N_2 for 1.5 hours. An additional 4 ml of DMSO was added along with 1.1 g of freshly prepared 4-chloropyridine. (The 4-chloropyridine was prepared by dissolving 2 g of 4-chloropyridine hydrochloride in 20 ml of H_2O, and adding dilute NaOH until basic. The aqueous solution was extracted withisopentane, the organic extract dried over Na_2SO_4, and

the isopentane removed on a rotovap to produce 4-chloropyridine in about 90% yield.[4]) The mixture was allowed to stir under N_2 for about 16 hours. The dark brown reaction mixture was suction filtered, and the brown precipitate was washed with 100 ml of hot benzene. The combined benzene-DMSO filtrate was extracted with two 30 ml portions of 2% NaOH solution and one 30 ml portion of H_2O. The combined aqueous extracts were extracted with three 30 ml portions of ether. The ether extracts were combined with the benzene-DMSO solution and extracted with three 35 ml portions of 10% HCl. This acidic aqueous extract was then neutralized with sodium bicarbonate, made basic with 2% NaOH solution, and extracted with three 33 ml portions of ether. The ether extract was dried over Na_2SO_4, filtered, and the ether removed on a rotovap, leaving 1.3 g of a yellow oil (65% crude yield). The crude product was purified on a 10-inch Silica-gel column, using an ether to 60% MeOH/ether solvent gradient. This produced 400 mg of 5. NMR ($CDCl_3$) 8.46(d, 2), 6.83(d, 2), 4.55(m, 1), 3.84(m, 1), 1.68 (m, 5), 1.32(d, 3), 1.20(d, 2).

Preparation of 2-hexanone-5-(4-pyridine) ether (6)

The modified procedure of Bergman and Napierski[4] was used for the preparation of (6): A solution of 1 g CrO_3 in 1 ml of H_2O was added dropwise, with stirring, to 12 ml of pyridine cooled in an ice

bath. To this solution was added dropwise a mixture of 400 mg of 5 dissolved in 3 ml of pyridine. This mixture was allowed to stir for one hour while warming to room temperature. The flask was stoppered and allowed to sit at room temperature for about 30 hours. The dark brown reaction mixture was poured into twice its volume of H_2O and filtered through a Celite pad. The filtrate was extracted with four 25 ml portions of ether, and the ether extract dried over Na_2SO_4. The ether was removed on a rotovap, and the pyridine removed by pumping on the solution with a vacuum pump for 1/2 hour, leaving 145 mg of a pink oil (37% yield). The NMR spectrum was consistent with the structure of 6. NMR ($CDCl_3$) 8.38(d, 2), 6.78(d, 2), 4.54(m, 1), 2.58(t, 2), 2.13(s, 3), 2.00(t, 2), 1.32(d, 3).

Preparation of 2-hexanone-5-(p-N-methylpyridinium) ether (4)

The modified procedure of Bergman and Napierski [4] was again used for preparing (4): A solution of 145 mg of 6 in 10 ml of CH_2Cl_2 was dried for 5 hours over Na_2SO_4. The solution was filtered and cooled to -78°. To this cooled solution under N_2 was added a solution of 0.1 ml of methyl trifluoromethanesulfonate (methyl triflate, Cationics, Inc.) in 2 ml of CH_2Cl_2 (also at -78°) in small portions. The mixture was kept at -78° for 15 minutes and allowed to warm up to room temperature for 10 minutes. Removal of the CH_2Cl_2 by

rotovap produced 90 mg (34% yield) of a brown oil (4). NMR ($CDCl_3$) 8.55(d, 2), 7.34(d, 2), 4.83(m, 1), 4.22(s, 3), 2.59(t, 2), 2.11(s, 3), 2.03(t, 2), 1.38(d, 3). IR (CCl_4 on NaCl plates) 3065, 1713, 1652, 1525, 1324, 1270, 1229, 1168, 1035, 795, 765 cm^{-1}.

Preparation of 2-methylcyclopropylmethyl ketone (2)

In order to characterize the desired cyclopropane products of the ring closure reactions and to establish analytical conditions for their detection, it was necessary to synthesize 2, using the modified procedure of Bergman and Napierski.[4]

A mixture of 750 mg of 5-chlorohexan-2-one (prepared by Napierski using the modified procedure of Cannon[5]), 230 ml of H_2O, and 20 ml of 0.75 M NaOH was allowed to stir for 2 hours at room temperature. The solution was then made acidic (pH = 5) by dropwise addition of a 10% solution of HCl. Then, 75 g of NaCl was added and the solution extracted with three 33 ml portions of isopentane. The organic extract was dried over Na_2SO_4, filtered, and the isopentane removed on a rotovap, leaving 250 mg (45% yield) of a light yellow liquid (2). The NMR spectrum was consistent with a mixture of cis and trans 2. A pair of methyl singlets at δ 2.25 and δ 2.22 with relative intensities of 54 and 84, respectively, indicates a cis/trans or trans/cis ratio of 4/6. NMR ($CDCl_3$) 2.25(s, 1.2), 2.22(s, 1.8),

1.17(m, 7). IR ($CHCl_3$) 2946, 1690, 1395, 1372, 1347, 1161, 849 cm^{-1}.

GC conditions were then established for the separation of cis and trans 2. The best separation was obtained on a 27' × 1/8" stainless steel column of 15% carbowax on chrom W. A column temperature of 73° produced near baseline separation with a retention time of 40-44 minutes for both isomers.

Reaction of 2-hexanone-5-(p-N-methylpyridinium) ether (4) with base

A mixture of 7.6 mg of 4 and 0.115 ml of 0.52 M NaOH diluted to 1.0 ml with H_2O was allowed to sit at room temperature for 2 hours with occasional shaking. Then a 10% solution of HCl was added to pH = 2. The solution was saturated with NaCl and extracted with isopentane. The isopentane extract was dried over Na_2SO_4 and subjected to GC analysis. No 2 was detected.

The preceding experiment was repeated on a larger scale (46.4 mg of 4) and allowed to stir overnight at room temperature. GC analysis was inconclusive, in that, a number of peaks appeared, and two of the small peaks had approximately the same retention times as cis and trans 2. But additional experiments and NMR analysis were necessary to determine whether or not ring closure was actually occurring.

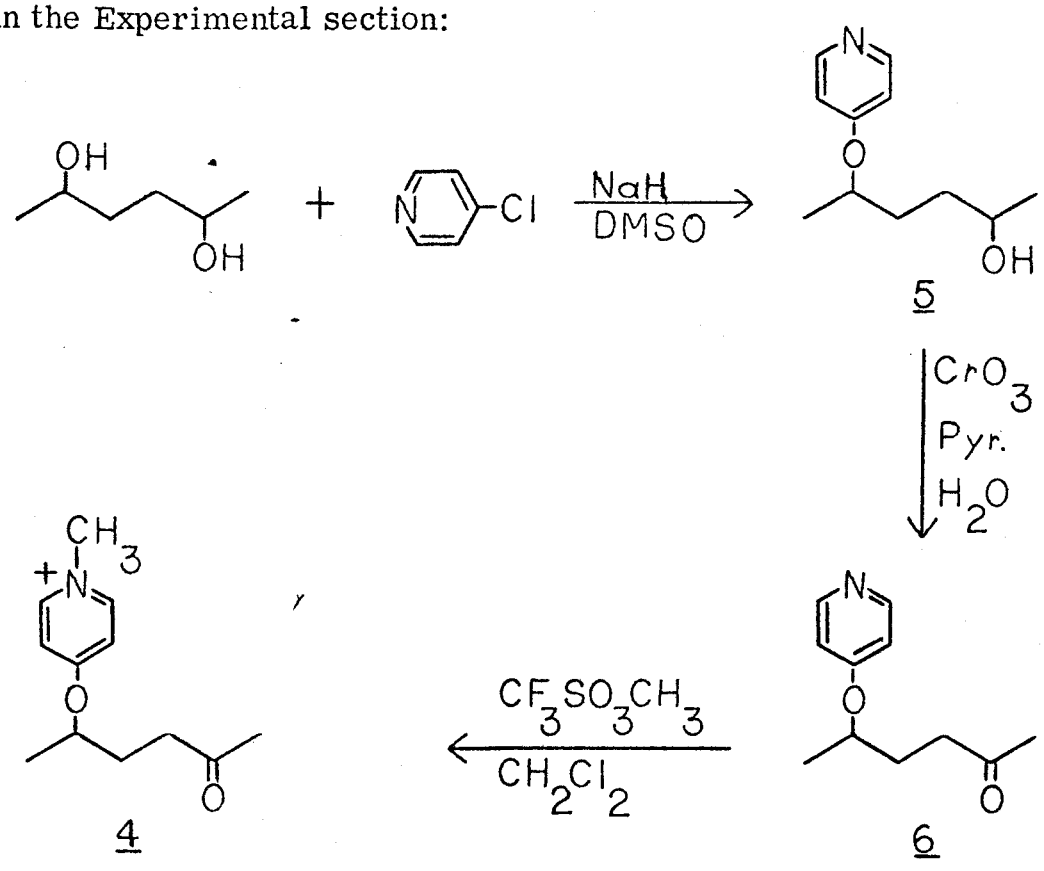
An NMR sample was prepared by mixing 30.1 mg of 4 and 540.3 mg of D_2O in an NMR tube, and the spectrum was recorded immediately, using an external TMS reference. NMR (D_2O) 8.26(d, 2), 7.17(d, 2), 4.50(m, 1), 3.99(s, 3), 2.56(t, 2), 2.09(s, 3), 1.95(t, 2), 1.24(d, 3). Small amounts of 0.46 N NaOD in D_2O were added periodically over a period of about 2 hours, with NMR spectra recorded after each addition. The last spectrum was recorded after 11 drops were added (126 minutes after the first spectrum). NMR (D_2O) 8.58 (d, 2), 7.86(d, 2), 4.20(m, 6), 1.85(m, 5), 1.12(m, 4). The observed changes in the NMR spectra (e.g., the sizable shifts in the aromatic peaks and the N-methyl peak) as the reaction progressed was clear evidence that a change had occurred in the starting material. However, the identity of the product or products could not be determined on the basis of the NMR spectra, so the sample was subjected to GC analysis to determine whether any 2-methylcyclopropylmethyl ketone was present: The NMR sample was saturated with NaCl, extracted with ether, and the ether extract dried over Na_2SO_4. After filtering and concentrating the ethereal solution, it was subjected to GC analysis, which gave no indication of the presence of 2. The remaining aqueous layer from the original NMR sample was then acidified with 10% HCl, extracted with ether, and the ether extract dried and concentrated as before. GC analysis of this ethereal solution also failed to detect the

presence of 2.

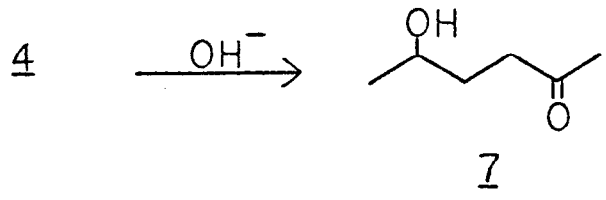
In a similar experiment, 9.2 mg of 4 and 378.4 mg of D_2O were mixed in a small screw-capped vial. Five drops of 0.46 N NaOD in D_2O were added, and the mixture allowed to sit at room temperature for about 40 minutes with occasional shaking. The solution was saturated with NaCl and extracted with four 1/2 ml portions of $CHCl_3$. The combined organic extract was dried over Na_2SO_4, and then vacuum distilled to remove most of the $CHCl_3$. The residue was analyzed by GC and by IR, with no detection of 2. IR ($CHCl_3$) 2953, 1704, 1640, 1570, 1273, 1025, 903 cm^{-1}, compared to IR of authentic sample of 2: IR ($CHCl_3$) 2946, 1690, 1395, 1372, 1347, 1161, 849 cm^{-1}.

RESULTS AND DISCUSSION

The synthesis of 2-hexanone-5-(p-N-methylpyridinium) ether (4) was accomplished according to the following scheme, as described in the Experimental section:



The reaction of 4 with aqueous sodium hydroxide was initially monitored by NMR (see Experimental), but the reaction products could not be identified with certainty by this method. A reasonable guess is that the major product was 5-hydroxyhexan-2-one (7), i.e., the product of a simple displacement reaction. This possibility was not ruled out by



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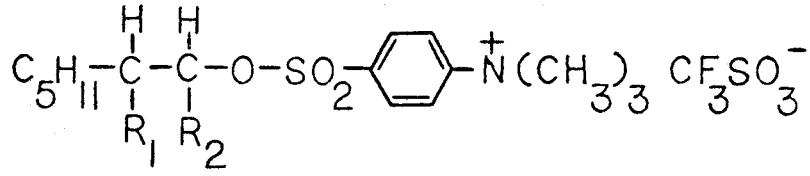
the NMR data. The formation of any detectable amount of 2-methylcyclopropylmethyl ketone was, however, ruled out by GC analysis (see Experimental), and the project was eventually abandoned.

Chapter II: Synthesis and Investigation of the Solvolysis of n-hexyl-p-carboxybenzenesulfonate

INTRODUCTION

In their investigations of the anionic micellar effects on solvolytic displacement reactions involving the alkyl p-trimethylammoniumbenzenesulfonate system (8a-c), Sukenik, Weissman, and



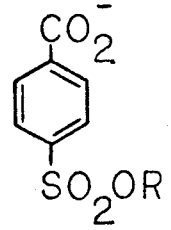
8a, $R_1=CH_3$, $R_2=H$

8b, $R_1=H$, $R_2=CH_3$

8c, $R_1=R_2=H$

Bergman[2b] found that "micelles formed from anionic surfactants bind (8a-c) strongly, retard their rate of aqueous solvolysis by at least two orders of magnitude, and change the observed stereochemistry of displacement in (8b) from 100% net inversion to 56% net inversion." However, cationic micelles appeared to have little or no effect on the system. These results suggested that a system similar to (8a-c), but oppositely charged, might exhibit the opposite effects, i.e., the solvolysis rate and stereochemistry might be affected by cationic micelles and unaffected by anionic surfactants.

The system proposed to test this hypothesis was the alkyl p-carboxybenzenesulfonate system (9). Thus, this project involved



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primarily the synthesis of this molecule, with the ultimate goal being to test the micellar effects on solvolytic displacement reactions of 9.

EXPERIMENTAL

General

For a description of the instruments used, see Chapter I Experimental,

SCHEME I

Preparation of p-carboxybenzenesulfonyl chloride (12)

The modified procedure of Everard and Mills [6] was used to prepare 12. In a typical preparation, 49 g of p-toluenesulfonyl chloride and 1000 ml of water were stirred mechanically while 14 g of NaOH pellets were added. The flask was equipped with a reflux condenser and the mixture heated to about 55° while stirring for 2 hours, or until all solid material had gone into solution. About 88 g of $KMnO_4$ was added, the temperature increased to 80°, and the mixture allowed to stir for about 40 hours. The mixture was cooled and treated with 95% ethanol to destroy any excess permanganate. The brown MnO_2 was removed by filtration, and the volume of the filtrate was reduced to about 500 ml on a rotovap. The solution was acidified to pH = 4 with dilute HCl. After refrigeration, the white sodium salt (11) was collected, recrystallized from water, and dried in a vacuum oven at 100°. Typical yields were 60-70%.

The chloride (12) was prepared from the salt as follows: 12.5 g of 11 was added in small portions to 50 ml of freshly distilled (70-80°, aspirator) chlorosulfonic acid stirring at 0°. The solution was stirred overnight at room temperature. The clear solution was poured slowly, with stirring into 300 g of ice and water. The granular white precipitate was collected and dried in vacuo over sulfuric acid; 10.5 g of 12 (86% yield) was obtained, M.P. 230-235° (decomp) (reported[6] M.P. 230-235° (decomp)). IR (KBr) 1690, 1374, 1287, 1171 cm^{-1}. Mass spec, m/e 220 (m^+), 185, 121. NMR (acetone-d_6) 8.25 (d).

Attempt to prepare methyl-p-carboxybenzenesulfonate (9, R = Me)

(A) The procedure of Roos et al.,[7] for making n-butyl tosylate was modified to attempt the preparation of the methyl ester (9). A flask containing 133.6 mg of 12, 3 ml of methanol, and enough 10 M NaOH to make the solution basic was stoppered and allowed to sit overnight at room temperature. The pH was checked periodically, and NaOH solution was added when necessary to maintain an alkaline solution. A white precipitate was formed which was filtered and dried in a vacuum oven at 90°, M.P. >300°. IR (KBr) 1605, 1410, 1230, 1180 cm^{-1}. NMR (D_2O) 8.12(d, 2), 7.88(d, 2). The absence of methyl peaks in the NMR, the high melting point, the solubility in acidic H_2O, and the insolubility in common organic solvents (chloroform, acetone,

methanol) appear to rule out structure 9. The most reasonable conclusion is that either the mono- or bis-sodium salt was formed from 12.

(B) A solution of 307.2 mg of 12 in 4 ml of freshly distilled THF was stirred in an ice bath while a suspension of 76.9 mg of sodium methoxide (MCB) in 4 ml of dry THF was added dropwise over 5-10 minutes. The reaction mixture, which had turned white, was allowed to stir for about 15 minutes while warming to room temperature. Then, 10 ml of 10% HCl was added and the mixture extracted with ether. The ether extract was dried over Na_2SO_4, filtered, and stripped down, leaving a white solid residue. An IR spectrum of the residue indicated it was unreacted 12. IR (KBr) 1690, 1374, 1287, 1171 cm^{-1}.

(C) Following the modified procedure of Crossland and Service,[8] a mixture of 10.2 ml CH_2Cl_2, 70.4 mg methanol, and 342 mg of triethylamine was stirred at 0° while 0.5 g of 12 was added in small portions over a 10 minute period. After the addition was complete, the solution was allowed to stir while warming to room temperature for 20 minutes. The solution was washed with water, with dilute HCl, and again with water. The CH_2Cl_2 solution was dried over Na_2SO_4, filtered, and evaporated to dryness. There remained 75-100 mg of a white solid residue which decomposed at 143-150°. IR ($CHCl_3$) 1800,

1731, 1396, 1386, 1280, 1170 cm^{-1}. NMR ($CDCl_3$) 8.40(m, 3), 4.00 (d, 1), 3.88(d, 1). The structure of the compound could not be determined from this spectral data, but the NMR was inconsistent with the desired methyl sulfonate.

Attempt to prepare n-decyl-p-carboxybenzenesulfonate (9, R = n-decyl)

(A) The procedure of Crossland and Servis [8] was again modified in attempting to prepare the n-decyl sulfonate (9). A mixture of 327.4 mg of n-decanol, 317.7 mg of triethylamine, and 10 ml of CH_2Cl_2 was stirred in an ice bath, while 500.7 mg of 12 was added in small portions over 10 minutes. The mixture was allowed to stir at room temperature for 4 hours. The solution was washed twice with water, 3 times with 10% HCl, and three additional times with water. The CH_2Cl_2 solution was dried over Na_2SO_4, filtered, and stripped down on a rotovap, leaving about 2 ml of a cloudy oil. An NMR was taken, indicating the oil was primarily n-decanol plus a minor component which could possibly be the desired ester (9). NMR ($CDCl_3$) 8.17 (m, 2), 4.26(m, 1), 3.61(t, 2), 2.93(s, 1), 1.28(m, 23).

(B) The previous experiment was repeated with 330.5 mg of n-decanol, 531.7 mg of triethylamine, 531.7 mg of 12, and 10 ml of CH_2Cl_2. After the addition of 12 was completed, and flask was stoppered and stored in a refrigerator for 3 days. The solution was

worked up as before, and removal of solvent produced a cloudy oil. An NMR spectrum indicated a mixture of n-decanol and unidentifiable products. NMR ($CDCl_3$) 8.08(m, 2), 4.20(m, 1), 3.60(t, 1), 3.13(m, 1), 1.30(m, 23). The oil was chromatographed on a 10-inch Silica-gel column using an ether to 60% methanol/ether solvent gradient. Fractions of 25 ml were collected with fraction 4 containing n-decanol. Fractions 13-15 contained a white solid of undetermined structure, which was insoluble in $CHCl_3$ and CCl_4, but was quite water-soluble. An NMR recorded in D_2O contained only a singlet due to H_2O at 4.7 δ. An IR was also recorded, but was not helpful in determining the structure. IR (KBr) 2905, 2325, 1708, 1195 cm^{-1}. Due to the absence of NMR signals, the compound was assumed to be an inorganic salt.

Attempt to prepare n-hexyl-p-carboxybenzenesulfonate (9, R = n-hexyl)

(A) The procedure of Feiser and Feiser[9] for the preparation of tosylates was modified to attempt to prepare 9. A solution of 631.7 mg of 1-hexanol in 1 ml of dry pyridine was added dropwise, with swirling, to a mixture of 1.5 g of 12 in 12 ml of pyridine at 0°. After swirling the mixture in an ice bath for several minutes a 1/2 ml aliquot was removed and the flask was stoppered and placed in a refrigerator. The aliquot was worked up, showing only unreacted starting material. After 4 days, the reaction mixture contained white needle-shaped

crystals (presumably pyridinium chloride). The solution was filtered and stirred into 180 g of ice and water. Attempts to induce crystallization failed, and the cloudy aqueous solution (A) was saturated with NaCl and extracted with ether. A white precipitate appeared in the ether layer and was removed by filtration. The ether extract (B) was washed with dilute HCl, and with 2% aqueous NaOH. The NaOH extract was acidified with dilute H_2SO_4, saturated with NaCl, and extracted with ether (C). The original aqueous solution (A) was acidified, saturated with NaCl, and extracted with ether (D). Each of the ether extracts (B, C, and D) were dried over Na_2SO_4. Removal of the solvent in each case produced nothing. The white solid material which appeared during the first ethereal extraction was insoluble in $CHCl_3$, CH_2Cl_2, CCl_4, and acetone. It was soluble in water, and had a M.P. $>300°$. NMR (D_2O) 7.80(s, 4), 4.12(t, 2), 1.15(m, 11). IR (KBr) 2945, 2915, 1709, 1395, 1275, 1195, 1100 cm^{-1}. Mass spectrum m/e 310 (m^+), 291, 219, 200, 166, 132, 113.

(B) The preceding experiment was repeated with 215.5 mg of 1-hexanol, 509.6 mg of 12, and 5 ml of dry pyridine. This time, the reaction mixture was heated at 90° for 2.5 hours and 55° for 4 hours. Most of the pyridine was removed on a rotovap, and a saturated NaCl solution was poured into the oily residue. The mixture was acidified with dilute H_2SO_4, producing white crystals. After cooling, the

crystals were removed by filtration and dried in a vacuum oven at 100°. An IR indicated that the compound was identical to that obtained in the preceding experiment. A water solution of 154.6 mg of the compound was titrated to a phenolphthailein endpoint with a standardized (KHP) 0.108 N NaOH solution. Only 0.05 ml (1 drop) of base was required to reach the endpoint, indicating the unknown compound was not acidic.

(C) This experiment was again repeated, heating the reaction mixture for 8.5 hours at 60°. After removing most of the residual clear oil, ice cold dilute H_2SO_4 was poured into the mixture, and the ether layer removed. The aqueous acidic solution was extracted with 2 additional portions of ether, and the ether extracts combined and dried over Na_2SO_4. Subsequent removal of the ether produced only a clear oil, identified as 1-hexanol. The aqueous acidic solution was saturated with NaCl and extracted with ether. After drying and removal of the ether, there remained the same unidentified white solid material obtained in the first two attempts at this synthesis.

(D) A mixture of 0.4219 g of 1-hexanol, 20 ml of freshly distilled DMSO, and 0.1966 g of a 57% dispersion of NaH in mineral oil was mechanically stirred for 2 hours under an atmosphere of N_2. One gram of 12 was added and the mixture allowed to stir overnight at room temperature under N_2. The resulting light brown reaction mixture was filtered and the white precipitate washed with hot benzene.

The combined DMSO-benzene filtrate was extracted with 10% HCl, and the aqueous acidic extract was extracted with ether. The ether layer was combined with the original DMSO-benzene mixture and extracted with 2% aqueous NaOH. The aqueous extract was acidified with dilute HCl, extracted with ether, and the ether extract dried ove Na_2SO_4. The ether solution was stripped down, leaving only a few drops of a dark yellow oil. The oil was insoluble in $CHCl_3$, acetone, and water, and was assumed to be something other than the desired product. The acidified NaOH extract from above was saturated with NaCl and extracted again with ether. The ether extract was dried over Na_2SO_4, and stripped down producing nothing.

SCHEME II

Preparation of n-hexyl-p-toluenesulfonate (14, R = n-hexyl)

The procedure of Feiser and Feiser[9a] was used to prepare 14 from 4 g of 1-hexanol, 50 ml of dry pyridine, and 15 g of p-toluene-sulfonyl chloride (13). The reaction mixture was allowed to stand in the refrigerator for about 20 hours, turning pink and forming white needles of pyridinium chloride. The mixture was poured into 300 g of ice and water, forming a brown oil. After saturating with NaCl and extracting with ether, the ether extract was washed with 10% HCl, with water, and dried over Na_2SO_4. Removal of the ether left 10 g

(quantitative yield) of a yellow oil (14). The NMR was in reasonable agreement with that reported by Jacobs and Macomber:[9b] NMR ($CDCl_3$) 7.86(m, 2), 7.40(m, 2), 4.07(t, 2), 2.45(s, 3), 1.25(m, 11). IR (neat) 2930, 2955, 1594, 1365, 1191, 1183 cm^{-1}.

Attempt to prepare n-hexyl-p-carboxybenzenesulfonate (9) by oxidation of n-hexyl-p-toluenesulfonate (14)

(A) The procedure of Ross and Davis[10] was modified in attempting to oxidize 14 to the carboxyl compound (9). A mixture of 10 ml concentrated H_2SO_4, 10 ml of H_2O, and 1 g of 14 was stirred at room temperature while a solution of 3 g of CrO_3 in 8 ml of H_2O was added dropwise. The resulting mixture was heated at 97° for about 20 minutes, cooled, and poured into 50 g of ice and water. The aqueous solution was extracted with ether, and the ether extract (A) was extracted with a 2 M solution of Na_2CO_3. The aqueous layer was acidified with dilute H_2SO_4 and extracted with ether (B). After drying the ethereal solutions (A and B), and removing the solvent, solution A was found to contain only unreacted 14. Solution B contained nothing.

(B) The permanganate oxidation procedure of Clarke and Taylor[11] was modified in attempting to oxidize 14. A heterogeneous mixture of 4.5 g of $KMnO_4$, 3 g of 14, and 50 ml of water was stirred while heating slowly to 110°. After 5 hours at this temperature, the

reaction mixture was cooled and filtered. The MnO_2 precipitate was washed with hot water, and the washings combined with the filtrate, which was observed to contain an insoluble oil. After acidification with dilute HCl, the aqueous solution was extracted with ether. After the organic extract was dried and the solvent removed, only unreacted 14 was found. Apparently the tosylate (14) was not sufficiently soluble under the reaction conditions for the oxidation to succeed.

(C) A mixture of 2 g of 14, 20 ml of H_2O, and 20 ml of t-butanol was stirred at room temperature while a mixture of 3 g of $KMnO_4$ in 10 ml of H_2O was added. The mixture was stirred overnight at room temperature, after which time a 20 ml aliquot was removed. The remainder of the reaction mixture was allowed to continue stirring at room temperature for another day and night, while the aliquot was worked up as follows: Ethanol was added to destroy excess $KMnO_4$. Then the mixture was filtered to remove the MnO_2, and the precipitate washed with 1% aqueous NaOH. The combined aqueous filtrate was acidified with dilute HCl and extracted with ether (ether #1). This ether extract was extracted with dilute aqueous NaOH, and the aqueous extract was acidified with dilute HCl and extracted with ether (ether #2). The two ether solutions were dried over Na_2SO_4 and stripped down. Ether #1 produced a clear oil which was shown by NMR to contain only ethanol, t-butanol, and some unreacted 14. Ether #2 contained only

ethanol and t-butanol.

After about 48 hours of stirring at room temperature, the original reaction mixture was heated to 70° for about 4 hours. The mixture was then filtered and the precipitate washed with 1% aqueous NaOH. The combined aqueous filtrate was acidified by the addition of 1 drop of 6 N HCl, at which time the solution turned brown and a small amount of brown oil separated. The mixture was extracted with ether. The brown oil was not soluble in ether, but was removed with the ether extract (ether #3) which was dried over Na_2SO_4. The aqueous layer was saturated with NaCl and extracted with ether, producing a light brown precipitate. The precipitate was filtered out and the ether extract (ether #4) dried over Na_2SO_4. The precipitate was insoluble in $CHCl_3$ and acetone, soluble in water, and had a melting point greater than 320°. It was therefore concluded that this was not the desired product. Ether #3 and ether #4 were stripped down and shown by NMR to contain primarily t-butanol and small amounts of unidentified impurities. The brown oil was separated from ether #3 and shown by NMR to consist primarily of t-butanol and small amounts of unidentified impurities.

(D) A mixture of 10 ml H_2O, 10 ml pyridine, and 1 g 14 was stirred while 2.2 g $KMnO_4$ was added in several portions. The mixture was heated slowly up to 60° over 1 hour, and then filtered while

hot. The MnO_2 precipitate was washed with water. The combined aqueous filtrate was acidified with dilute HCl and extracted with ether. The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2. The organic extracts were dried separately over Na_2SO_4. Removal of solvent produced nothing from the CH_2Cl_2. The ether extract was stripped down, leaving about 150 mg of yellow oil. NMR and IR spectra showed the oil to be a mixture of unreacted tosylate (14) and an unidentified component, having aromatic peaks in the NMR. NMR ($CDCl_3$) 8.13(d, 5), 7.58(m, 34), 4.00(m, 5), 3.35(m, 27), 2.25(m, 17), 1.27(m, 230). IR ($CHCl_3$) 2925, 1690, 1355, 1185 cm^{-1}.

(E) A mixture of 3 g 14, 30 ml pyridine, and 30 ml H_2O was stirred and heated to 45°. Over a period of 1 hour, 6.6 g of $KMnO_4$ was added in small portions. After the addition was complete, a 25 ml aliquot was taken and the remainder of the reaction mixture allowed to stir at 45-50°. After an hour, another 25 ml aliquot was taken, the heating was discontinued, and the reaction mixture was left stirring at room temperature for 2 days. The remaining reaction mixture, as well as each of the aliquots was worked up as follows: Each portion was first filtered and the MnO_2 precipitate washed with water. The combined aqueous filtrate was acidified with dilute HCl, extracted with CH_2Cl_2, and the organic extract dried over Na_2SO_4. In each case, removal of solvent produced an oil which was shown by NMR to contain

unreacted tosylate (14) and the same unidentified product as the preceding experiment produced. The three NMR samples were combined and dissolved in 30 ml of CH_2Cl_2. This solution was extracted with 1% aqueous NaOH. After drying over Na_2SO_4, the organic layer was stripped down, leaving a clear oil which still contained the unidentified product, as well as unreacted 14. NMR ($CDCl_3$) 8.12(s, 2), 7.80(m, 2), 7.35(m, 2), 4.02(m, 2), 3.33(m, 6), 2.45(s, 3), 1.64(m, 68). IR (neat) 2930, 1665, 1381, 1176, 912, 734 cm^{-1}. The aqueous alkaline extract from above was acidified with dilute HCl, extracted with CH_2Cl_2, and the organic extract dried over Na_2SO_4. Removal of the solvent produced a small amount of clear oil, which was unidentifiable from the spectra. NMR ($CDCl_3$) 8.18(s, <1), 7.57(m, 1), 3.32(m, 3), 2.35(t, 2), 1.25(m, 31). IR ($CHCl_3$) 2920, 1700, 1351, 905 cm^{-1}.

(F) A mixture of 2 g of 14 in 40 ml glacial acetic acid was heated on a steam bath while 6 g CrO_3 was added in small portions. After addition was complete, the mixture was stirred while heating for an additional 1/2 hour. Water was added and the mixture was cooled and extracted with ether. The organic layer was extracted with 1% aqueous NaOH. The aqueous extract was acidified with dilute HCl, extracted with ether, and the ether extract dried over Na_2SO_4. Removal of the ether produced only acetic acid.

(G) A mixture of 3 g 14, 60 ml acetone, and 6.6 g $KMnO_4$ was stirred at 42° for 1 hour. A 20 ml aliquot was then removed and the remainder of the reaction mixture was allowed to continue stirring overnight at 42°. Another 20 ml aliquot was removed, the temperature was increased to 55-60°, and an additional 20 ml acetone was added. The mixture was stirred overnight again, before the remaining portion was worked up. Each aliquot was worked up as follows: The mixture was filtered, and the filtrate evaporated to leave a deep purple oil. The oil was taken up in water, acidified with dilute HCl, and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4 and stripped down. Each aliquot produced 3/4-1 g of unreacted 14, as identified by NMR. There was no detectable trace of the desired oxidation product in any of the three aliquots.

Preparation of n-hexyl-p-carboxybenzenesulfonate (9) by oxidation of n-hexyl-p-toluenesulfonate (14)

A mixture of 8 g of 14, 60 ml H_2O, 120 ml acetone, and 8 g $KMnO_4$ was stirred at 60-65° for 1 hour. An additional 16 g $KMnO_4$ was then added and the mixture was stirred for another 1.5 hours. A 50 ml aliquot was removed, an additional 16 g of $KMnO_4$ was added, and the mixture was stirred for another 12 hours. Each aliquot was worked up as follows: The mixture was filtered while hot to remove

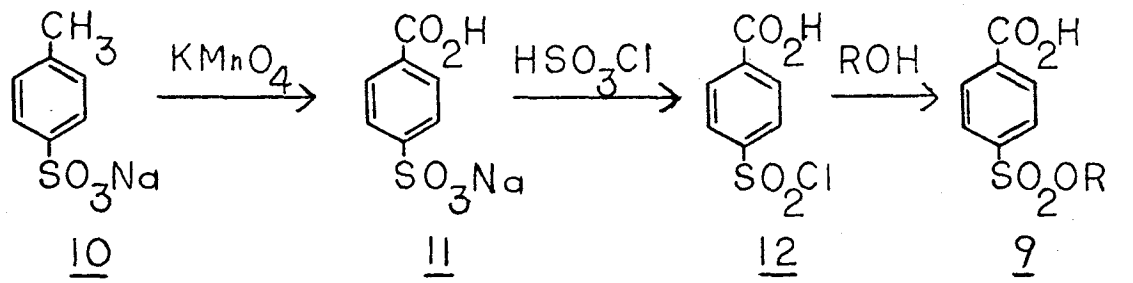
the MnO_2. The precipitate was washed with acetone, water, and 1% aqueous NaOH. The washings were combined with the filtrate and extracted with ether. The aqueous layer was then acidified with dilute HCl, extracted with ether, and the ether extract dried over Na_2SO_4. Removal of the ether produced a white solid material. A total of 643 mg of crude material was recovered (7.2% crude yield). The compound was recrystallized from toluene; M.P. 149-149.5°. NMR (acetone-d_6) 8.22(quart, 4), 4.19(t, 2), 1.28(m, 11). IR ($CHCl_3$) 2955, 1704, 1363, 1183 cm^{-1}. Mass spec, m/e 286 (m^+), 269, 203, 185, 121.

Reaction of n-hexyl-p-carboxylbenzenesulfonate (9) with base

An NMR sample was prepared by dissolving 17.0 mg of (9) in 0.5 ml of 0.95-1.0 N NaOD/D_2O (prepared by Chaim Sukenik by dissolving Na metal in D_2O, and standardized by titration with KHP). The reaction was monitored by NMR over a period of 30 hours, 42 minutes, at room temperature. After 12 hours, 41 minutes, the reaction was approximately 45% complete, as determined by the relative integrals of the signals of the α-protons in reactant and product: NMR (t = 12 hours, 41 minutes) (D_2O, chemical shifts based on external TMS reference) 8.33(m, 4), 4.43(t, 1.1), 3.88(t, 0.9), 1.54(m, 11).

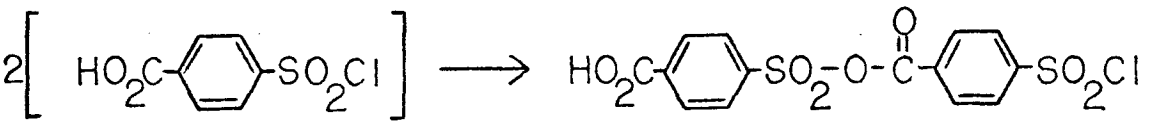
RESULTS AND DISCUSSION

The synthesis of 9 was initially attempted according to Scheme I:



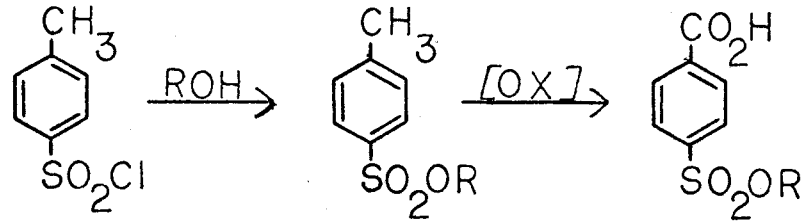
Scheme I

The synthesis of p-carboxybenzenesulfonyl chloride (12) was accomplished by this method. But many attempts to complete the final esterification step to 9 (see Experimental) were unsuccessful. The cause for failure of this method is not known for certain. However, one possible explanation is that the chloride (12) could undergo esterification with itself under the reaction conditions, i.e.,



In fact, 12 could conceivably polymerize under the reaction conditions, thus explaining the unidentifiable products obtained in several instances.

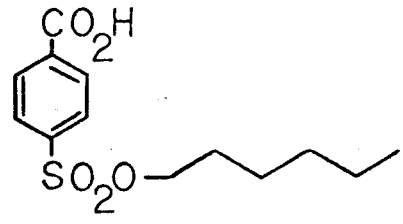
Scheme I was eventually abandoned in favor of Scheme II:



13 14 9

Scheme II

This method eventually proved successful for synthesizing n-hexyl-p-carboxybenzenesulfonate (9, R = n-hexyl).



9

The generality of this synthetic method is not yet known. The method would appear to be useful for most primary systems, but its usefulness

for secondary systems has not yet been demonstrated.

Due to the unexpected amount of time required for the synthesis of 9, little time was left for investigating the solvolysis of the molecule. One crude experiment was done, however, to obtain an estimate of the reactivity of the hexyl sulfonate (9) in base (see Experimental). It was found that in approximately 1.0 N aqueous NaOD at room temperature, 9 has a half-life on the order of 14 hours.

On the basis of these results, it appears that the secondary system is worth investigating. This system should have a considerably shorter half-life, making it a reasonable candidate to study for comparison to the alkyl-trimethylammoniumbenzenesulfonate system investigated by Sukenik, Weissman, and Bergman.[2b]

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