NMR ($CDCl_3$) $\delta^{13}C$ 132.1 (d), 68.8 (t), 41.9 (d), and 38.3 (t).

3-Cyclopentenemethyl Tosylate. To 14.6 g of 3-cyclopentenemethanol (0.149 mol) dissolved in 40 mL of dry pyridine at 0 °C was added dry *p*-toluenesulfonyl chloride (28.69 g, 0.15 mol) in several portions. After the addition was complete the mixture was stirred for 10 h at 0 °C. Then the reaction mixture was poured into 100 mL of ice water, and the product tosylate was extracted in chloroform (3 × 150 mL). The chloroform extract was washed several times with cold water to get rid of any trace of pyridine. The washed chloroform layer was dried over anhydrous $MgSO_4$ and evaporated to give almost pure 3-cyclopentenemethyl tosylate. Attempted distillation of the tosylate, however, resulted in substantial decomposition. The crude tosylate was used for the next reaction without any further purification; ^{13}C NMR ($CDCl_3$), $\delta^{13}C$ 147.7 (s), 136.1 (s), 132.8 (t), 132.0 (d), 130.6 (d), 76.7 (t), 38.9 (d), 38.1 (t), and 24.0 (q).

3-Cyclopentenemethyl Iodide. To the crude 3-cyclopentenemethyl tosylate (34 g, 0.135 mol) dissolved in 300 mL of acetone was added 39.6 g (0.136 mol) of dry sodium iodide with stirring. The whole mixture was refluxed for 36 h under a nitrogen atmosphere. After the reaction was complete, the precipitated sodium tosylate was filtered, the pale yellow acetone layer was evaporated, and the crude residue was distilled to obtain 24.7 g of pure 3-cyclopentenemethyl iodide (88% yield): bp 54 °C (1.2 mm); ^{13}C NMR ($CDCl_3$) $\delta^{13}C$ 128.2 (d), 39.3 (d), 39.0 (t), and 13.9 (t).

3-Cyclopenteneacetic Acid (95% ^{13}C Enriched at the Carboxylic Carbon). About 4.4 g of 95% ^{13}C-enriched carbon dioxide generated form 20 g of 95% ^{13}C-enriched barium carbonate and 30 mL of 30% sulfuric acid was condensed into a cooled solution of 3-cyclopentenemethylmagnesium iodide in 200 mL of dry ether (prepared from 24.7 g of 3-cyclopentenemethyl iodide and 3.6 g of magnesium turnings) under argon at −120 °C (with liquid nitrogen/ethanol slush). The reaction mixture was slowly warmed to room temperature followed by gentle reflux for 4 h. The reaction mixture was quenched with 100 mL of ice-cold 10% ammonium chloride solution. The ether layer was evaporated and the crude 95% ^{13}C-enriched 3-cyclopenteneacetic acid was further purified by base extraction: 7 g (50% yield based on CO_2); ^{13}C NMR ($CDCl_3$) $\delta^{13}C$ 178.4 (s), 128.9 (d), 39.9 (t of d, $J_{^{13}C-^{13}C}$ = 54.9 Hz), 38.1 (t), and 32.9 (d).

β-3-Cyclopenteneethanol (95% ^{13}C Enriched at the Hydroxymethylene Position). A total of 6.10 g of 95% ^{13}C-enriched β-3-cyclopenteneacetic acid (0.044 mol) dissolved in 50 mL of ether was slowly added to a slurry of 3.7 g of lithium aluminum hydride in 150 mL of ether dropwise so as to maintain a gentle reflux. After the addition was complete the mixture was refluxed for 5 h under a nitrogen atmosphere. After the reflux the mixture was allowed to cool down and was carefully quenched with 3 mL of water followed by 10 mL of 40% sodium hydroxide solution. The precipitated hydroxides were filtered, and the clear ether layer was dried over anhydrous magnesium sulfate. The ether layer on evaporation gave pure 95% ^{13}C-enriched β-3-cyclopenteneethanol: 5.3 g (97% yield); bp 92 °C (20 mm) [lit. bp[15] 90–95 °C (20 mm)]; ^{13}C NMR ($CDCl_3$) $\delta^{13}C$ 129.4 (d), 60.6 (t), 38.8 (t), 37.8 (d), 35.2 (t of d, $J_{^{13}C-^{13}C}$ = 50.2 Hz).

Preparation of the Carbocation. The 2-norbornyl cation was prepared by addition of the precursor *exo*-2-chloronorbornane in SO_2ClF solution to excess $SbF_5/SO_2ClF/SO_2F_2$ solution at −78 °C so as to obtain roughly 5% of the ion in solution. These solutions were then transferred into precooled NMR tubes for the spectroscopic studies.

^1H NMR spectra were obtained on a 395-MHz superconducting NMR spectrometer equipped with a low-temperature probe (built at UCLA).

^{13}C NMR spectra (50 MHz) were obtained on a Varian Associates Model XL-200 NMR spectrometer equipped with a broad-band variable-temperature probe. The chemical shifts are referenced from external capillary tetramethylsilane. Both ^1H and ^{13}C NMR spectra were taken in the Fourier transform mode without any field lock. The ^1H NMR spectra depicted in Figure 1 were obtained with a line broadening function of 8 Hz. The ^{13}C NMR spectrum recorded at −159 °C was resolution enhanced by the convolution difference method with a convolution difference (CD) of 0.7 and constant of convolution difference (CCD) of 0.99.

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Registry No. 1, 24321-81-1; 3-cyclopentenecarboxylic acid, 7686-77-3; 3-cyclopentenemethyl tosylate, 25125-22-8; 3-cyclopentenemethanol, 25125-21-7; 3-cyclopentenemethyl iodide, 83528-59-0; 3-cyclopenteneacetic-*1*-^{13}C acid, 83528-60-3; β-3-cyclopenteneethanol-α-^{13}C, 83528-61-4; *exo*-2-chloronorbornane-^{13}C, 83572-19-4; *exo*-2-norborneol-^{13}C, 83572-20-7.

Betylates. 3. Preparative Nucleophilic Substitution by Way of [2]-, [3]-, and [4]Betylates. Stoichiometric Phase Transfer and Substrate–Reagent Ion-Pair (SRIP) Reactions of Betylates

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Abstract: The preparation of [2]-, [3]-, and [4]betylates ((trialkylammonio)alkanesulfonates) and the corresponding norbetylates ((dialkylammonio)alkanesulfonates) is described, and their use as intermediates in the transformation of the hydroxyl group of primary and secondary alcohols is illustrated by examples involving 36 different nucleophiles and 10 different alkyl groups; for a number of products these procedures provide what appears to be the best, or only, access. The reactions generally take place under mild conditions, are easily worked up giving good to excellent yields, and may be carried out in solvents ranging from water to hydrocarbons. Clean inversion is generally found in reactions at chiral secondary centers; a substrate–reagent ion-pair (SRIP) procedure provides a method for preparing both the *R* and *S* series of derivatives from a single enantiomer of the chiral alcohol. The notable ease of these reactions is discussed in terms of generally applicable stoichiometric phase-transfer processes, especially substrate phase transfer into the aqueous phase, and SRIP reactions in nonpolar solvents.

A particularly useful functional group interchange in organic synthesis is the conversion of an alcohol, ROH, into a product, RZ, using a nucleophile (e.g., Z^-) as a source of the Z grouping. Since hydroxide itself is a feeble nucleofuge in bimolecular nucleophilic displacements, the transformation requires the conversion of the alcohol to an intermediate in which the leaving tendency of the oxygen is enhanced. Ideally such an intermediate should be formed easily and cheaply and react readily with a wide array of nucleophiles in a variety of solvents to give a high yield of product in a readily purified form. It may be too much to expect that a single intermediate species will show all of these properties under all circumstances, but a synthetic chemist may reasonably

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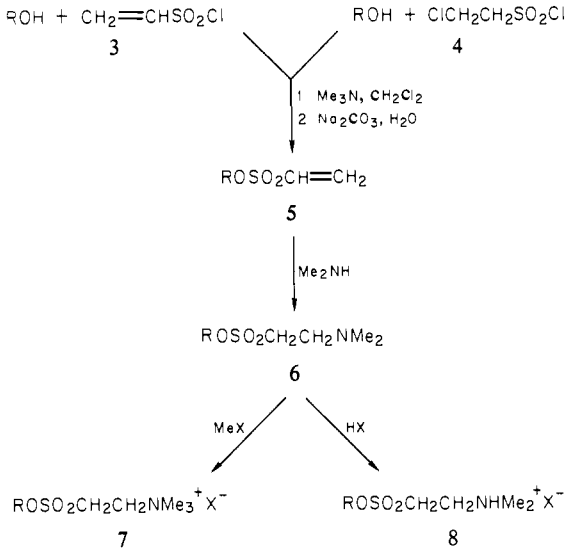
Scheme I



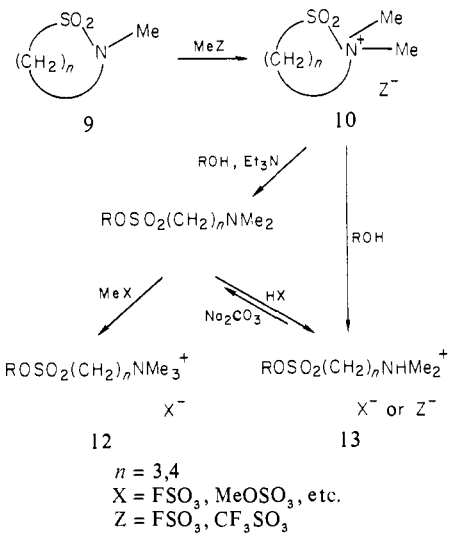
hope to have a sufficient selection available that for any particular conversion he may have a satisfactory method at hand. Extensive work in the last two decades or so has produced an array of procedures leading to new reactive leaving groups[1] and such valuable methods as phase-transfer catalysis[2] and the use of dipolar aprotic solvents.[3] The continued effort in this line may be taken as a sign that there is still a place for improvement in preparative nucleophilic substitution, and in this connection we wish to point to the advantages of using ammonioalkanesulfonate esters, especially ω-(trimethylammonio)alkanesulfonates—"betylates" (**1**)—and their protonated analogues, ω-(dimethylammonio)al-

$ROSO_2(CH_2)_nNMe_3^+X^-$ (**1**) $ROSO_2(CH_2)_nNHMe_2^+X^-$ (**2**)

kanesulfonates "norbetylates" (**2**).

This paper describes the general preparations[4] and reactions of [2]betylates (**1**, n = 2) and [3]betylates (**1**, n = 3) together with a brief description of [4]betylates (**1**, n = 4). Some aspects of this work have already been reported in preliminary communications;[5] a full report of our investigations of [0]betylates (**1**, n = 0), the first member of the betylate series, has already appeared.[6]

Scheme II



Results and Discussion

Synthesis of Betylates. [2]Betylates are readily prepared as shown in Scheme I. Either ethenesulfonyl chloride (**3**) or 2-chloroethanesulfonyl chloride (**4**) may be used in the first step; the former seems to react more quickly and to give slightly higher yields, but the latter is more convenient since it is both commercially available and readily prepared from inexpensive starting materials. Ethenesulfonyl chloride (**3**) is normally prepared by the reaction of **4** with tertiary amines[7] and, not surprisingly, is formed initially in the preparation of ethenesulfonates (**5**) from **4** as well.[8a] Reaction of **3** with Me_3N is believed[8] to take place via the sulfene $Me_3N^+CH_2CH{=}SO_2$, which on reaction with the alcohol gives the ethenesulfonate (**5**) plus a smaller amount of the betylate (**7**, X = Cl). The betylate (**7**, X = Cl) is not isolated at this stage but is simply converted to **5** with aqueous Na_2CO_3. Yields of primary and secondary esters (**5**) are normally 90 ± 10%, with conversion to the betylate (**7**) or norbetylate (**8**) being essentially quantitative.[9] Although consisting of three steps, the preparation of [2]betylates as in Scheme I is typically carried out in 1–3 h, depending on the scale and the alkylating agent used; the norbetylate preparation is, of course, quicker.

Both [3]- and [4]betylates are prepared from the corresponding cyclic sulfonylammonium salts (**10**), which are in turn made from reaction of the *N*-methylsultam (**9**) with methyl fluorosulfate or methyl triflate, as shown in Scheme II. Alcoholysis of the five-membered cyclic sulfonylammonium salt (**10**, n = 3, Z = FSO_3) is catalyzed by triethylamine to give a good yield of the ester (**11**, n = 3), which is readily converted to the betylate (**12**,

(1) E.g., alkoxyphosphonium salts, for leading references see: (a) Beck, P. In "Organic Phosphorus Compounds"; Kosolapoff, G. M.; Maier, L.; Eds.; Wiley-Interscience; New York, 1972; pp 189–508 (especially Table 17). (b) Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811. (c) Mitsunobu, O. *Synthesis* **1981**, 1–28. (d) Cadogan, J. I. G.; Mackie, R. K. *Chem. Soc. Rev.* **1974**, *3*, 87–137. Fluorinated sulfonic esters: (e) Su, T. W.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386–5388 and references cited therein. (f) Subramanian, L. R.; Hanack, M. *Ber.* **1972**, *105*, 1465–1470. (g) Ahmed, M. G.; Alder, R. W.; James, G. H.; Sinnott, M. L.; Whiting, M. C. *Chem. Commun.* **1968**, 1533–1534. (h) Crossland, R. K.; Wells, W. E.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4217–4219. Trimethylsilyl groups in the presence of alkali halides: (i) Olah, G. A.; Gupta, B. G. B.; Malbotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638–1639. (j) PhSeCN–Bu_3P–THF: Sevrin, M.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1980**, 656–657. Alkoxysulfonium salts: (k) Furukawa, N.; Inoue, T.; Aida, T.; Oae, S. *J. Chem. Soc., Chem. Commun.* **1973**, 212.

(2) (a) Starks, C. M. and Liotta, C. "Phase Transfer Catalysis Principles and Techniques"; Academic Press: New York, 1978. (b) Weber, W. P.; Gokel, G. W. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: Berlin, 1977. (c) Makosza, M. *Surv. Prog. Chem.* **1977**, *15*, 267–330. (d) Brändström, A. *Adv. Phys. Org. Chem.* **1977**, *15*, 267–230. (e) Dehmlow, E. V. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 493–558.

(3) (a) Parker, A. J. *Adv. Phys. Org. Chem.* **1967**, *5*, 173–235. (b) Parker, A. *J. Chem. Rev.* **1969**, *69*, 1–32. (c) Ritchie, C. D. In "Solute–Solvent Interactions"; Coetzie, J. F.; Ritchie, C. D.; Eds.; Marcel Dekker: New York, pp 219–300. (d) Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1046–1067. (e) Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133–202.

(4) The only previous synthesis of betylates that we are aware of is the alkylation of betaines, $Me_3N^+(CH_2)_nSO_3^-$, in refluxing dimethyl and diethyl sulfates: (a) Blumbergs, P.; Ash, A. B.; Daniher, F. A.; Stevens, C. L.; Michel, H. O.; Hackley, B. E., Jr.; Epstein, J. *J. Org. Chem.* **1969**, *34*, 4065–4070. Although their work was restricted to methyl and ethyl derivatives, and their method gives poorer yields and requires more strenuous conditions than ours, these authors have clearly shown betylates to be excellent water-soluble alkylating agents. Related also is a recent report describing the preparation and hydrophilic and nucleofugal properties of "amsylates" (trimethylammonium benzenesulfonates): (b) Sukenik, C. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 6613–6623.

(5) (a) King, J. F.; Loosmore, S. M.; Lock, J. D.; Aslam, M. *J. Am. Chem. Soc.* **1978**, *100*, 1637–1639. (b) King, J. F.; Aslam, M.; Lock, J. D. *Tetrahedron Lett.* **1979**, 3615–3618. (c) King, J. F.; Aslam, M. *Synthesis* **1980**, 285–287. (d) King, J. F.; Aslam, M. *Tetrahedron Lett.* **1981**, *22*, 3573–3576.

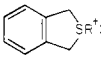
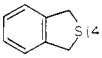
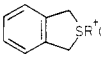
(6) King, J. F.; Lee, T. M. L. *Can. J. Chem.* **1981**, *59*, 356–361, 362–372.

(7) (a) Rondestvedt, C. S. *J. Am. Chem. Soc.* **1954**, *76*, 1926–1929. (b) Etienne, A.; Lonchambon, G.; Benard, C. *Bull. Soc. Chim. Fr.* **1976**, 483–486.

(8) (a) King, J. F.; Hillhouse, J. H. unpublished observations. (b) King, J. F.; Loosmore, S. M. *J. Chem. Soc., Chem. Commun.* **1979**, 454–456.

(9) The methyl ester (**5**, R = Me), however, is isolated in only about 40% yield; when the reagents are mixed in an NMR tube the spectrum obtained shortly afterward shows the presence of **5** (R = Me) and methyl chloride, the latter presumably arising from a very rapid SRIP reaction of the betylate chloride (**7**, R = Me, X = Cl). It was the remarkable ease of this reaction which first drew our attention to SRIP reactions of betylates. Sulfonic esters of tertiary alcohols are usually too reactive for convenient use in synthetic transformations of alcohols. Cf. *tert*-butyl *p*-toluenesulfonate: (a) Hoffmann, H. M. R. *J. Chem. Soc.* **1965**, 6748–6753. *tert*-Butyl methanesulfonate: (b) King, J. F.; du Manoir, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 2566–2567.

Table I. Reaction of [2]Betylates, $ROSO_2CH_2CH_2NMe_3^+X^-$, with Added Nucleophiles

substrate R	substrate X^-	mmol	procedure[a]	reagent	conditions: medium, (temp, °C, time)	isolated product	% yield[b]
butyl	FSO_3^-	11	A	KSCN	H_2O (25, 2 h)	RSCN	91
	FSO_3^-	8	A	Na_2SO_3	H_2O (pH 6.0) (25, 1 h)	$RSO_3^-Na^+$	(90)[c,d]
	ClO_4^-	2	A	$Me_2NCS_2^-Na^+$	H_2O (25, 0.5 h)	$RS-CS-NMe_2$	99
	$CF_3SO_3^-$	5	A	$Na_2S_2O_3$	H_2O (25, 0.45 h)	RSO_2Cl[e]	94
	ClO_4^-	1.5	C	Bu_2S	MeCN (82, 20 h)	$RSBu_2^+ClO_4^-$	75
	$CF_3SO_3^-$	2	C		MeCN (82, 48 h)		66 (80)
	ClO_4^-	2	C		MeCN (82, 96 h)		88 (100)
	ClO_4^-	2	C	Ph_3P	MeCN (82, 24 h)	$RPPh_3^+ClO_4^-$	86
	BF_4^-	2	C	$(EtO)_3P$	MeCN (82, 24 h)	$RPO(OEt)_2$ (plus RPO(OEt)OR and $RPO(OR)_2$)	
3-butenyl	FSO_3^-	7	A	Na_2SO_3	H_2O (pH 6.0) (25, 1 h)	$Na^+SO_3^-(CH_2)_4SO_3^-Na^+$	95[d]
neopentyl	FSO_3^-	8	C	$(NH_2)_2CS$	DME (plus p-$MeC_6H_4SO_3H$) (80, 72 h)	RSO_2Cl[e]	43
octyl	ClO_4^-	0.5	B	KSCN	$CHCl_3$-H_2O (25, 24 h)	RSCN	88
	FSO_3^-	0.5	B	KSCN	$CHCl_3$-H_2O (61, 0.25 h)	RSCN	(90)
	ClO_4^-	0.5	B	$(NH_2)_2CS$	PhH-H_2O (25, 21.5 h)	$[RSC(NH_2)_2]^+ClO_4^-$	75
(±)-1-methylheptyl	FSO_3^-	9	C	HOAc	HOAc (75, 1 h)	ROAc	55
						octene mixture	(22)
	FSO_3^-	39[f]	C	$(NH_2)_2CS$	DME (75, 2 h)	RSO_2Cl[e]	76[f]
	FSO_3^-	0.5		NaN_3	H_2O (25, 0.25 h)	RN_3	85
3-phenylpropyl	FSO_3^-	18	C	$(NH_2)_2CS$	DME (75, 0.5 h)	RSO_2Cl[e]	84
2-*trans*-decalyl[g]	FSO_3^-	2.7	C	$(NH_2)_2CS$	DME (80, 1 h)	RSO_2Cl[e,g]	18
hexadecyl	FSO_3^-	2.0	A	NaN_3 (satd)	H_2O (25, 4 h)	RN_3	90
	FSO_3^-	0.25	A	NaN_3	H_2O (25, 4 H)	RN_3	88
	FSO_3^-	0.25	B	NaN_3	PhH-H_2O (25, 2.5 h)	RN_3	82
	FSO_3^-	1.0	A	KBr	H_2O (25, 5 h)	RBr	90
	FSO_3^-	0.5	A	KCN	H_2O (25, 60 h)	$ROSO_2CH_2CH_2CN$	90
	FSO_3^-	0.5	B	NaCl	CH_2Cl_2-H_2O (50, 18 h)	RCl	80
	FSO_3^-	0.5	B	KNO_3	CH_2Cl_2-H_2O (50, 16 h)	$RONO_2$	65
	FSO_3^-	0.5	B	$(NH_2)_2CS$	PhH-H_2O (25, 1 h)	$[RSC(NH_2)_2]^+FSO_3^-$	75
	FSO_3^-	8.1	B	$(NH_2)_2CS$	CH_2Cl-H_2O (25, 48 h)	RSO_2Cl[e]	43
	FSO_3^-	8.0	C	$(NH_2)_2CS$	DME (80, 2 h)	RSO_2Cl[e]	79
	FSO_3^-	0.25	B	NaOAc	CH_2Cl_2-H_2O (25, 2.5 h)	$ROSO_2CH=CH_2$	90
	FSO_3^-	0.25	B	NaSH	CH_2Cl_2-H_2O (25, 0.25 h)	$ROSO_2CH=CH_2$	60
	FSO_3^-	0.25	C	NaOEt	EtOH-PhH (25, 3 h)	$ROSO_2CH_2CH_2OEt$	55
	FSO_3^-	2	A	$Na_2S_2O_3$	Me_2CO-H_2O (75, 3 h)	RSO_2Cl[e]	80
	FSO_3^-	2.5	A	NaSCN (75 mmol)	H_2O (25, 2 h)	RSCN	88
	FSO_3^-	2	B	$Me_2NCS_2^-Na^+$	CH_2Cl_2-H_2O (25, 1.5 h)	$RS-CS-NMe_2$	98
	FSO_3^-	4.3	C	HCOOH	HCOOH (80, 1 h)	ROCHO	74
docosyl	FSO_3^-	0.2	B	NaN_3 (satd)	PhH-H_2O (25, 1 h)	RN_3	77
	FSO_3^-	0.2	A	KBr	H_2O (25, 3.5 h)	RBr	74
	FSO_3^-	13	A	$(NH_2)_2CS$	Me_2CO-H_2O (25, 24 h)	RSO_2Cl[e]	83

[a] Procedures: (A) A suspension (or solution) of the substrate is stirred with an aqueous solution of the reagent (in 10-fold excess). (B) A solution of the substrate in the organic phase is stirred with an aqueous solution of the reagents (10-fold excess except as otherwise noted). (C) Reaction in the specified organic solvent. [b] Yields without parentheses refer to isolated yields of products judged >98% pure by NMR and (or) IR spectra. Yields within parentheses have been estimated from NMR spectra. [c] The salt contained ~10% of the betaine, as judged by NMR. [d] Characterized by conversion to the sulfonyl chloride. [e] The initially formed salt was converted directly to RSO_2Cl with Cl_2. [f] Substrate quantities refer to, and yields are based on, ethenesulfonate ester (**5**). [g] Axial betylate → equatorial sulfonyl chloride exclusively.

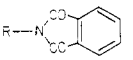
n = 3) or norbetylate (**13**, n = 3). By contrast, the reaction of the six-membered cyclic sulfonylammonium salt (**10**, n = 4, Z = CF_3SO_3) with 1-butanol in the presence of triethylamine gave only intractable material, but in the absence of the tertiary amine the alcohol reacted cleanly, though comparatively slowly, with **10** (n = 4, Z = CF_3SO_3) to give the norbetylate (**13**, n = 4, Z = CF_3SO_3), from which **11** (in solution) and **12** were readily made.

Reactions of [2]-, [3]-, and [4]Betylates with Added Nucleophiles. Tables I and II summarize the reactions of [2]-, [3]-, and [4]-betylates with added nucleophiles; a few additional reactions with their stereochemistry are also given in Table III. The range of alkyl groups listed includes a typical small primary group (butyl), large hydrophobic primary alkyl groups (hexadecyl and docosyl), a highly hindered primary system (neopentyl), and a typical secondary alkyl grouping (1-methylheptyl). Included also is a considerable array of anionic and neutral nucleophiles and solvent systems varying from water through one- and two-phase aqueous–organic systems to straight organic solvents. A number of points emerge on inspection of the results. (1) [2]- and [3]Betylates, and probably [4]betylates as well, react cleanly with a wide array of nucleophiles; (2) reaction conditions are mild and yields generally favorable; (3) even hydrophobic alkyl groups such as hexadecyl or docosyl are easily transferred in aqueous media; and (4) secondary systems give inversion of stereochemistry.

One clear limitation of [2]betylates is their tendency in basic medium (pH >6.5) or with basic reagents (e.g., EtO^-) to undergo Hofmann elimination to give back the ethenesulfonate ester (**5**). The reactions of hexadecyl [2]betylate with sodium acetate or hydrosulfide (Table I) illustrate this. The same reaction is presumed to be the first step in the reaction with sodium cyanide in water or sodium ethoxide in ethanol–benzene; this is followed by conjugate addition[10] to give the 2-cyano- and 2-ethoxyethanesulfonate esters, respectively. With comparatively slow reactions even very weak bases (or perhaps very small quantities of adventitious stronger base) serve to form the ethenesulfonate (**5**).

(10) For precedents, see: Distler, H. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 300–311.

Table II. Reaction of [3]Betylates (12, $n = 3$) and [4]Betylates (12, $n = 4$) with Added Nucleophiles

substrate R	substrate X	mmol	procedure[a]	reagent	conditions: medium (temp, °C, time)	isolated product	% yield[a]
				A. [3]Betylates			
ethyl	FSO_3^-	7.8	A	NaSCN	H_2O (25, 18 h)	RSCN	(66)
	FSO_3^-	3.3	C	potassium phthalimide	DMF (25, 6 h)		75
butyl	FSO_3^-	7.2	A	$Na_2S_2O_3$	H_2O (25, 18 h)	RSO_2Cl[b]	78
	FSO_3^-	1.1	B	imidazole	$CHCl_3$-H_2O (25, 17 h)		84
	FSO_3^-	1	C	BuLi	THF (−78, 2 h)		76
(±)-1-methylheptyl	FSO_3^-	1	B	NaSPh	$CHCl_3$-H_2O (25, 18 h)	RSPh	60
hexadecyl	FSO_3^-	0.5	B	NaN_3	CH_2Cl_2-H_2O (25, 24 h)	RN_3	100
	ClO_4^-	0.5	B	NaI	CH_2Cl_2-H_2O (25, 72 h)	RI	90
	ClO_4^-	0.5	B	NaSCN	$CHCl_3$-H_2O (25, 72 h)	RSCN	93
	FSO_3^-	0.5	B	NaSPh	PhH-H_2O (25, 18 h)	RSPh	85
	FSO_3^-	0.5	B	NaCN	PhH-H_2O (25, 72 h)	RCN	95
	FSO_3^-	0.5	B	NaBr	PhH-H_2O (25, 48 h)	RBr	95
	ClO_4^-	13	C	NaOEt	EtOH (25, 48 h)	ROEt	100
	FSO_3^-	2	C	$MeNH_2$	DME (25, 24 h)	$RNH_2Me^+Cl^-$[c]	60
				B. [4]Betylates			
butyl	FSO_3^-	0.5	A	NaSCN	H_2O (25, 72 H)	RSCN	(90)
hexadecyl	FSO_3^-	0.5	B	NaSCN	CH_2Cl_2-H_2O (25, 72 h)	RSCN	68[d]
	FSO_3^-	0.5	B	NaN_3	CH_2Cl_2-H_2O (25, 72 h)	RN_3	55[d]

[a] Procedures and yield description are as given in Table I, footnotes *a* and *b*. [b] The initially formed salt was converted to RSO_2Cl with Cl_2. [c] HCl added on workup. [d] Yield after removal of unreacted betylate.

This may arise because the elimination is a chain process, each reaction forming a new molecule of trimethylamine that can in turn induce elimination from another [2]betylate, and so on. An example is the reaction of neopentyl [2]betylate fluorosulfate with thiourea, followed by reaction of the product with chlorine in water. In addition to a low yield (5%) of the anticipated neopentanesulfonyl chloride, we observed a very small amount (1%) of neopentyl ethenesulfonate and a much larger quantity (30% yield) of a crystalline product, which was shown by independent synthesis to be **14**, and which probably arose via adduct **15**. The presence

$$\underset{\mathbf{14}}{Me_3CCH_2OSO_2CH_2CH_2SO_2Cl}$$

$$\underset{\mathbf{15}}{Me_3CCH_2OSO_2CH_2CH_2SC(=NH_2)NH_2^+FSO_3^-}$$

of added acid in a subsequent experiment completely inhibited the side reaction, and the sulfonyl chloride was obtained in what, for this compound, is a respectable yield (43%).[11]

The problems arising from the easy formation of ethenesulfonates (**5**) from [2]betylates are avoided by using [3]betylates. With basic nucleophiles such as ethoxide, thiophenoxide, and amines, the expected substitution products are formed cleanly, although with butyllithium 1,3 elimination takes place, giving the cyclopropanesulfonate ester (see Table II). The insertion of additional methylene groups between the Me_3N^+ substituent and the SO_2O grouping has the expected effect of lowering the reactivity of the esters, [3]betylates and [4]betylates hydrolyzing (in D_2O at 25 °C) respectively 10 and 20 times more slowly than [2]betylates. Under some circumstances, particularly with secondary alkyl derivatives, the slower hydrolysis of [3]betylates can confer a distinct advantage over [2]betylates. This may arise simply because the latter are readily hydrolyzed by atmospheric moisture and therefore require extra care in handling or because the lower selectivity which accompanies the greater reactivity of secondary alkyl [2]betylates restricts the range of possible reaction conditions. Compare, for example, the reactions of thiocyanate with the [2]- vs. [3]betylates in Table III.

(11) Neopentanesulfonyl chloride has been prepared from neopentyl chloride (21% yield) and neopentane (20% conversion): Scott, R. B., Jr.; McLeod, H. L. *J. Org. Chem.* **1956**, *21*, 388–390.

Betylates also react smoothly in organic solvents if the nucleophile is adequately soluble. It was found, for example, that the reaction of [2]betylates and [2]norbetylates with thiourea, as the first step in their conversion to the sulfonyl chloride, RSO_2Cl, was conveniently carried out in refluxing 1,2-dimethoxyethane (DME). Not only did the reaction go cleanly, but the betaine byproduct, which is essentially insoluble in this solvent, precipitates as it forms, making it easy both to follow the reaction and subsequently to remove the byproduct. Another useful feature appears in the reactions of such neutral nucleophiles as triphenylphosphine or the two thioethers in Table I. Like alkyl halides, tosylates, and so forth, the [2]betylates give the corresponding onium salts, but with the betylates the counterion of the product is not the leaving group from the alkylation but rather the original anion of the betylate. It is therefore particularly easy to select the counterion of the onium salt simply by picking the appropriate anion for the betylate. In the heterocyclic example in Table I, it is at least partly because of the lower solubility of the sulfonium perchlorate vis-à-vis the triflate that a distinctly higher yield (88% vs. 65%) of the recrystallized product was isolated.

Substrate–Reagent Ion-Pair (SRIP) Reactions. Synthetic Results. Of the reactions in nonpolar media, those involving substrate–reagent ion-pair (SRIP) reactions are of especial interest; these include all of the reactions in Table IV and half of those in Table III. The term SRIP reaction denotes a transformation in which the substrate and reagent constitute a salt; typically but not exclusively, the salt is preformed and the reaction induced by heating in a nonpolar solvent. With betylates these reactions are generally formulated as in eq 1 and are notable for the wide

$$\underset{\mathbf{1}\ (X = Nu)}{Nu^-ROSO_2(CH_2)_nNMe_3^+} \xrightarrow{\Delta} R\text{-}Nu + \underset{\mathbf{16}}{Me_3N^+(CH_2)_nSO_3^-} \quad (1)$$

array of nucleophiles which may participate. Not only are such normally reactive anions as cyanide, thiocyanate, azide, chloride, bromide, and iodide readily alkylated, but so also are fluoride, picrate, perchlorate, and sulfonates, including even triflate. Some of these are much better known as leaving groups or else as unreactive spectator anions, and yet their reactions as nucleophiles take place under fairly mild conditions to give clean products.

Table III. Stereochemistry of Reactions of (*R*)-1-Methylheptyl, Betylates (7 and 12) and Norbetylates (8 and 13)

substrate					product				
structure	mmol	optical purity,[a] %	nucleophile	reaction conditions	structure	% yield	[α],[b] deg (all +)	estimated[f] maximum [α], deg	estimated[h] % inversion
$ROSO_2CH_2CH_2NMe_3^+I^-$	8.8	93.5	(I^-)	PhH, 80 °C, 1.5 h	RI	71	45.8	47.87[c]	102
								48.6[i]	101
								49.7[j]	99
$ROSO_2CH_2CH_2NMe_3^+FSO_3^-$	20	94.4	$(NH_2)_2CS$ (0.1 mol)	DME, 75 °C, 2 h	$[RSC(NH_2)_2]^+FSO_3^-$	>70			~100[k]
	2.3	94.6	NaSCN(satd)	$H_2O:CH_2Cl_2$, 25 °C, 1 h	RSCN	53	61.6	64.7[d]	101
							81.0	85.1[m]	101
$ROSO_2CH_2CH_2NMe_3^+CH_2{=}CHSO_3^-$	15.5	93.4	($CH_2{=}CHSO_3^-$)	PhMe, 110 °C, 1 h	$ROSO_2CH{=}CH_2$	72	0.7	0.9	>89[n]
$ROSO_2CH_2CH_2NHMe_2^+Cl^-$	13.3	94.6	(Cl^-)	PhH, 80 °C, 0.5 h	RCl	85	34.4	36.15[c]	101
								37.4[i]	97
								37.1[j]	98
$ROSO_2CH_2CH_2NHMe_2^+Br^-$	8.7	93.5	(Br^-)	PhH, 80 °C, 1 h	RBr	90	38.6	40.64[c]	102
								40.3[i]	101
								41.3[j]	99
$ROSO_2CH_2CH_2NHMe_2^+OTs^-$	6.6	93.4	(OTs^-)	PhMe, 110 °C, 1 h	ROTs	68	6.3	7.0	96[o]
$ROSO_2CH_2CH_2CH_2NMe_3^+FSO_3^-$	21	94.6	NaSCN	$H_2O:CH_2Cl_2$, 25 °C, 15 h	RSCN	89	62.4	64.7[d]	102
							83.6	85.1[m]	104
$ROSO_2CH_2CH_2CH_2NMe_3^+FSO_3^-$	16.5	94.6	NaN_3	$H_2O:CH_2Cl_2$, 25 °C, 15 h	RN_3	85	44.2	45.4[p]	103
								48.1[q]	97
$ROSO_2CH_2CH_2CH_2NMe_3^+FSO_3^-$	20	94.6	NaI	$H_2O:CH_2Cl_2$, 25 °C, 15 h	RI	63	43.7	47.87[c]	96
								48.6[i]	95
								49.7[j]	94

[a] Different samples of (*R*)-(−)-2-octanol (Aldrich) showed slightly different rotations;[b] optical purities were estimated using $[\alpha]^{20}_D$ 9.93° for optically pure 2-octanol[c]. [b] Except as otherwise noted [α] values are $[\alpha]_D$ values determined on neat samples at 21–22 °C. The following densities were used to convert α to [α]: ROH, 0.8205;[c] RCl, 0.8655;[c] RBr, 1.1055;[c] RI, 1.3219;[c] RSCN, 0.919;[d] RN_3, 0.8555;[e] ROTs, 1.0227; $ROSO_2CH{=}CH_2$, 1.000. [c] Brauns, H. *Recl. Trav. Chim. Pays-Bas.* 1946, *65*, 799–806. [d] Rose, W. G.; Haller, H. L., *J. Am. Chem. Soc.* 1936, *58*, 2648–2649. Jackman, W. F. H.; Kenyon, J. *Ibid.* 1937, *59*, 2473. [e] Levene, P. A.; Rothen, A. *J. Chem. Phys.* 1937, *5*, 985–988. [f] Values reported by Brauns[c] were obtained from 2-octanol having $[\alpha]^{20}_D$ 9.93° and are quoted directly. Others are highest specific rotations from the source cited after correcting for the optical purity of the alcohol using $[\alpha]_D$ 9.93°[c] or $[\alpha]_{546}$ 11.8°,[g] and the above densities. [g] Kenyon, J. "Organic Syntheses"; Wiley: New York, 1944; Collect. Vol. I (2nd ed.), pp 418–421. [h] Estimated % inversion = [10⁴ ([α] of product)]/[(% optical purity of alcohol) (estimated maximum [α] of product)]. [i] Hoffmann, H. M. R. *J. Chem. Soc.* 1964, 1249–1251. [j] Hudson, H. R. *Synthesis* 1969, 112–119. [k] Reaction of the isothiuronium salt with aqueous Cl_2 gave (*S*)-(+)-2-octanesulfonyl chloride, $[\alpha]_D$ +3.1° (neat) and $[\alpha]_{546}$ +3.9° (abs EtOH, c 8.3), values slightly higher than those of previous workers.[l,m] Reduction of the sulfonyl chloride with $LiAlH_4$ gave (*S*)-(+)-2-octanethiol, $[\alpha]_{546}$ +35.7° (c 5.1, absolute EtOH), which in treatment with 2,4-dinitrofluorobenzene gave 1-methylheptyl 2,4-dinitrophenyl sulfide,[m,p] $[\alpha]_{546}$ −51.1° (c 5.7, $CHCl_3$). Reported values of $[\alpha]_{546}$ of +37.6° (*c* 5.05, absolute EtOH) and −52.45° (c 4.45, $CHCl_3$)[m] (from (+)-2-octanol with $[\alpha]_{546}$ +11.55°, neat) lead to "estimated % inversion" values of 98.5% and 101%, respectively. [l] Herbrandson, H. F.; Kelly, W. S.; Versnel, J. *J. Am. Chem. Soc.* 1958, *80*, 3301–3303. [m] Crani, D. J.; Trepka, R. D.; Janiak, P. S. *Ibid.* 1966, *88*, 2749–2759. [n] The low $[\alpha]_D$ values precluded accurate determination of % inversion directly. Conversion of the (*S*)-(+)-ethenesulfonate via the norbetylate gave (*R*)-(−)-bromooctane, $[\alpha]^{21}_D$ −34.5°; comparison with the (*S*)-(+)-2-bromooctane, $[\alpha]_D$ +38.6°, prepared directly (i.e., through the (*R*)-(−)ester) from the same sample of (*R*)-(−)-2-octanol leads to the estimate of 89% inversion in the conversion of the betylate to ethenesulfonate (see also text and Scheme III). [o] A sample of (*R*)-(−)-1-methylheptyl tosylate prepared directly from tosyl chloride and the same (*R*)-(−)-2-octanol showed $[\alpha]^{21}_D$ −6.5°. [p] Moss, R. A.; Schueler, P. E. *J. Am. Chem. Soc.* 1974, *96*, 5792–5798. [q] San Filippo, J.; Romano, L. J. *J. Org. Chem.* 1975, *40*, 1514–1515.

Octyl and hexadecyl perchlorates, for example, were formed by heating the [2]betylate perchlorates in toluene at reflux for 1.5 h. The betylate dissolved on warming and, after a short time, the betaine (**16**) started to precipitate; as with most of the reactions in Table IV, simple removal of the betaine by filtration or washing with water, followed by evaporation of the solvent, gave clean product in high yield.

Among the sulfonic esters formed by SRIP reactions are some not conveniently prepared in the standard manner from the sulfonyl chloride and alcohol with a tertiary amine. 2-Chloroethanesulfonic esters, for example, are not formed in this way from 2-chloroethanesulfonyl chloride, since, as has already been mentioned (see Scheme I), this gives a mixture of the ethenesulfonate and betylate.[12] The SRIP procedure, however, readily gave butyl 2-chloroethanesulfonate in good yield (see Table IV). Similarly, alkyl hydroxyalkanesulfonates (**17**), which are not generally accessible by any previously known route, may be seen from the examples in Table IV to be, with one exception, available by the SRIP method.[13] The esters of the simplest acid of the series, viz., hydroxymethanesulfonic acid, are the exception, the reaction having given only the alcohol. We think that the ester (**17**, n = 1) was in fact formed but then underwent fragmentation to the alcohol, SO_2, and formaldehyde.[14]

$$\underset{\mathbf{17}}{ROSO_2(CH_2)_nOH} \qquad \underset{\mathbf{18}}{RO(CH_2)_nSO_3H}$$

(12) 2-Chloroethanesulfonate esters have been prepared by reaction of the acid with chloroformate esters: Etienne, A.; Vincent, J.; Lonchambon, G. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1970**, *270*, 841–844.

(13) The preparation of butyl 2-hydroxyethanesulfonate in modest yield (30%) from 2-hydroxyethanesulfonyl chloride has recently been described: (a) King, J. F.; Hillhouse, J. H. *J. Chem. Soc., Chem. Commun.* **1981**, 295–296. The only other report of an alkyl hydroxyalkanesulfonate that we are aware of describes the preparation of ethyl 2-hydroxyethanesulfonate in low yield from silver 2-hydroxyethanesulfonate and ethyl iodide: (b) Stempnewsky, N. *Zh. Russ. Fiz.-Khim. O-va.* **1882**, *14*, 95–99. See also: *Ber.* **1882**, *15*, 947–948; *Chem. Zentralbl.* **1882**, *53*, 757.

(14) Such a fragmentation may conceivably take place by either a concerted 1,4 H shift formally analogous to the reaction $R^1R^2CHCR^3R^4SO_2Cl \rightarrow R^1R^2C{=}CR^3R^4 + SO_2 + HCl$, observed in flow-system thermolysis: (a) Geiseler, G.; Reinhardt, H. *Z. Phys. Chem.* (*Frankfurt am Main*), **1961**, *28*, 24–32; (b) King, J. F.; Harding, D. R. K. *J. Am. Chem. Soc.* **1976**, *98*, 3312–3316. Alternatively it could occur via an ionic process, e.g., $ROSO_2CH_2OH \rightarrow RO^- + SO_2 + CH_2{=}OH^+$, akin to those proposed for (i) the first step in the general acid catalyzed breakdown of ketone bisulfites and their *O*-alkyl analogues [(c) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 1228–1235] or (ii) the thermal decomposition of aryl diphenylmethanesulfonates [(d) King, J. F.; Aslam, M. *Can. J. Chem.* **1979**, *57*, 3278–3291].

The formation of the hydroxyalkanesulfonic esters (**17**, n = 2–5) was accompanied by a side reaction which was most fully investigated for the reaction of hexadecyl [2]betylate 4-hydroxy-1-butanesulfonate, $CH_3(CH_2)_{15}OSO_2(CH_2)_2NMe_3^+HO(CH_2)_4SO_3^-$. In addition to a 53% yield of ester (**17**, n = 4, R = hexadecyl), we observed significant amount (18%) of **18** (n = 4, R = hexadecyl), presumably arising from alkylation of the hydroxyl group instead of the sulfo anion.[15] The other alkoxyalkanesulfonic acids (**18**, n = 2, 3, and 5) have not been characterized, but the formation of emulsions on workup and the observation of a characteristic peak ascribable to **18** was taken as evidence for their presence. The yields of the alkoxyalkanesulfonic acids (**18**) (see Table IV) appear to be greatest when n = 3 or 4, suggesting that alkylation of the hydroxyl group is facilitated by an intramolecular interaction between the sulfo anion and the hydroxyl hydrogen[5d] (perhaps in both the starting material and the transition state). To obtain some idea of the relative nucleophilicities of hydroxyl vs. sulfo anion when they do not interact, it would seem better to look at the product ratios when n = 2 or 5, in which the roughly 10-fold greater yield of the ester (**17**) points to a 10-fold greater nucleophilicity of the sulfo anion.[16] Since intramolecular effects are by no means excluded even when n = 2 or 5, this factor of 10 must be regarded as a minimal value for the relative nucleophilicities of the sulfo anion vs. the hydroxyl group for bimolecular displacement of a sulfonate anion from a tetrahedral carbon in a nonpolar medium.

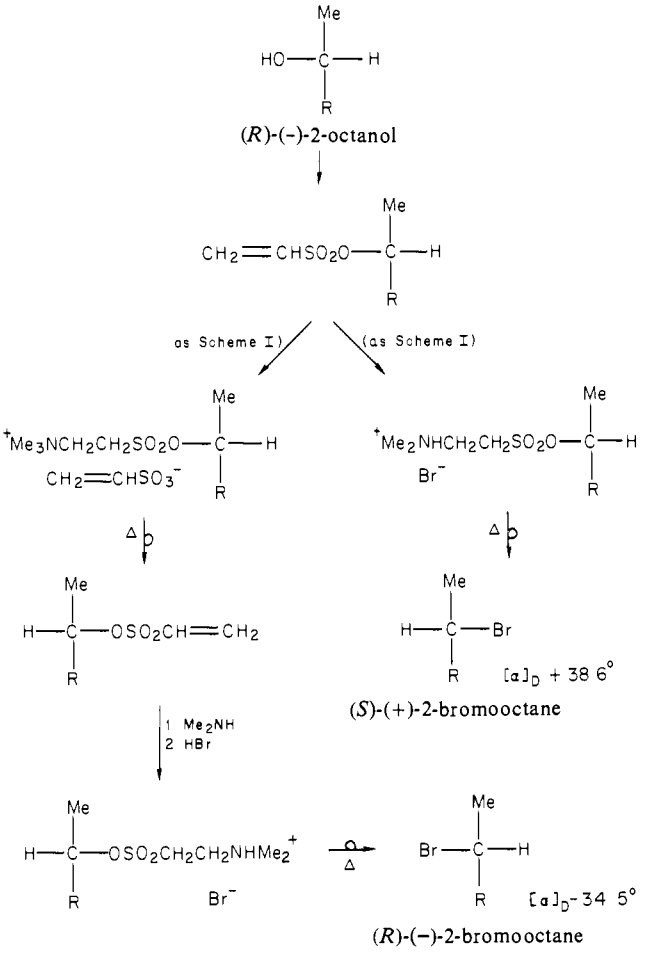
Returning to the reactions listed in Table IV, we note some unexpected products. The SRIP reaction of hexadecyl [2]betylate fluorosulfate gave no hexadecyl fluorosulfate[17] but only dihexadecyl sulfate in good yield. The latter compound probably arises from hydrolysis of the fluorosulfate anion to bisulfate,[18] and in agreement with this picture a sample of hexadecyl [2]betylate bisulfate gave dihexadecyl sulfate on heating. Presumably related is the SRIP reaction of hexadecyl [2]betylate methylsulfate, which gave mostly dihexadecyl sulfate, again, we suppose, by preliminary hydrolysis of the anion.

Also unexpected was the product formed in excellent yield on heating hexadecyl [2]betylate hexafluorophosphate (**1**, R = hexadecyl, X = PF_6). The exact mass established the molecular formula as $C_{32}H_{66}FO_3P$, which, in conjunction with ^{31}P and ^{19}F NMR absorption at −18.8 and −82.0 ppm, respectively, with J_{PF} = 978 Hz, $J_{PH} \sim 7$ Hz, a "quartet" in the ^1H NMR spectrum ($J \sim 7$ Hz) at 4.18 ppm, and appropriate absorption in the infrared, clearly shows the product to be dihexadecyl phosphorofluoridate[19] (**19**). Again we postulate initial hydrolysis of the

$$\underset{\textbf{1}\ (R = \text{hexadecyl},\ X = PF_6)}{CH_3(CH_2)_{15}OSO_2CH_2CH_2NMe_3^+PF_6^-} \xrightarrow[\text{toluene } (+H_2O)]{110\ ^\circ C} \underset{\textbf{19}}{CH_3(CH_2)_{15}OP(=O)F—O(CH_2)_{15}CH_3}$$

anion, in this case PF_6^-, which is essentially nonnucleophilic to carbon and stable to neutral and most basic conditions, but subject to acidic hydrolysis.[20] Monofluorophosphoric acid is evidently the most stable of the fluorophosphoric acids[20] formed by hydrolysis of PF_6^-, and the participation of a derived anion in a SRIP reaction with the betylate cation is not unreasonable.[21]

Scheme III



In the context of examining reactions of anions of low nucleophilicity we looked at those of hexadecyl [2]betylate fluoroborate and hexafluoroantimonate as well. The former was unchanged in refluxing benzene after 6 h but in refluxing toluene gave the betaine and a product that appeared from NMR and mass spectra to be a mixture of hexadecenes. The [2]betylate hexafluoroantimonate was quantitatively recovered after refluxing in toluene for 24 h, but gave a similar betaine–hexadecene mixture after 18 h in *m*-xylene at 130 °C; the greater stability of an "onium" hexafluoroantimonate over a fluoroborate has been reported in another connection.[22] Hexafluoroantimonate is thus the least reactive counteranion for [2]betylates that we have found, and hence for reactions with unreactive neutral nucleophiles the alkyl [2]betylate hexafluoroantimonate may be regarded as the betylate reagent of choice since it is the least likely to introduce byproducts derived from a competing SRIP reaction.

Another aspect of SRIP processes is shown by the experiments with chiral 1-methylheptyl betylates. As shown in Table III, high levels of inversion are found with these reactions. The 2-iodo- and 2-bromooctanes, which are formed in reasonable yields with complete inversion, are noteworthy because most routes give partly

(15) 4-(Hexadecyloxy)-1-butanesulfonic acid (**18**, n = 4, R = hexadecyl) was identified by independent synthesis and is easily detected by its ability to emulsify CH_2Cl_2–H_2O mixtures, a property not shown by the esters (**17**). The nonaqueous workup given in the Experimental Section avoids emulsions.

(16) Control experiments showed both the ester (**17**, n = 4) and the acid (**18**, n = 4) to be stable to the reaction conditions.

(17) Alkyl fluorosulfates are formed, however, in the reaction of alkyl *N*,*N*-dimethylsulfamates with methyl fluorosulfate, in which the product is believed to be formed by a SRIP reaction of the [0]betylate.[6]

(18) Jones, M. M.; Lockhart, W. L. *J. Inorg. Nucl. Chem.* **1968**, *30*, 1237–1243 and references cited therein.

(19) For comparison, see: (a) Schmutzler, R. *Adv. Fluorine Chem.* **1965**, *5*, 31–285, especially pp 251 and 264. (b) Daasch, L. W.; Smith, D. C. *Anal. Chem.* **1951**, *23*, 853–868.

(20) (a) Van Wazer, J. R. "Phosphorus and Its Compounds"; Interscience: New York, 1958; Vol. I, pp 805–817. (b) Toy, A. D. F. In "Comprehensive Inorganic Chemistry"; Bailar, J. C., Jr., Emeleus, H. J., Nyholm, R., Trotman-Dickenson, A. F., Eds.; Pergamon: Oxford, 1973; Vol. 2, pp 535–538.

(21) **Safety note**: Certain lower homologues of **19**, e.g. diisopropyl phosphorofluoridate, are highly toxic "nerve gases", and hence SRIP reactions of any lower alkyl betylate hexafluorophosphates should only be carried out with the appropriate stringent precautions: Saunders, B. C. "Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine"; Cambridge University Press: Cambridge, England, 1957, pp 42–86. Other "onium" hexafluorophosphates bearing displaceable small alkyl groups could conceivably also generate highly toxic dialkyl phosphorofluoridates under comparable conditions. Until further investigation dismisses this possibility, we suggest that due care be observed when heating such compounds.

(22) Wong, C. P.; Jackman, L. M.; Portman, R. G. *Tetrahedron Lett.* **1974**, 921–924.

Table IV. Substrate-Reagent Ion-Pair (SRIP) Reactions of [2]-, [3]-, and [4]Betylates and Norbetylates

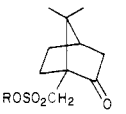
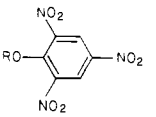
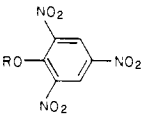
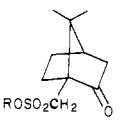
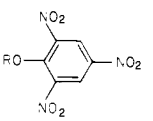
substrate					conditions, medium,		
cation	R	X^-	preparation[a]	mmol	(temp, °C, time)	product[b]	% yield[b]
$ROSO_2CH_2CH_2NMe_3^+$	neopentyl	I^-	A	30	DMF (110, 2 h)	RI	50
	octyl	ClO_4^-	B(1)	0.25	PhMe (110, 1.5 h)	$ROClO_3$	92
		I^-	B(2)	0.5	$CHCl_3$ (61, 0.25 h)	RI	70
		SCN^-	B(2)	0.5	$CHCl_3$ (61, 0.25 h)	RSCN	(90)
	hexadecyl	ClO_4^-	B(1)	0.2	PhMe (110, 1.5 h)	$ROClO_3$	100
		$CH_3SO_3^-$	A	0.4	PhMe (110, 1 h)	$ROSO_2CH_3$	74
		$CF_3SO_3^-$	A	0.2	PhMe (110, 2 h)	$ROSO_2CF_3$	67
		camphor-10-sulfonate	B(2)	2.6	PhH (80, 1.5 h)		80
		FSO_3^-	A	0.4	PhMe (110, 0.25 h)	$ROSO_2OR$	90
		$HOCH_2SO_3^-$	B(3)	2.0	PhMe (110, 2.5 h)	ROH	98
		$HO(CH_2)_2SO_3^-$	B(3)	2.5	PhH (80, 2.5 h)	$ROSO_2(CH_2)_2OH$[c]	(46)
						$(RO(CH_2)_2SO_3H)$	(5)
		$HO(CH_2)_3SO_3^-$	B(3)	1.4	PhH (80, 3 h)	$ROSO_2(CH_2)_3OH$[c]	(40)
						$(RO(CH_2)_3SO_3H)$	(27)
		$HO(CH_2)_4SO_3^-$	B(3)	0.9	PhH (80, 3 h)	$ROSO_2(CH_2)_4OH$[c]	(53)
						$RO(CH_2)_4SO_3H$	(18)
		SCN^-	B(2)	0.9	$CHCl_3$ (61, 0.5 h)	RSCN	77
		picrate	B(2)	0.8	PhMe (110, 1.5 h)		(46)
						$ROSO_2CH{=}CH_2$	(34)
		picrate	B(2)	2.0	PhMe, picric acid (trace) (110, 1.5 h)		99
		PF_6^-	B(2)	1.1	PhMe (110, 24 h)		98
		BF_4^-	A	1.0	PhH (80, 6 h)	no reaction	
		BF_4^-	A	1.0	PhMe (110, 12 h)	(hexadecene mixture)	(59)
		SbF_6^-	B(2)	0.4	PhMe (110, 24 h)	no reaction	
		SbF_6^-	B(2)	1.05	xylene (130, 18 h)	(hexadecene mixture)	(94)
$ROSO_2CH_2CH_2NHMe_2^+$	butyl	$HO(CH_2)_2SO_3^-$	C	7.0	PhMe (110, 1 h)	$ROSO_2(CH_2)_2OH$[c]	(55)
						$(RO(CH_2)_2SO_3H)$	(5)
		$Cl(CH_2)_2SO_3^-$	C	2.0	PhMe (110, 1 h)	$ROSO_2(CH_2)_2Cl$	80
	neopentyl	I^-	C	22	DMF (120-130, 2 h)	RI	68
		OTs^-	C	5	PhMe (110, 24 h)	ROTs	2
	hexadecyl	$HCOO^-$	C	3.3	HCOOH (80, 1 h)	ROCHO	94
		Cl^-	C	0.5	PhH (81, 0.5 h)	RCl	100
		I^-	C	0.5	PhH (81, 0.25 h)	RI	92
		camphor-10-sulfonate	C	2.6	PhMe (110, 6 h)		66
		$HO(CH_2)_2SO_3^-$	C	2.3	PhMe (110, 3 h)	$ROSO_2(CH_2)_2OH$[c]	(62)
						$(RO(CH_2)_2SO_3H)$	(6)
		$HO(CH_2)_5SO_3^-$	C	3.4	PhMe (110, 3 h)	$ROSO_2(CH_2)_5OH$[c]	(70)
						$(RO(CH_2)_5SO_3H)$	(7)
$ROSO_2CH_2CH_2CH_2NMe_3^+$	hexadecyl	Cl^-	B(3)	0.6	PhMe (110, 2 h)	RCl	95
		CN^-	B(3)	0.6	PhMe (110, 2.5 h)	RCN	(60)
		OAc^-	B(3)	4.0	PhH (80, 4 h)	ROAc	91
		F^-	B(3)	4.0	PhMe (110, 72 h)	RF	67
		SCN^-	B(2)	0.4	$CHCl_3$ (60, 18 h)	RSCN	92
		ClO_4^-	B(1)	0.4	PhMe (110, 4 h)	$ROClO_3$	32
		picrate	B(1)	0.65	PhMe (110, 3 h)		93
		FSO_3^-	A	0.5	PhMe (110, 2 h)	$ROSO_2OR$	85
		$MeOSO_3^-$	A	0.5	PhMe (110, 2 h)	$ROSO_2OR$	(70)
						$(ROSO_2OMe)$	(29)

Table IV (*Continued*)

substrate cation	R	X^-	preparation[a]	mmol	conditions, medium, (temp, °C, time)	product[b]	% yield[b]
$ROSO_2CH_2CH_2CH_2NHMe_2^+$	hexadecyl	Br^-	C	0.6	PhMe (110, 2 h)	RBr	70
$ROSO_2CH_2CH_2CH_2CH_2NMe_3^+$		FSO_3^-	A	0.7	PhMe (110, 8 h)	$ROSO_2OR$	88
$ROSO_2CH_2CH_2CH_2CH_2NHMe_3$		Br^-	C	0.5	PhMe (110, 8 h)	RBr	92
		Cl^-	C	0.5	PhMe (110, 8 h)	RCl	(90)

[a] Different methods were used to introduce the appropriate anion, X^-. (A) Direct introduction during methylation of 6 or 11 i.e. $X^- = FSO_3^-$, etc. by reaction with $MeOSO_2F$, etc. or $X^- = BF_4^-$ from reaction with $Me_3O^+BF_4^-$. (B) Ion exchange, either by (1) crystallization (e.g. addition of aqueous $NaClO_4$ or methanolic $HClO_4$ to a solution of the betylate fluorosulfate, followed by collection of the precipitated betylate perchlorate), (2) ion-pair extraction (e.g., CH_2Cl_2 solution of betylate fluorosulfate shaken with aqueous $NaSbF_6$, etc., followed by separation of the CH_2Cl_2 layer and evaporation of the solvent), (3) Ion exchange in methanolic solution with Rexyn 201 or 202. (C) Addition of HX directly to 6 or 11. [b] Yields without parentheses refer to isolated yields of products judged >98% pure by NMR and (or) IR spectra. Yields within parentheses have been estimated from NMR spectra. The nature of products shown within parentheses has been deduced from spectra of the crude product; these materials were not further characterized. [c] The composition of the product from the reaction of $HO(CH_2)_4SO_3^-$ was determined by direct comparison of its NMR spectrum with that of an authentic mixture of $ROSO_2(CH_2)_4OH$ and $RO(CH_2)_4SO_3H$. The presence of the alkoxyalkanesulfonic acid in the other products was adduced by the presence in the crude product of peaks not present in the pure ester, and reasonably ascribable to $RO(CH_2)_nSO_3H$.

racemized products. The usual methods of obtaining high purity samples of 2-bromo- and 2-iodooctane require considerable care and give poor yields;[23] recent work involving use of either alkali halides in high-boiling glycols or phase-transfer catalysts gave 2-iodooctane described as 30.6% and 1.7% optically pure, respectively.[24]

The SRIP reaction of (+)-1-methylheptyl [2]betylate ethenesulfonate considerably extends the synthetic range of this procedure. The product of this reaction is (−)-1-methylheptyl ethenesulfonate, the *enantiomer* of the precursor to the original betylate, which may in turn, of course, be easily transformed into the enantiomers of all of the products shown in Table III. In this way one enantiomer of 2-octanol may provide both the *R* and the *S* series of the listed compounds and their further transformation products. One such synthesis of both enantiomers, shown in Scheme III, led to the estimate that formation of (+)-1-methylheptyl ethenesulfonate proceeded with about 89% inversion.

The Norbetylate Route. Included in Tables III and IV are a number of reactions using the norbetylate (**2**) rather than the betylate (**1**). Since norbetylates are prepared simply by neutralizing the amino ester (**6** or **11**) with an acid, it is evident that the use of norbetylates can have particular advantages, either in simple convenience or by avoiding unwanted methylation somewhere else in the substrate. The norbetylate SRIP procedure is clearly usable whenever HNu is strong and Nu^- reasonably nucleophilic, as, for example, when Nu^- is a halide or sulfonate anion. Even when HNu is not a particularly strong acid, its use as the solvent works well; formates and acetates were formed just by heating the amino ester (**6**) in formic or acetic acid, respectively.

Comparison of the reaction of betylates and norbetylates indicates the norbetylate process to be slower (see Table IV), probably because of the lower reactivity of the nucleophile due to hydrogen bonding with the hydrogen of the Me_2NH^+ group.

Norbetylates may also be used in reactions with added nucleophiles, though the nucleophile should not be so basic as to deprotonate the ammonio function. The reaction of hexadecyl [2]norbetylate tosylate with sodium thiocyanate, for example, gave a 99% yield of hexadecyl thiocyanate. The preparation of sulfonyl chlorides via isothiuronium salts formed from norbetylates appears to proceed well. Using the same procedure as that used in the corresponding betylate reaction listed in Table I, we obtained 3-phenylpropanesulfonyl and 1-hexadecanesulfonyl chlorides in, respectively, 61% and 86% yields from the ethenesulfonate esters (**5**) or 50% and 83% yields from the alcohols. We have had occasion to prepare a number of sulfonyl chlorides for other studies in this laboratory, and in our view the norbetylate route shows every sign of being the method of choice for the laboratory scale conversion of a primary or secondary alcohol to the corresponding sulfonyl chloride.

Stoichiometric Phase Transfer. Many of the most notable transformations listed in Tables I–IV involve reaction of either an organic substrate in water or of a hydrophilic nucleophile in an organic phase, and hence may be regarded as phase-transfer reactions. Since a molecule of the phase transfer agent is consumed in each reaction, the process is not catalytic but stoichiometric, and we therefore apply the term "stoichiometric phase transfer" (stoichiometric PT) to such reactions; depending on where the reaction takes place, we use the terms "substrate phase transfer" (for a reaction in the aqueous phase after transfer of the substrate from an organic or solid phase) and "reagent phase transfer" (for a reaction in the organic phase after transfer of the reagent from an aqueous or solid phase).[25] Solid–liquid substrate PT is illustrated by the "procedure A" reactions in Tables I and II. Liquid–liquid substrate PT and reagent PT are not always readily distinguished experimentally, though we point to likely examples of each in the discussion of the "procedure B" reactions (Tables I and II) later in this section. Substrate–reagent ion-pair (SRIP) reactions may be regarded as a form of solid–liquid stoichiometric reagent PT reaction; further mechanistic discussion of SRIP reactions is given in the next section. Stoichiometric reagent phase-transfer processes are not new,[26] though they would seem to have been overshadowed by phase-transfer catalysis (or "catalytic reagent phase transfer") reactions. Aside from our preliminary report,[5a] substrate PT processes do not appear to have been discussed previously.

Stoichiometric substrate PT has three logically distinct steps: (i) attachment of a hydrophilic group to the substrate, (ii) reaction in an aqueous medium, and (iii) removal of the hydrophilic group. We may illustrate the actual operation of the method with the example of hexadecyl [2]betylate with aqueous sodium azide (see Table I). Conversion of 1-hexadecanol into the betylate (**7**) represents step i, while subsequent dissolution or dispersion in water (the actual phase transfer) followed by reaction with azide ion constitutes steps ii and iii. As this example shows, substrate PT need not be as clumsy as it may appear at first glance, since the individual steps of substrate PT may be combined with one another or with other useful operations. The formation of the betylate not only adds the hydrophilic Me_3N^+ group (step i of substrate PT) but also converts the hydroxyl function into a suitably nucleofugal group—a necessary step in any event. In addition, in this example the actual reaction and the removal of the hydrophilic

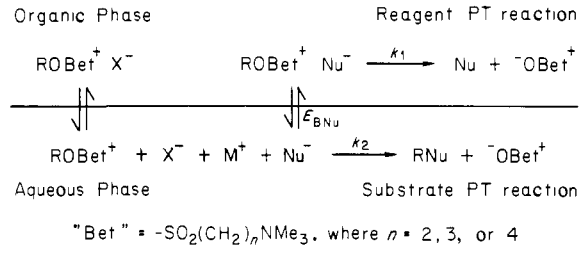
(23) (a) Hudson, H. R. *Synthesis* **1969**, 112–119. Reaction of (+)-1-methylheptyl tosylate with MgI_2 in ether apparently gives 2-iodooctane with high optical purity, though we are unable to ascertain the % inversion in this reaction from the data given: (b) Place, P.; Roumestant, M. L.; Gore, J. *Bull. Soc. Chim. Fr.* **1976**, 169–176.

(24) (a) San Filippo, J.; Romano, L. J. *J. Org. Chem.* **1975**, *40*, 1514–1515. (b) Landini, D.; Quici, S.; Rolla, F. *Synthesis* **1975**, 430–431.

(25) Possible confusion as to which reactant is the "substrate" and which the "reagent" is easily resolved with S_N reactions by defining the nucleophile as the reagent.

(26) See, for example: Brändström, A.; Junggren, U. *Acta Chem. Scand.* **1969**, *23*, 2203–2204. See also: Brändström, A. "Preparative Ion Pair Extraction"; Apotekarsocieteten: Stockholm, 1974.

Scheme IV



"Bet" = $-SO_2(CH_2)_nNMe_3$, where n = 2, 3, or 4

group (steps ii and iii) occur at the same time.

The power of the substrate PT tactic is shown by comparison of the reactions of hexadecyl [2]betylate, mesylate, and 2,2,2-trifluoroethanesulfonate ("tresylate").[1h] Whereas the [2]betylate gave respectively 88% and 90% yields of hexadecyl azide on stirring with 0.25 M and saturated aqueous sodium azide at room temperature for 4 h, the tresylate showed only about 25% reaction after 28-h stirring with 0.5 M sodium azide, and the mesylate showed no sign of any reaction even after 16 days; the tresylate reaction appeared complete after 15 days. These differences are not attributed to any remarkable differences in nucleofugality since hydrolysis of butyl [2]betylate at 35 °C is only 16 times faster than that of butyl mesylate,[27] and tresylates are reported to be many times more reactive than mesylates.[1h] It seems likely that substrate PT is responsible for much of the comparative ease of the "procedure A" reactions[28] in Tables I and II.

Whereas in "procedure A" reactions the phase transfer is from the solid to the liquid phase, "procedure B" processes, on the other hand, use a mixture of water and an immiscible organic solvent. In addition to a substrate PT reaction between substrate and nucleophile in the aqueous phase, it is also quite possible when the nucleophile is an anion, for the anion simply to associate with the substrate, migrate to the organic phase, and react there. This is, of course, reagent PT, and is shown in Scheme IV along with the corresponding substrate PT reaction. One may readily show on the basis of Scheme IV that the ratio of reagent PT product to substrate PT product is given by (2), where k_1 and k_2 are defined

$$\frac{\text{reagent PT product}}{\text{substrate PT product}} = \frac{E_{BNu}k_1}{k_2} \qquad (2)$$

in Scheme IV, and E_{BNu} is the stoichiometric extraction constant[2d] defined by (3), in which the concentration terms refer to the ion

$$E_{BNu} = [ROBet^+Nu^-]_{org}/[ROBet^+]_{aq}[Nu^-]_{aq} \qquad (3)$$

pair in the organic phase and the dissociated ions in the aqueous phase. From eq 2 it is evident that the ratio of substrate PT to reagent PT product is independent of such factors as the nature of X^- or the total concentration of Nu^- and depends only on structure- and medium-dependent constants. The ratio k_1/k_2 will be generally greater than 1, but the value of the extraction constants, E_{BNu}, may vary widely depending on both R and Nu^-. Octyl [2]betylate fluorosulfate, for example, on shaking with equal volumes of $CDCl_3$ and D_2O appears almost entirely in the aqueous phase, whereas with either the perchlorate or thiocyanate anions the octyl [2]betylate is extracted into the organic phase. As would be expected hexadecyl [2]betylate, even with the fluorosulfate anions, is found entirely in the organic layer, and butyl [2]betylate completely in the aqueous phase. The following experiment is in accord with a reagent PT reaction of those betylates, such as octyl [2]betylate thiocyanate, for which the extraction coefficient, E_{BNu}, is clearly greater than 1. Octyl [2]betylate fluorosulfate was stirred with potassium thiocyanate in $CHCl_3$–H_2O for 15 min and the $CHCl_3$ layer separated; after 15-min reflux, octyl thiocyanate was obtained from the latter in ~90% yield. A parallel experiment in which the mixture was refluxed for 15 min without separation of the layers gave a similar yield of octyl thiocyanate.

In contrast to the two-phase reactions with anionic nucleophiles (at least with the larger alkyl groups), reaction with a neutral nucleophile would appear to be a substrate PT process. Hexadecyl [2]betylate fluorosulfate on stirring for 1 h with thiourea in benzene–water at 25 °C gave the isothiuronium salt in 75% yield. By contrast, neither hexadecyl tresylate after 6 days nor the mesylate after 19 days showed any sign of reaction at all; the tresylate after 19 days was perhaps 25% converted to the salt. In our view the simplest explanation for the much more rapid reaction of the betylate is substrate PT; that is, with the betylate the hydrophilic character imparted by the ammonio grouping leads to the presence in the aqueous phase of enough of the betylate to give ready reaction. Hexadecyl [2]betylate is, however, a surface-active compound, and the possibility that the reaction takes place in micelles (with catalysis thereby), or in water pools in reverse micelles, or at the liquid–liquid interface is not easily dismissed.

From the point of view of synthetic application, however, the question of whether these reactions occur by substrate phase transfer, reagent phase transfer, or yet another process is less important than their usefulness. In addition to the above example of the easy reaction of thiourea with the betylate, we may point to similar facile reaction with anionic nucleophiles as well. Hexadecyl [2]betylate fluorosulfate on stirring with a mixture of benzene–0.5 M aqueous sodium azide for 2.5 h gave hexadecyl azide in 82% yield; similarly hexadecyl [3]betylate fluorosulfate with CH_2Cl_2–1 M NaN_3 in water for 24 h gave a quantitative yield of the azide. Hexadecyl tresylate, on the other hand, even after stirring for 19 days with benzene–1 M aqueous NaN_3, showed virtually no reaction (i.e., <5%).

It is evident that the phase-transfer reactions summarized above are related to the well-known Starks mechanism[31] for phase-transfer catalysis (PTC). The important difference is that the product-forming reaction in PTC regenerates a new molecule of phase-transfer agent, whereas with the stoichiometric PT reactions described here, one molecule of the PT agent is consumed with each individual reaction. Our experience with betylates in one- or two-phase aqueous media has been that the phase transfer has always worked, in the sense that there has been an increase in rate over that, say, of a mesylate or tresylate. The stoichiometric PT reactions may thus lack the elegance and economy that distinguish the most successful examples of PTC, but they would appear to have a dependability which may well prove useful.[32]

SRIP Reactions. Mechanistic Aspects. We suggest that the speed, completeness, and stereoselectivity of SRIP reactions of

(27) Measurement of the rate of hydrolysis of butyl [2]betylate methylsulfate (7, R = Bu, X = $MeOSO_3$) at 35.0 °C (pH 4.0, pH-stat) gave k_{obsd} = 1.8 × 10^{-4} s^{-1}; a rate constant of 1.13 × 10^{-5} s^{-1} for hydrolysis of butyl mesylate may be estimated from the data of Barnard and Robertson [Barnard, P. W. C.; Robertson, R. E. *Can. J. Chem.* **1961**, *39*, 881–888].

(28) Given the high likelihood that the larger betylates form micelles in aqueous medium, the possibility arises that the faster reaction of betylates vs. tresylates and mesylates derives from micellar catalysis,[29] rather than (or in addition to) the simple substrate PT effect of having the substrate and reagent in the aqueous phase so that an otherwise uncatalyzed reaction may occur. Though we see little reason to invoke micellar catalysis, we have found signs of micellar *inhibition* in a reaction of hexadecyl [2]betylate fluorosulfate. Whereas its reaction with NaSCN is essentially complete in 2 h (see Table I), the corresponding reaction with $Na_2S_2O_3$ in water is scarcely 50% complete in that time. Butyl [2]betylate, which is presumably in true solution, reacts readily with both reagents (Table I), but, as expected from its greater nucleophilicity in protic media,[30] thiosulfate reacts more rapidly than thiocyanate. These observations fit nicely with the idea of mixed cationic–anionic micelles proposed by Sukenik and Bergman[4b] to explain inhibition of solvolysis of amsylates by sodium lauryl sulfate and sodium dodecanoate. The mixed micelles in the present study would consist of betylate cation and the alkyl thiosulfate anion produced by the reaction; such mixed micelle formation would be maximal at 50% reaction. Except, however, for reactions which give anionic products, the transformations with hexadecyl compounds are not very different from the corresponding reactions of butyl betylates, suggesting, as has been noted by Sukenik and Bergman with amsylates, that micelle formation in itself does not influence these reactions unduly.

(29) See, for example: (a) Cordes, E. H.; Ed. "Reaction Kinetics in Micelles"; Plenum Press: New York, 1973. (b) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975.

(30) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141–147.

(31) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.

(32) Cf.: Aesop. "The Hare and the Tortoise". In "Aesop's Fables"; James, T., Ed.; John Murray: London, 1848; pp 39–40.

betylates arise from the combined effect of three distinct phenomena, (a) poor solvation of anions in the solvents used, (b) the insolubility of the betaine, and (c) ion pairing (or higher aggregation) of the starting materials. The high reactivity of poorly solvated anions, known also by the picturesque tag "naked" anions,[33] has been well established for systems involving dipolar aprotic solvents, crown ether complexes, and onium salts in nonpolar media. With betylate reactions in benzene and toluene the reactivity is also consistent with considerable anionic nudity.

The very low solubility of the betaines in nonpolar media is almost certainly a factor in driving the reactions with such nucleophiles as perchlorate or triflate to the extent observed. The sulfo anion in [2]-, [3]-, and [4]betylates may be alkylated by dimethyl and diethyl sulfates in the refluxing alkylating agent.[4a] There is thus good reason to believe that the nucleophilicity of the betaine *in solution* is probably "normal", i.e., may be expected from simple consideration of field effects to be greater than that of the triflate. If there were no perturbation of the equilibrium by the insolubility of the betaine, the product would then be expected to consist mostly of unreacted betylate triflate salt. This aspect of SRIP reactions of betylates invites comparison with silver salt–alkyl halide alkylations, which are presumably driven to completion by the insolubility of the silver halide. Betylate reactions in nonpolar media normally require higher temperatures than the silver salt process, but the betylate method is not only cheaper, it is frequently simpler owing to the easy removal of the betaine by either filtration or washing with water.

Ion pairs are the principal species present in dilute solutions of salts in nonpolar media[34] (with larger aggregates becoming important with increasing concentration). A SRIP reaction under conditions of ion-pair formation would be expected (a) to be kinetically first order and (b) to go faster than an otherwise similar bimolecular reaction. The latter point follows from the reasonable expectation that the lower entropy of the ion-paired state relative to dissociated species would result in a smaller entropy loss on going from starting material to transition state and thus a faster reaction rate than, for example, the reaction with the same anion (paired to an inert cation) with a comparable neutral substrate in the same medium. Though first (and lower) order behavior[35] of SRIP reactions has been reported, direct experimental confirmation of the second point does not seem to be available; the observed high optical purity of the 2-iodooctane, however, is nicely consistent with such a picture. It would seem likely from the extensive racemization found in the phase transfer catalyzed and the alkali iodide in tetraethylene glycol reactions mentioned above[24] that in these systems the rate of the reaction of the iodide ion with the 2-iodooctane is comparable to the rate of its reaction with the starting material. That the 1-methylheptyl [2]betylate iodide forms 2-iodooctane unaccompanied by any significant reaction of the betylate ion pair with the product is most simply explained in our view by the increased rate of the SRIP process by reason of the less negative $\Delta S^{\ddagger}$ postulated here. The magnitude of the proposed effect is not known, but even an entropy change of 10 cal K^{-1} mol^{-1}, which is in the lower part of the range found for formation of hydrogen-bonded or charge-transfer complexes in solution,[36] would lead to a sufficient (roughly 100-fold) rate enhancement to account for the observed stereoselectivity. Another quite separate factor, of course, that may also inhibit racemization of the product is the simple fact that the SRIP reaction has, by its nature, only the stoichiometric amount of the anion present.

SRIP reactions are not, of course, unique to betylates; their history goes back well over a century to the Hofmann elimination of quaternary ammonium hydroxides[37] and may very well just be getting started. In our opinion the SRIP procedure is a *general* method which may help any reaction involving an ionic species. The method is basically simple: just make the other reactant the counterion of the original ionic reactant and go on from there. The advantages are (a) this can enable the reaction to be carried out in nonpolar medium (with the advantages already described) and (b) exactly stoichiometric quantities are obtained automatically, which may be not only convenient but also useful in inhibiting side reactions. On the negative side, the two neutral products (most commonly formed if both cation and anion are monovalent) may be a nuisance to separate. In the reactions of betylates, however, the neutral byproduct is a betaine, the properties of which lead to easy separation from most products.

Summary

In this study we have looked at the consequences of attaching an ammonio group to the sulfonic acid part of an alkyl alkanesulfonate. We have found [2]betylates and [2]norbetylates to be uncommonly versatile intermediates for the efficient conversion of alcohols into a host of other derivatives by way of nucleophilic substitution reactions, and we particularly commend their use to synthetic chemists for laboratory scale applications. Typically, the reaction sequence may be carried out reasonably quickly and under mild conditions; commercially available reagents and a wide range of solvents and nucleophiles may be used, and product and byproduct are readily separated. With the preparation of alkyl hydroxyalkanesulfonates, we have found a way to a class of compounds hitherto virtually unknown and inaccessible. High stereoselectivity and fair yields or better were found in substitutions with halogen, nitrogen, sulfur, and oxygen nucleophiles attacking a typical secondary alkyl system.

In comparison with the more familiar—and in many ways similar—mesylates and tosylates, betylates are perhaps somewhat more reactive to added nucleophiles in polar organic or homogeneous aqueous–organic media, but their real merits appear in reactions in wholly or partly aqueous systems and in SRIP reactions in nonpolar media; these have simply no parallel with tosylates and mesylates or even triflates. The preparation of betylates requires more experimental operations than that of mesylates and tosylates, though [2]betylates and [2]norbetylates can be made in considerably less time than that recommended in the standard tosylate preparation.[41] The final step in the betylate preparation is a methylation, and although the reaction is readily carried out with dimethyl sulfate, or even more easily with methyl fluorosulfate or triflate,[42] such treatment may be inappropriate for some substances.

The main limitation in the use of [2]betylates and [2]norbetylates is their incompatibility with basic reagents. [3]Betylates work well with bases, but their preparation is at present more laborious, requiring six or seven steps from materials currently available commercially; our limited study of [4]betylates indicates them to have basically the same sins and virtues.

(33) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250–2252.

(34) See, for example: Szwarc, M. In "Ions and Ion Pairs in Organic Reactions"; M. Szwarc, Ed.; Wiley-Interscience: New York, 1972; Chapter 1, pp 1–26.

(35) (a) Beringer, F. M.; Geering, E. J.; Kuntz, I.; Mausner, M. *J. Phys. Chem.* **1956**, *60*, 141–150. (b) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 1218–1223. (c) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 4853–4858. (d) Landiou, D.; Maia, A.; Montanari, F.; Mikolajczyk, M.; Zatorski, A. *Nouv. J. Chim.* **1980**, *4*, 723–725.

(36) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Orgaic Reactions"; Wiley: New York, 1963; pp 52–53. Arnett, E. M.; Joris, L.; Mitchell, E.; Murty, T. S. S. R.; Gorrie, T. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 2365–2377.

(37) Other likely examples: (i) displacement reactions of quaternary ammonium salts[38] and the analogous transformations of sulfonium salts,[39] (ii) the Schiemann synthesis of fluoroarenes from arenediazonium fluoroborates,[40] (iii) the cleavage of diaryliodonium salts,[35a] and (iv) the numerous alkylation reactions of alkoxyphosphonium salts,[1a–d] including the second step of the Arbusov–Michaelis reaction. Noteworthy in the last category is the remarkable formation of neopentyl chloride from tetraneopentyloxyphosphonium chloride in chloroform at 25 °C: Denney, D. B.; Relles, H. M. *Tetrahedron Lett.* **1974**, 573–577.

(38) See, for example: Smith, P. A. S. "Open-Chain Nitrogen Compounds"; W. A. Benjamin: New York, 1965; Vol. 1, pp 52–58.

(39) Stirling, C. J. M. In "Organic Chemistry of Sulfur"; Oae, S.; Ed.; Plenum Press: New York, 1977; especially pp 492–493, 498.

(40) Roe, A. *Org. React.* **1949**, *5*, 193–228.

(41) Schleyer, P. v. R. cited in: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1968; Vol. 1, pp 1180–1181.

(42) **Safety note**: Because of the acute toxicity and probable carcinogenic properties of these and other strong alkylating agents, due care should be exercised with these materials: (a) van dem Ham, D. M. W.; van der Meer, D. *Chem. Br.* **1976**, 362. (b) *Org. Synth.* **1976**, *56*, 127–8; **1978**, *58*, 168.

On a broader level we wish to stress the general applicability of stoichiometric PT reactions of all kinds. The reactions in one- and two-phase aqueous media are efficient and dependable processes with betylates, and should be so with other systems as well. SRIP reactions, as observed with betylates, show reactivity and stereoselectivity which in some cases appear to be unique, the closest parallel being with silver salt reactions and PT processes catalyzed by crown ethers and related materials. SRIP reactions, in our view, warrant immediate inclusion as a standard method in chemical synthesis.

Experimental Section

Instruments. IR: Beckman IR 4520 or Perkin-Elmer 621, in $CHCl_3$ with 0.1-mm NaCl or KBr cells unless otherwise specified. NMR: Varian T-60 or XL-100, with all chemical shifts from the latter unless otherwise noted and expressed in ppm downfield from Me_4Si (^1H and ^{13}C), $CFCl_3$ (^{19}F), and $(MeO)_3PO$ (^{31}P spectra). MS: Varian MAT 311A. Mp: Kofler hot stage (uncorrected). Refractive indices: Bausch and Lomb Abbé refractometer. [α]: Rudolph Model 80 polarimeter (Na or Hg source).

Solvents. Benzene, toluene, and 1,2-dimethoxyethane were dried by distillation from CaH_2, and acetonitrile by distillation over P_2O_5, and stored over molecular sieves (Fisher 3 Å grade 564, 8–12 mesh). All other solvents were reagent grade unless otherwise specified. Ethenesulfonyl chloride was made from 2-chloroethanesulfonyl chloride which was obtained from sodium 2-hydroxyethanesulfonate (isethionic acid, sodium salt, Eastman) by reaction with thionyl chloride and dimethylformamide.[43] Other reagents (or their conjugate acids) were commercial materials, except for axial *trans*-2-decalol,[44] sodium *N,N*-dimethyldithiocarbamate,[45] and 1,3-dihydrobenzo[*c*]thiophene;[46] 3-hydroxy-1-propanesulfonic and 4-hydroxy-1-butanesulfonic acids were prepared by hydrolysis of the appropriate sultones,[47] and 5-hydroxy-1-pentanesulfonic acid by the method of Kharasch et al.,[48] followed by ion exchange (Rexyn 101 H^+ form); methyl methanesulfonate was made from methanesulfonyl chloride, methanol, and triethylamine.[49]

Methylene chloride and ether extracts were dried over anhydrous $MgSO_4$. Solvents were evaporated under reduced pressure using a rotary evaporator connected to a water aspirator. "Short path distillation" refers to a distillation using a cold finger sublimation apparatus with two wells (each 2 cm long, 1 cm wide) in the bottom, one for use as the still pot and the other as the receiver; the cold finger was arranged to allow the liquid to drip directly into the receiving well. The distance between the tip of the cold finger and the lowest portion of the liquid being distilled was 3 cm.

Preparation of Alkyl Ethenesulfonates (5) from 2-Chloroethanesulfonyl Chloride. The alcohol (0.02–0.11 mol) was dissolved in methylene chloride (100–200 mL), 2-chloroethanesulfonyl chloride (2.0–2.5 equiv) added, and the mixture cooled in ice. Ice-cold trimethylamine (~3–4 equiv) was added to the stirred reaction mixture either directly or through a special addition funnel (equipped with a surrounding dish that can be filled with dry ice–acetone mixture to cool the trimethylamine). After 0.5 h the mixture was worked up by washing with cold 10% aqueous Na_2CO_3 (3 × 100 mL) and water (100 mL). Drying of the CH_2Cl_2 layer was followed by evaporation of the solvent; the product, unless otherwise indicated, was used without further purification. An illustrative example follows.

Butyl Ethenesulfonate (5, R = Butyl). Trimethylamine (~15–16 mL) with 1-butanol (5.0 g, 0.067 mol) and 2-chloroethanesulfonyl chloride (22.9 g, 0.14 mol) in methylene chloride (150 mL) as above gave butyl ethenesulfonate (8.5 g, 77% yield). Distillation of a small sample for analysis gave a colorless liquid: bp 51 °C (0.02 torr); ^1H NMR δ 6.74–6.15 (ABC multiplet, 3 H; computer simulation consistent with δ_A 6.55, δ_B 6.38, δ_C 6.15, J_{AC} 16.2 Hz, J_{AB} 10 Hz, and J_{BC} −0.5 Hz), 4.12 (t, 2 H), 1.6 (m, 4 H), 0.93 (t, 3 H); IR (neat) ν_{max} 1615 (w), 1465 (m), 1360 (vs), 1170 (vs), 1150 (m), 940 (vs), 882 (s) cm^{-1}. Anal. Calcd for $C_6H_{12}O_3S$: C, 43.88; H, 7.36; S, 19.53. Found: C, 43.69; H, 7.51; S, 19.41. The following were made similarly; the vinyl group showed in each case an ABC multiplet similar to that found with butyl ester. **2,2-Dimethylpropyl ethenesulfonate** (**5**, R = neopentyl): bp 62 °C (0.02 torr); 88% yield; ^1H NMR δ 6.74–6.1 (ABC m, 3 H), 3.77 (s, 2 H), 0.98 (s, 9 H); IR (neat) ν_{max} 1615 (w), 1472 (s), 1362 (vs), 1262 (m), 1172 (vs), 965 (vs) cm^{-1}. Anal. Calcd for $C_7H_{14}O_3S$: C, 47.17; H, 7.92; S, 17.99. Found: C, 47.23; H, 8.01; S, 18.12. ***R*-(−)-1-Methylheptyl ethenesulfonate** (**5**, R = (*R*)-1-methylheptyl): (from (*R*)-(−)-2-octanol, $[\alpha]^{21}_D$ −9.3°) 95% yield; after short-path distillation (0.001 torr, bath 75 °C) d^{21} 1.000, $[\alpha]_D$ −0.9° (neat); ^1H NMR δ 6.72–6.02 (ABC m, 3 H), 4.66 (m, 1 H), 1.62 (m, 2 H), 1.40 (d, 3 H), 1.31 (br s, 8 H), 0.88 (t, 3 H); IR (neat) ν_{max} 1612 (w), 1465 (s), 1360 (vs), 1170 (vs), 1112 (m), 970 (s), 802 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15; S, 14.55. Found: C, 54.39; H, 9.06; S, 14.38. **(±)-1-Methylheptyl ethenesulfonate** (**5**, R = 1-methylheptyl): 87% yield. **3-Phenylpropyl ethenesulfonate** (**5**, R = 3-phenylpropyl): liquid, 80.5% yield; ^1H NMR δ 7.18 (s, 5 H) 6.7–5.9 (ABC m, 3 H), 4.08 (t, 2 H), 2.7 (t, 2 H), 2.02 (m, 2 H); IR (neat) ν_{max} 1602 (m), 1495 (s), 1452 (s), 1358 (vs), 1168 (vs), 1085 (w), 922 (s) cm^{-1}; calcd M^+ for $C_{11}H_{14}O_3S$, 266.0664; found, 226.0668. **Hexadecyl ethenesulfonate** (**5**, R = hexadecyl): 96% yield, white crystals (from hexanes); mp 32–33 °C; ^1H NMR δ 6.7–6.0 (ABC m, 3 H), 4.12 (t, 2 H), 1.72 (m, 2 H), 1.3 (br s, 26 H), 0.88 (t, 3 H); IR ν_{max} 1388 (m), 1362 (vs), 1168 (vs), 950 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{36}O_3S$: C, 65.01; H, 10.91; S, 9.64. Found: C, 65.20; H, 11.07; S, 9.48. **Docosyl ethenesulfonate** (**5**, R = docosyl): 87% yield. **2-(2α,4aβ,8aα-Decahydro)naphthalenyl ethenesulfonate** (**5**, R = axial *trans*-2-decalyl): 94% yield. **3-Butenyl ethenesulfonate**: >75% yield.

Preparation of Alkyl Ethenesulfonates (5) from Ethenesulfonyl Chloride. Hexadecyl ethenesulfonate (5, R = hexadecyl). To an ice-cooled solution of ethenesulfonyl chloride (13.7 g, 0.11 mol) and 1-hexadecanol (17.5 g, 0.07 mol) in CH_2Cl_2 (125 mL) was added trimethylamine (~25 mL) at such a rate that the mixture just did not boil. After stirring for 10 min the mixture was shaken with concentrated aqueous Na_2CO_3 (125 mL); an emulsion formed that was separated by addition of water. The CH_2Cl_2 layer was evaporated to give a white solid (22.3 g, 93%), which was dissolved in benzene and shaken gently with silica gel (3 g); filtration and evaporation gave hexadecyl ethenesulfonate (21.9 g, 92%), identical in ^1H NMR and IR spectra with that prepared as above. Similarly prepared were **octyl ethenesulfonate** (92% yield) and **docosyl ethenesulfonate** (88% yield).

[2]Betylates. General Procedure. Dimethylamine (5- to 10-fold excess) was added to an ice-cooled, stirred solution of the ethenesulfonate in CH_2Cl_2. After 10 min the solvent and excess Me_2NH were evaporated. The alkyl 2-(dimethylamino)ethanesulfonate (**6**) so obtained is converted directly to the betylate (to avoid isomerization to the betaine, $RMe_2N^+CH_2CH_2SO_3^-$) by treating a CH_2Cl_2 solution with the alkylating agent[42] (1.0–1.1 equiv) for an appropriate period: methyl triflate or methyl fluorosulfate, 15 min; dimethyl sulfate, 30 min; methyl iodide, 1 h; methyl ethenesulfonate,[10] 3 h; methyl methanesulfonate, 4 h (all at room temperature); trimethyloxonium fluoroborate at 0 °C for 1 h.

2-(Butoxysulfonyl)-*N,N,N*-trimethylethanaminium trifluoromethanesulfonate (butyl [2]betylate triflate) (**7, R = butyl, X = CF_3SO_3**). Dimethylamine (~0.7 mL) and butyl ethenesulfonate (**5**, R = butyl) (0.5 g, 3.0 mmol) in methylene chloride (25 mL) as above gave the dimethylamino ester (**6**, R = butyl), which was immediately dissolved in CH_2Cl_2 (25 mL). Methyl trifluoromethanesulfonate (0.35 mL, 1.1 equiv) was added and after 15 min the solvent was evaporated, the residue triturated with anhydrous ether and the ether removed by filtration to give the [2]betylate (**7**, R = butyl, X = CF_3SO_3) (0.95 g, 84% yield). The material was used without further purification in the reactions listed in the tables. The analytical specimen was prepared by recrystallization from absolute ethanol: mp 101–102 °C; ^1H NMR (acetone-d_6) δ 4.40 (t, 2 H), 4.06 (s, 4 H), 3.48 (s, 9 H), 1.93–1.24 (m, 4 H), 0.94 (t, 3 H); IR (Nujol) ν_{max} 1370 (s), 1345 (s), 1260 (vs), 1167 (vs), 1150 (w), 1130 (s), 950 (s), 842 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{22}F_3NO_6S_2$: C, 32.16; H, 5.94; F, 15.26; N, 3.75; S, 17.17. Found: C, 31.73; H, 6.20; F, 14.88; N, 3.46; S, 16.88. Similar treatment of **6** (R = butyl) with methyl fluorosulfate (15 min) and dimethyl sulfate (30 min) gave butyl [2]betylate fluorosulfate (mp 81–83 °C) and methylsulfate (**7**, R = butyl, X = FSO_3 and CH_3OSO_3) in 92% and 90% yields, respectively. The perchlorate (**7**, R = butyl, X = ClO_4) was prepared by dissolving the fluorosulfate in the minimum amount of cold water, adding a saturated solution of $NaClO_4$, and cooling (method B1, Table IV). The solid was isolated by filtration and drying (77% yield), mp 110–115 °C.

2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium fluorosulfate (hexadecyl [2]betylate fluorosulfate) (**7, R = Hexadecyl, X = FSO_3**). Dimethylamine (~15 mL) was added to a stirred, ice-cooled solution of hexadecyl ethenesulfonate (**5**, R = hexadecyl) (11.6 g) in CH_2Cl_2 (125 mL). After 10 min the solvent and excess Me_2NH were

(43) LeBerre, A.; Etienne, A.; Dumaitre, B. *Bull. Soc. Chim. Fr.* **1970**, 946–953.
(44) Mion, L.; Casadevall, A.; Casadevall, E. *Bull. Soc. Chim. Fr.* **1968**, 2950–2957.
(45) Octavee, D.; Stefanec, J.; Siles, B.; Konecky, V.; Garaj, J. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2487–2493.
(46) King, J. F.; Hawson, A.; Huston, B. L.; Danks, L. J.; Komery, J. *Can. J. Chem.* **1971**, *49*, 943–955.
(47) Helberger, J. H.; Lantermann, H. *Liebigs Ann. Chem.* **1954**, *586*, 158–164.
(48) Kharasch, M. S.; May, E. M.; Mayo, F. R. *J. Org. Chem.* **1938**, *3*, 175–192.
(49) Crossland, R. R.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.

evaporated, leaving **6** (R = hexadecyl) as a white solid (13.1 g, 99%): ^{1}H NMR 4.22 (t, 2 H), symmetric pattern of 3.38–3.18 (m, 2 H) and 2.88–2.64 (m, 2 H), 2.26 (s, 6 H), 1.74 (m, 2 H), 1.26 (br s, 26 H), 0.88 (t, 3 H); IR ν_{max} (CH_2Cl_2) 1350 (vs), 1160 (vs), 950 (s) cm^{-1}. This was dissolved in CH_2Cl_2 (125 mL) and cooled in ice. Methyl fluorosulfate (3.95 g, 1.0 equiv) was added; a white precipitate formed immediately. Evaporation of the solvent gave the [2]betylate (**7**, R = hexadecyl, X = FSO_3) as a white solid (16.86 g, 99% from **6**, R = hexadecyl, and 92% from 1-hexadecanol): ^{1}H NMR δ 4.31 (t, 2 H), 3.70 (s, 4 H), 3.10 (s, 9 H), 1.74 (m, 2 H), 1.3 (br s, 26 H), 0.86 (t, 3 H); ^{19}F NMR (acetone-d_6) δ 38.3; IR ν_{max} (KBr) 1340 (s). 1270 (vs), 1165 (s), 950 (s), 718 (s) cm^{-1}. Similarly, reaction with methyl trifluoromethanesulfonate, dimethyl sulfate, and trimethyloxonium fluoroborate gave the [2]betylate triflate, methylsulfate (91%), mesylate (72%), and fluoroborate (96%) (**7**, R = hexadecyl, X = CF_3SO_3, $MeOSO_3$, $MeSO_3$, and BF_4, respectively). The perchlorate was obtained by dropwise addition of aqueous $HClO_4$ (70%) to a methanolic solution of **6** (R = hexadecyl, X = $MeOSO_3$); three recrystallizations from absolute ethanol gave the analytical specimen. Anal. Calcd for $C_{21}H_{46}ClNO_7S$: C, 51.32; H, 9.37; Cl, 7.13; N, 2.85; S, 6.52. Found: C, 51.21; H, 9.51; Cl, 7.16; N, 2.81; S, 6.39. In like manner the following were prepared. **2-[(2,2-Dimethylpropoxy)sulfonyl]-*N,N,N*-trimethylethanaminium iodide** and **fluorosulfate** (**7**, R = neopentyl, X = I and FSO_3) in 94% and 98% yields, respectively. The iodide melted at 135 °C dec; ^{1}H NMR (CD_3CN) δ 4.09 (s, 2 H), 3.84 (s, 4 H), 3.22 (s, 9 H), 1.01 (s, 9 H). **(±)-*N,N,N*-Trimethyl-2-[[(1-methylheptyl)oxy]sulfonyl]ethanaminium trifluoromethanesulfonate** (92%), **fluorosulfate** (87%), **iodide** (81%) (**7**, R = 1-methylheptyl, X = CF_3SO_3, FSO_3, and I, respectively). **(*R*)-*N,N,N*-Trimethyl-2-[[(1-methylheptyl)oxy]sulfonyl]ethanaminium fluorosulfate, ethenesulfonate** (85%) **and iodide** (89%) (**7**, R = (*R*)-1-methylheptyl, X = FSO_3, C-H_2=$CHSO_3$, and I, respectively). ***N,N,N*-Trimethyl-2-[(3-phenylpropoxy)sulfonyl]ethanaminium fluorosulfate** (**7**, R = $PhCH_2CH_2CH_2$, X = FSO_3) (90% yield). ***N,N,N*-Trimethyl-2-[(octyloxy)sulfonyl]ethanaminium perchlorate** (**7**, R = octyl, X = ClO_4), mp 109–110 °C (from methanol). Anal. Calcd for $C_{13}H_{30}ClNO_7S$: C, 41.16; H, 7.91; Cl, 9.23; N, 3.69; S, 8.44. Found: C, 40.90; H, 8.37; Cl, 9.01; N, 3.69; S, 8.14. **2-[(Docosyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium fluorosulfate** (**7**, R = docosyl, X = FSO_3) (83% yield). **2-[[(2α,4aβ,8aα-Decahydro-2-naphthalenyl)oxy]sulfonyl]-*N,N,N*-trimethylethanaminium fluorosulfate** (**7**, R = axial *trans*-decalyl, X = FSO_3) (76% yield). **2-[[(3-butenyl)oxy]sulfonyl]-*N,N,N*-trimethylethanaminium fluorosulfate** (**7**, R = CH_2=$CHCH_2CH_2$, X = FSO_3^-) (74% yield).

Exchange of betylate counteranions (in addition to the crystallization procedure described above for perchlorates) was effected by ion-pair extraction (method B2) or the use of an ion-exchange resin (method B3), as illustrated by the following examples. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium picrate** (**7**, R = hexadecyl, X = picrate). Hexadecyl [2]betylate fluorosulfate (**7**, R = hexadecyl, X = FSO_3) (2.2 g, 4.5 mmol) in methylene chloride (50 mL) was shaken gently in a separatory funnel with a solution of picric acid (2.1 g, 2 equiv) in water (50 mL). The methylene chloride layer was separated, washed with water (2 × 50 mL), and dried. Evaporation of the methylene chloride, trituration with anhydrous ether, and removal of the ether by filtration gave a yellow solid (2.1 g, 75%). Recrystallization from methylene chloride–anhydrous ether yielded yellow crystals: mp 76–77 °C; ^{1}H NMR δ 8.68 (s, 2 H), 4.31 (t, 2 H), 4.05 (br s, 4 H), 3.45 (s, 9 H), 1.72 (m, 2 H), 1.3 (br s, 26 H), and 0.88 (t, 3 H); IR ν_{max} 1631 (s), 1482 (m), 1368 (s), 1315 (s), 1262 (s), 1165 (vs), 930 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{48}N_4O_{10}S$: C, 52.24; H, 7.79; N, 9.03; S, 5.16. Found: C, 52.52; H, 7.90; N, 8.92; S, 5.36. The following were similarly prepared in comparable yields. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium hexafluoroantimonate** (**7**, R = hexadecyl, X = SbF_6); ^{1}H NMR (acetone-d_6) δ 4.37 (t, 2 H), 4.09 (s, 4 H), 3.51 (s, 9 H), 1.77 (m, 2 H), 1.30 (br s, 26 H), 0.88 (t, 3 H); IR (KBr pellet) ν_{max} 1350 (m), 1170 (m), 950 (s), 850 (w), 660 (vs) cm^{-1}. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium hexafluorophosphate** (**7**, R = hexadecyl, X = PF_6); IR (KBr) ν_{max} 1360 (s), 1165 (s), 1025 (w), 950 (m), 832 (vs), 560 (m) cm^{-1} (no sign of the band at 1270 cm^{-1} due to FSO_3^-). **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium camphor-10-sulfonate** (**7**, R = hexadecyl, X = camphor-10-sulfonate); IR (Nujol) ν_{max} 1742 (s), 1370 (m), 1348 (m), 1220 (m), 1182 (s), 1170 (vs), 1040 (m) cm^{-1}. **[2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium thiocyanate** (**7**, R = hexadecyl, X = SCN). **2-[(Octyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium thiocyanate** and **iodide** (**7**, R = octyl, X = SCN and I, respectively) (the latter was prepared from the perchlorate salt). **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium hydroxymethanesulfonate** (**7**, R = hexadecyl, X = $HOCH_2SO_3$). Amberlite IRA-400 ion-exchange resin (Cl^- form) (BDH) (250 mequiv) was washed with an aqueous solution of sodium hydroxymethanesulfonate (sold as "formaldehyde sodium bisulfite addition compound", Aldrich) until the eluent gave a negative test for Cl^-; the column was rinsed with water and then with methanol. A solution of hexadecyl [2]betylate fluorosulfate (**7**, R = hexadecyl, X = FSO_3) (25 mmol) in methanol (100 mL) was passed through the resin and the resin rinsed a few times with fresh methanol. Evaporation of methanol gave the product; IR (Nujol) ν_{max} 3290 (br m), 1365 (s), 1212 (s), 1168 (vs), 1020 (s), 942 (s), 850 (m), 810 (w) cm^{-1}. The characteristic fluorosulfate band at 1270 cm^{-1} was absent. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium 2-hydroxyethanesulfonate** (**7**, R = hexadecyl, X = $HOCH_2CH_2SO_3$). Rexyn 203 (OH) (Fisher) (20 mL, 55 mequiv) was washed with a solution of 2-hydroxyethanesulfonic acid (>54 mmol, 6.8 g) in water (50 mL). The eluent was recycled until the resin was slightly acidic. The resin was washed with water until the water layer stayed neutral, and the water was replaced with methanol. Hexadecyl [2]betylate fluorosulfate (**7**, R = hexadecyl, X = FSO_3) (2.3 g, 4.7 mmol) in warm methanol (~25 mL) was added to the resin and the resin was eluted with fresh methanol (~150 mL). Evaporation of methanol, trituration with anhydrous ether, and removal of the ether by filtration gave a solid (2.3 g, 95%): IR (Nujol) ν_{max} 3370 (br m), 1362 (m), 1342 (m), 1208 (s), 1192 (m), 1168 (vs), 1035 (s), 950 (s), 868 (w) cm^{-1}. The following were made in the same way. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium 3-hydroxypropanesulfonate** (**7**, R = hexadecyl, X = $HO(CH_2)_3SO_3$): IR (Nujol) ν_{max} 3358 (br m), 1365 (s), 1348 (s), 1220 (m), 1188 (vs), 1165 (vs), 1058 (m), 1035 (s), 1025 (vs), 940 (s), 868 (m) cm^{-1}. **2-[(Hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium 4-hydroxybutanesulfonate** (**7**, R = hexadecyl, X = $HO(CH_2)_4SO_3$); IR (Nujol) ν_{max} 3460 (br m), 1348 (m), 1170 (vs), 1034 (s), 972 (m), 948 (m) cm^{-1}.

Preparation of [3]Betylates. (a) 3-Chloropropanesulfonyl Chloride. A mixture of 1,3-propanesultone (200 g, 1.64 mol) and thionyl chloride (400 g, 3.36 mol) with dimethylformamide (~1 mL) was refluxed overnight. The excess thionyl chloride was removed by distillation and the product (271.7 g, 94%) obtained as a pale yellow liquid by vacuum distillation (bp 102–104 °C (55 torr)), identified by comparison of spectra with those of a specimen prepared by the method of Bliss et al.:[50] IR (CH_2Cl_2) ν_{max} 3065 (w), 3000 (w), 2972 (w), 2925 (w), 2876 (w), 1443 (m), 1369 (s), 1356 (m), 1311 (w), 1192 (m), 1170 (s), 1026 (w), 963 (w), 860 (w) cm^{-1}; ^{1}H NMR δ 3.84 (m, 4 H), 2.49 (m, 2 H).

(b) *N*-Methyl-3-chloropropanesulfonamide. To a solution of 3-chloropropanesulfonyl chloride (50 g, 0.28 mol) in ether (50 mL) at 0 °C was added dropwise an aqueous solution of methylamine (40%, 60 mL). The organic phase was dried and the solvent removed to give the product (45 g, 93%) as an oil. This material was unstable and used without further purification; IR (CH_2Cl_2) ν_{max} 3393 (m), 3310 (broad, w), 3061 (w), 2969 (w), 2939 (w), 1444 (w), 1397 (m), 1328 (s), 1260 (w), 1152 (s), 1129 (m), 1074 (m), 874 (m), 838 (m) cm^{-1}; ^{1}H NMR δ 4.76 (br s, 1 H), 3.73 (t, 2 H), 3.13 (m, 2 H), 2.79 (s, 3 H), 2.18 (m, 2 H).

(c) *N*-Methylpropanesultam (9, *n* = 3). *N*-Methyl-3-chloropropanesulfonamide (45 g, .26 mol) was dissolved in absolute ethanol (150 mL, freshly distilled from potassium hydroxide) and added dropwise to a refluxing solution of potassium hydroxide (15 g, 0.27 mol) in absolute ethanol (150 mL, also distilled from KOH) over 1.5 h. The reaction mixture was refluxed for a further 15 min, kept basic by addition of a small amount of KOH, and then cooled and acidified with concentrated hydrochloric acid, dried, and evaporated to give a gold oil, which was recrystallized from ether–petroleum ether (bp 30–60 °C) with charcoal to give white crystals (23.3 g, 66%): mp 46–49 °C, identified by mixture melting point and comparison of spectra with an authentic specimen;[50] IR ν_{max} 3058 (w), 2967 (w), 2945 (w), 2883 (w), 2866 (w), 1308 (s), 1257 (m), 1239 (w), 1187 (m), 1143 (s), 1128 (s), 1047 (w), 1015 (w), 994 (m) cm^{-1}; ^{1}H NMR δ 3.24 (t, 2 H), 3.19 (t, 2 H), 2.68 (s, 3 H), 2.34 (m, 2 H).

(d) 2,2-Dimethylisothiazolidinium 1,1-Dioxide Fluorosulfate (10, *n* = 3, Z = FSO_3). In a well-ventilated fume hood, *N*-methylpropanesultam (**9**, *n* = 3) (0.97 g, 7.2 mmol) was dissolved in excess methyl fluorosulfate. Precipitation was observed almost immediately. After 0.5 h the product was collected by vacuum filtration, using methylene chloride as a wash, to give 1.8 g (98%) of white crystals, mp (sealed capillary) 178–180 °C. This material was used without further purification for the preparation of (dimethylamino)propanesulfonates. Under conditions of high humidity, the salt was prepared in a glove box. Larger scale preparations (3–5 g) were cooled initially with an ice-water bath. The analytical sample was prepared in a glove box by recrystallization from dry acetonitrile–methylene chloride, which gave crystals: mp (sealed capillary) 188–189 °C; ^{1}H NMR (CD_3CN) δ 3.95 (m, 4 H), 3.25 (s, 6 H), 2.63 (m, 2 H). Anal. Calcd for $C_5H_{12}FNO_5S_2$: C, 24.09; H, 4.85; N, 5.62;

(50) Bliss, A. D.; Cline, W. K.; Hamilton, C. E.; Sweeting, O. J. *J. Org. Chem.* **1963**, *28*, 3537–3541.

S, 25.72. Found: C, 23.86; H, 4.91; N, 5.49; S, 25.56.

(e) Alkyl 3-(Dimethylamino)propanesulfonates (11, n = 3). General Method. To a stirred mixture of the alcohol and **10** (n = 3, Z = FSO_3) (1.1–2.0 equiv) in CH_2Cl_2 at 0–4 °C was added dropwise triethylamine (1.1–2.0 equiv, i.e., equimolar to **10** (n = 3, Z = FSO_3)). The reaction mixture was stirred for 2–12 h, then washed with brine, and dried and the solvent evaporated; to avoid decomposition this material was converted directly to the [3]betylate. For example, **butyl 3-(dimethylamino)propanesulfonate (11, n = 3, R = butyl)** (1.72 g, 91% yield) was obtained from **10** (n = 3, Z = FSO_3) (2.77 g, 11 mmol), 1-butanol (0.63 g, 8.5 mmol), and triethylamine (1.13 g, 11 mmol) in CH_2Cl_2 (30 mL) after 4 h at 0 °C: IR (CH_2Cl_2) ν_{max} 1465 (m), 1357 (s), 1168 (s), 940 (s) cm^{-1}; ^1H NMR δ 4.23 (t, 2 H), 3.19 (m, 2 H), 2.33 (m, 2 H), 2.12 (s, 6 H), 2.03 (m, 2 H), 1.71 (m, 2 H), 1.44 (m, 2 H), 0.96 (t, 3 H). The following esters were made similarly: (i) ethyl (**11**, n = 3, R = Et) (~100% yield); IR (CH_2Cl_2) 1460 (m), 1350 (s), 1170 (s), 915 (s) cm^{-1}; ^1H NMR 4.30 (q, 2 H), 3.19 (m, 2 H), 2.37 (m, 2 H), 2.23 (s, 6 H), 2.00 (m, 2 H), 1.40 (t, 3 H); (ii) (*R*)-1-methylheptyl (**11**, n = 3, R = (*R*)-1-methylheptyl) (from (*R*)-(−)-2-octanol, $[\alpha]_D$ −9.39° (neat) in 89% yield); IR (CH_2Cl_2) ν_{max} 1463 (s), 1340 (vs), 1207 (m), 1166 (s), 1120 (m), 1055 (m), 1042 (m), 1031 (m), 955 (vs) cm^{-1}; ^1H NMR δ 4.82 (m, 1 H), 3.15 (m, 2 H), 2.24 (s, 6 H), 1.90–2.40 (complex m, 2 H), 1.64 (m, 2 H), 1.41 (d, 3 H), 1.32 (br s, ~10 H), 0.89 (t, 3 H); (iii) hexadecyl (**11**, n = 3, R = hexadecyl) (87% yield); IR (CH_2Cl_2) 1466 (m), 1358 (s), 1290 (m), 1257 (m), 1209 (m), 1167 (s), 1029 (m), 945 (br s) cm^{-1}; ^1H NMR δ 4.18 (t, 2 H), 3.16 (m, 2 H), 2.39 (t, 2 H), 2.22 (s, 6 H), 2.01 (m, 2 H), 1.73 (m, 2 H), 1.27 (br s, ~26 H), 0.88 (t, 3 H).

(f) 3-(Alkoxysulfonyl)-*N*,*N*,*N*-trimethylpropanaminium salts (Alkyl [3]Betylates) (12, n = 3) were prepared by reaction of the dimethylamino ester (**11**, n = 3) with methyl fluorosulfate (1.0–1.1 equiv) in CH_2Cl_2 at 0 °C for 1 h, whereupon the solvent was evaporated. **3-(Ethoxysulfonyl)-*N*,*N*,*N*-trimethylpropanaminium fluorosulfate (12, n = 3, R = Et, X = FSO_3)** (78% yield): IR (KBr) ν_{max} 1479 (m), 1280 (s), 1165 (s), 1076 (m), 1040 (m), 998 (m), 920 (s), 739 (s) cm^{-1}; ^1H NMR (CD_3CN) δ 4.43 (q, 2 H), 3.0–3.5 (m, 4 H), 3.11 (s, 9 H), 2.24 (m, 2 H), 1.38 (t, 3 H); aqueous $HClO_4$ (70%) in warm absolute EtOH gave the **perchlorate (12, n = 3, R = Et, X = ClO_4)** (90% yield): mp 95–96.5 °C (lit.[4a] 95.5–96.5 °C); IR (KBr) ν_{max} 1478 (m), 1357 (m), 1340 (m), 1304 (m), 1162 (s), 1094 (vs), 995 (m), 912 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ 4.38 (q, 2 H), 3.74 (m, 2 H), 3.43 (m, 2 H), 3.39 (s, 9 H), 2.46 (m, 2 H), 1.49 (t, 3 H). Anal. Calcd for $C_8H_{20}ClNO_7S$: C, 31.02; H, 6.51; Cl, 11.45; N, 4.52; S, 10.35. Found: C, 31.06; H, 6.78; Cl, 11.57; N, 4.38; S, 10.24. **3-(Butoxysulfonyl)-*N*,*N*,*N*-trimethylpropanaminium fluorosulfate (12, n = 3, R = butyl, X = FSO_3)** (99% yield): IR (KBr) ν_{max} 1479 (m), 1282 (br vs), 1163 (s), 1074 (m), 932 (s) cm^{-1}; ^1H NMR (D_2O) 4.39 (t, 2 H), 3.49 (m, 4 H), 3.17 (s, 9 H), 2.36 (m, 2 H), 1.77 (m, 2 H), 1.40 (m, 2 H), 0.93 (t, 3 H); picric acid (1.3 equiv) in warm ethanol gave the **picrate (12, n = 3, R = butyl, X^- = picrate)**, yellow crystals, mp 122–123 °C; IR (KBr) ν_{max} 1639 (s), 1611 (m), 1553 (m), 1506 (m), 1490 (m), 1471 (m), 1435 (m), 1363 (s), 1310 (s), 1290 (m), 1219 (s), 1172 (s), 1160 (m), 950 (m) cm^{-1}; ^1H NMR (acetone-d_6) δ 8.69 (s, 2 H), 4.30 (t, 2 H), 3.86 (m, 2 H), 3.48 (s, 9 H, superimposed on m, 2 H), 2.51 (m, 2 H), 1.72 (m, 2 H), 1.43 (m, 2 H), 0.93 (t, 3 H). Anal. Calcd for $C_{16}H_{26}N_4O_{10}S$: C, 41.20; H, 5.62; N, 12.01; S, 6.87. Found: C, 40.98; H, 5.77; N, 12.21; S, 6.69. **(*R*)-*N*,*N*,*N*-Trimethyl-3-[[(1-methylheptyl)oxy]sulfonyl]propanaminium fluorosulfate (12, n = 3, R = (*R*)-1-methylheptyl, X = FSO_3)** (89% yield): IR (CH_2Cl_2) ν_{max} 1478 (m), 1342 (m), 1289 (s), 1167 (s), 1069 (s), 910 (s) cm^{-1}; ^1H NMR δ 4.80 (m, 1 H), 3.20 (s, 9 H), 3.0–3.7 (complex m, 2 H), 2.30 (m, 2 H), 1.64 (m, 2 H), 1.39 (d, 3 H), 1.27 (br s, ~10 H), 0.86 (t, 3 H). **3-[(Hexadecyloxy)sulfonyl]-*N*,*N*,*N*-trimethylpropanaminium fluorosulfate (12, n = 3, R = hexadecyl, X = FSO_3)** (91% yield): IR (CH_2Cl_2) ν_{max} 1480 (m), 1363 (m), 1289 (s), 1170 (s), 1072 (s), 951 (m), 925 (m) cm^{-1}; ^1H NMR δ 4.23 (t, 2 H), 3.59 (m, 2 H), 3.25 (m, 2 H), 3.20 (s, 9 H), 2.30 (m, 2 H), 1.75 (m, 2 H), 1.26 (br s, ~26 H), 0.87 (t, 3 H); in warm methanol 70% aqueous $HClO_4$ gave the **perchlorate** (98% yield): mp 81–82 °C (recrystallized from absolute EtOH); IR (CH_2Cl_2) ν_{max} 1359 (m), 1168 (m), 1096 (vs), 943 (m), 919 (m), 895 (m) cm^{-1}; ^1H NMR δ 4.27 (t, 2 H), 3.59 (m, 2 H), 3.31 (m, 2 H), 3.21 (s, 9 H), 2.33 (m, 2 H), 1.76 (m, 2 H), 1.27 (br s, ~26 H), 0.88 (t, 3 H). Anal. Calcd for $C_{22}H_{48}ClNO_7S$: C, 52.21; H, 9.56; Cl, 7.00; N, 2.77; S, 6.33. Found: C, 51.96; H, 9.54; Cl, 7.55; N, 3.03; S, 6.90. The fluorosulfate (**12**, n = 3, R = hexadecyl, X = FSO_3) in warm ethanol with picric acid gave the **picrate** (95% yield): mp 101–102 °C (from EtOH); IR (KBr) 1628 (s), 1609 (m), 1557 (m), 1479 (m), 1360 (m), 1330 (s), 1301 (m), 1263 (m), 943 (m) cm^{-1}; ^1H NMR (acetone-d_6) δ 8.70 (s, 2 H), 4.30 (t, 2 H), 3.86 (m, 2 H), 3.48 (s, 9 H, superimposed on m, 2 H), 2.50 (m, 2 H), 1.75 (m, 2 H), 1.30 (br s, ~26 H), 0.90 (t, 3 H). Anal. Calcd for $C_{28}H_{50}N_4O_{10}S$: C, 52.98; H, 7.94; N, 8.83; S, 5.05. Found: C, 52.86; H, 7.91; N, 8.71; S, 4.89. The **methylsulfate** (**12**, n = 3, R = hexadecyl, X = $MeOSO_3$) was obtained from **11** (n = 3, R = hexadecyl) in 74% yield by reaction with dimethyl sulfate (1 equiv) for 2 h in CH_2Cl_2 at 0 °C: IR (CH_2Cl_2) 1477 (m), 1359 (m), 1244 (s), 1167 (m), 1060 (m), 1013 (s), 945 (m), 920 (m), 893 (m) cm^{-1}; ^1H NMR δ 4.27 (t, 2 H), 3.70 (m, 2 H), 3.68 (s, 3 H), 3.38 (m, 2 H), 3.27 (s, 9 H), 2.31 (m, 2 H), 1.75 (m, 2 H), 1.26 (br s, ~26 H), 0.88 (t, 3 H).

Preparation of [4]Betylates. (a) *N*-Methyltetrahydro-1,2-thiazine *S*,*S*-Dioxide (9, n = 4) was prepared by the method in Kaiser and Knutson[51] as a clear, viscous oil: bp 109–110 °C (0.7 torr); n^{20}_D 1.4878; ^1H NMR δ 3.34 (t, 2 H), 3.01 (5, 2 H), 2.80 (s, 3 H), 2.06–2.30 (m, 2 H), 1.58–1.83 (m, 2 H); IR (CH_2Cl_2) ν_{max} 1460 (m), 1357 (m), 1334 (s), 1320 (s), 1292 (s), 1255 (m), 1217 (m), 1160 (m), 1139 (s), 970 (s) cm^{-1}. Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43; N, 9.39; S, 21.49. Found: C, 40.45; H, 7.61; N, 9.20; S, 21.32.

(b) 2,2-Dimethyltetrahydro-1,2-thiazinium *S*,*S*-Dioxide Trifluoromethanesulfonate (10, n = 4, Z = CF_3SO_3). A mixture of the sultam (**9**, n = 4) (3 g, 20 mmol) and methyl trifluoromethanesulfonate (4.1 g, 25 mmol) in dry CH_2Cl_2 (50 mL) was kept at room temperature in a drybox for 3 days. The product after filtration and washing with anhydrous ether was obtained as colorless plates (5.6 g, 90%), mp 142–143 °C. Two recrystallizations from acetonitrile–ether gave the analytical specimen: mp 143–144 °C; ^1H NMR (CD_3CN) δ 4.17 (t, 2 H), 3.87 (t, 2 H), 3.34 (s, 6 H), 2.20 (m, 4 H); IR (Nujol) ν_{max} 1380 (s), 1272 (s), 1250 (s), 1220 (m), 1160 (s), 1030 (s), 813 (m), 730 (m), 637 (s) cm^{-1}. Anal. Calcd for $C_7H_{14}F_3NO_5S$: C, 26.83; H, 4.50; F, 18.19; N, 4.47; S, 20.47. Found: C, 27.05; H, 4.68; F, 17.93; N, 4.29; S, 20.61.

(c) 4-[(Hexadecyloxy)sulfonyl]-*N*,*N*-dimethylbutanamonium Trifluoromethanesulfonate (13, n = 4, R = Hexadecyl, Z = CF_3SO_3). A mixture of 1-hexadecanol (2.4 g, 10 mmol) and the cyclic sulfonylammonium salt **10** (n = 4, X = CF_3SO_3) in dry benzene–acetonitrile (1:1, 10 mL) was heated at 62 °C for 36 h; evaporation of the solvent gave the [4]norbetylate **13** (n = 4, R = hexadecyl, Z = CF_3SO_3) as a white solid (5.6 g, 100%), which was recrystallized 3 times from anhydrous ether: mp 67–68 °C; ^1H NMR (CD_3CN) 7.8 (br m, 1 H), 4.19 (t, 2 H), 3.1–3.3 (m, 4 H), 2.83 (d, 6 H), 1.6–2.0 (m, obscured by CHD_2CN), 1.27 (br s, 26 H), 0.88 (t, 3 H); IR (CH_2Cl_2) ν_{max} 1462 (m), 1348 (s), 1290 (s), 1235 (s), 1215 (s), 1165 (s), 1024 (s), 947 (m), 634 (m) cm^{-1}. Anal. Calcd for $C_{23}H_{48}F_3NO_6S$: C, 49.71; H, 8.71; F, 10.26; N, 2.52; S, 11.54. Found: C, 49.59; H, 8.64; F, 10.09; N, 2.38; S, 11.44.

(d) 4-[(Hexadecyloxy)sulfonyl]-*N*,*N*,*N*-trimethylbutanaminium Trifluoromethanesulfonate (12, n = 4, R = Hexadecyl, X = CF_3SO_3). A solution of the [4]norbetylate **13** (n = 4, R = hexadecyl, Z = CF_3SO_3) (5.55 g, 10 mmol) in CH_2Cl_2 (100 mL) was washed with cold, saturated aqueous Na_2CO_3 (2 × 50 mL) and dried. Methyl trifluoromethanesulfonate (1.65 g, 10.1 mmol) was added to this solution of **11** (n = 4, R = hexadecyl) and the mixture left overnight at room temperature; evaporation of the CH_2Cl_2 gave a white solid which after recrystallization from absolute EtOH melted at 69–70 °C (5.4 g, 95%). Two more recrystallizations gave the analytical sample, which was dried over P_2O_5: mp 70–71 °C, ^1H NMR (CD_3CN) δ 4.21 (5, 3 H), 3.1–3.4 (m, 4 H), 3.06 (s, 9 H), 1.6–2.0 (m, obscured), 1.2–1.4 (br s, ~28 H), 0.88 (t, 3 H); IR (CH_2Cl_2) ν_{max} 1355 (m), 1278 (s), 1245 (m), 1165 (s), 1035 (s), 950 (m) cm^{-1}. Anal. Calcd for $C_{24}H_{50}F_3NO_6S_2$: C, 50.59; H, 8.85; N, 2.46. Found: C, 50.35; H, 9.08; N, 2.19. The fluorosulfate **12** (n = 4, R = hexadecyl, X = FSO_3) (95% yield) and **4-(butoxysulfonyl)-*N*,*N*,*N*-trimethylbutanaminium fluorosulfate (12, n = 4, R = butyl, X = FSO_3)** (95% yield) were obtained similarly.

Preparation of Norbetylates (2). The general procedure is to add the acid (1.1–1.2 equiv) to a solution of the amino ester (**6** or **11**) in CH_2Cl_2, let the mixture stand for a few minutes, evaporate the solvent, and triturate the residue with anhydrous ether, whereupon the norbetylate is obtained as a solid by filtration. With the reactions in formic or acetic acid the norbetylate **8** was simply prepared in situ by adding the amino ester **6** to excess acid.

***N*,*N*-Dimethyl-2-[(2,2-dimethylpropoxy)sulfonyl]ethanaminium *p*-Toluenesulfonate (8, R = Neopentyl, X = OTs).** *p*-Toluenesulfonic acid monohydrate (1.18 g, 1.25 equiv) was added to a solution of neopentyl 2-(dimethylamino)ethanesulfonate (**6**, R = neopentyl) (0.89 g, 5 mmol) in CH_2Cl_2 (25 mL) as above (1.95 g, 99% yield). Recrystallization from CH_2Cl_2–ether gave white crystals: mp 138–139 °C; ^1H NMR δ 7.74, 7.20 (analyzed as AB quartet, J = 9 Hz, 4 H), 3.93 (s, 2 H), 3.8 (m, 2 H), 3.5 (m, 2 H), 2.92 (s, 7 H), 2.35 (s, 3 H), 0.95 (s, 9 H); IR ν_{max} 2415 (br m), 1355 (s), 1265 (s), 1172 (vs), 1118 (s), 1004 (vs), 950 (vs), 932 (s), 680 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{29}NO_6S_2$: C, 48.58; H, 7.39; N, 3.54; S, 16.21. Found: C, 48.63; H, 7.43; N, 3.51; S, 16.10.

(*R*)-*N*,*N*-Dimethyl-2-[[(1-Methylheptyl)oxy]sulfonyl]ethanaminium Bromide (8, R = 1-Methylheptyl, X = Br). Anhydrous HBr was bubbled into a cold solution of (*R*)-1-methylheptyl 2-(dimethylamino)ethane-

(51) Kaiser, E. M.; Knutson, P. L. A. *J. Org. Chem.* **1975**, *40*, 1342–1346.

sulfonate (**6**, R = (*R*)-1-methylheptyl) (4.0 g, 15 mmol) in CH_2Cl_2 (50 mL). The crystalline [2]norbetylate **8** (R = (*R*)-1-methylheptyl, X = Br) was collected by filtration (4.3 g, 83%): mp 87–88 °C dec after recrystallization from CH_2Cl_2–pentane; ^1H NMR δ 4.9 (m, 1 H), 3.9 (m, 2 H), 3.7 (m, 2 H), 3.01 (d, 7 H), 1.7 (m, 2 H), 1.47 (d, 3 H), 1.34 (br s, 8 H), 0.89 (t, 3 H). Anal. Calcd for $C_{12}H_{27}BrNO_3S$: C, 41.74; H, 7.88; Br, 23.14; N, 4.06. Found: C, 41.86; H, 7.96; Br, 22.69; N, 3.74.

Reactions of Alkyl Betylates. (a) In Aqueous Solution or Suspension (Method A, Tables I and II). The alkyl betylate salt was stirred with a solution of the nucleophilic reagent (roughly 10-fold excess unless otherwise specified) in water as specified in Tables I and II. Workup of nonpolar products was effected by extraction with a low-boiling organic solvent, drying of the organic layer, and evaporation of the solvents. The yield (given without parentheses in the tables) was determined from the weight of the product obtained at this stage provided the NMR and IR spectra showed no significant (<5% total) impurities. The product was normally purified for characterization by recrystallization or short-path distillation; spectra, other physical properties, and either the method of identification, or elemental analyses or exact mass, are given in Tables V and VI (and VII) (supplementary material). Example: **Hexadecyl Azide.** Hexadecyl [2]betylate fluorosulfate (**7**, R = hexadecyl, X = FSO_3) (0.98 g, 2 mmol) was suspended in an aqueous solution (50 mL) of sodium azide (1.3 g, 20 mmol) and the mixture stirred for 4 h at 25 °C. Extraction with CH_2Cl_2 followed by evaporation of the solvent gave hexadecyl azide as a colorless oil (0.48 g, 90%).

(b) In Two-Phase Aqueous–Organic Media (Method B, Tables I and II). The betylate was dissolved or suspended in the organic solvent and stirred under the specified conditions with a solution of the nucleophile (10-fold excess unless otherwise indicated) in a volume of water roughly equal to that of the organic phase. The mixture was diluted with water (or occasionally aqueous NaCl) and CH_2Cl_2, and workup and characterization were completed as above. Example: **Hexadecyl bromide** (146 mg, 95%) was obtained by stirring a mixture of hexadecyl [3]betylate fluorosulfate (**12**, R = hexadecyl, X = FSO_3) (252 mg, 0.5) mmol) in benzene (5 mL) with aqueous sodium bromide (0.51 g, 10 equiv) solution (5 mL) for 48 h at 25 °C.

(c) In Organic Solvents (Method C, Tables I and II). A mixture of the betylate and the reagent (10-fold excess if not otherwise stated) in the specified solvent was allowed to react as indicated. Workup was effected either by removal of the betaine by filtration followed by evaporation of the solvent from the filtrate or by evaporation of the solvent followed by workup, as above. Example: **2-Butyl-1,3-dihydrobenzo[*c*]-thiophenium perchlorate.** A solution of butyl [2]betylate perchlorate (**7**, R = Bu, X = ClO_4) (0.65 g, 2 mmol) and dihydrobenzo[*c*]thiophene (0.54 g, 4 mmol) in dry acetonitrile (25 mL) was refluxed for 4 days. The betaine was removed by filtration, the solvent evaporated from the filtrate, and the residue triturated with dry ether to remove the excess of the thioether, leaving a white solid (0.59 g, ~100%). Recrystallization from absolute ethanol–ether gave the white crystalline product, mp 93–94 °C (0.51 g, 88%).

(d) SRIP Reactions (Table IV). Typically the betylate **7** or **12** or norbetylate **8** or **13** was dissolved or suspended in toluene, benzene, or chloroform and heated at reflux for the time indicated. The solvent was evaporated, the product was taken up in a mixture of water and either CH_2Cl_2 or ether, and the workup and characterization were completed as above; spectra and other features of characterization are given in Tables VII and VIII. Examples (some with variations in the procedure) follow.

Hexadecyl Perchlorate. Hexadecyl [2]betylate perchlorate (**7**, R = hexadecyl, X = ClO_4) was suspended in dry toluene and the mixture heated at reflux for 1.5 h; the betylate dissolved as the mixture was warmed, and shortly afterward a crystalline precipitate formed. Workup as above gave a white solid (69 mg, 100%).

Neopentyl Iodide. Aqueous hydriodic acid (57%, 7.5 g, 33 mmol) was added to a solution of neopentyl 2-(dimethylamino)ethanesulfonate (**6**, R = neopentyl) (5.0 g, 22.5 mmol) in *N*,*N*-dimethylformamide (25 mL) cooled in ice. The flask was fitted for distillation through a short Vigreux column and the mixture heated in a bath at 120–130 °C for 2.5 h. The material coming over between 80 and 115 °C was dissolved in pentane (50 mL) and washed with water (3 × 50 mL). Removal of the pentane by distillation gave the product (3.0 g, 68%), which was purified by short-path distillation.

Hexadecyl 2-Hydroxyethanesulfonate. Hexadecyl [2]norbetylate 2-hydroxyethanesulfonate (**8**, R = hexadecyl, X = $HOCH_2CH_2SO_3$) (1.15 g, 2.3 mmol) was heated at reflux in toluene (25 mL) for 3 h. The toluene was evaporated, the product triturated with methylene chloride (50 mL), and the insoluble dimethyltaurine removed by filtration; evaporation of the filtrate gave a solid. Trituration of the solid with anhydrous ether and evaporation of the ether gave the product (0.54 g, 68% yield). Three recrystallizations with hexanes gave a white solid, mp 49–50 °C. The precipitated dimethyltaurine from the reaction was recrystallized from ethanol–water (9:1) giving a white solid: mp 318–320 °C dec; ^1H NMR (D_2O) δ 3.70–3.47 (m, 2 H), 3.44–3.23 (m, 2 H), 2.97 (s, 6 H).

(e) Stereochemistry of Reactions of 1-Methylheptyl Betylates. 1-Methylheptyl [2]betylates (**7**, R = 1-methylheptyl) are fairly rapidly hydrolyzed in aqueous medium or merely standing in (humid) air; maximum efficiency was therefore achieved by using them as soon as they were made. Otherwise the procedures are the same as those described above. Rotations, optical purities, and percentage inversions in the reactions are listed in Table III; other properties are given in Table VII. **(*S*)-(+)-2-Iodooctane.** (*R*)-1-Methylheptyl [2]betylate iodide (**7**, R = (*R*)-1-methylheptyl, X = I) (3.6 g, 8.8 mmol) was refluxed in benzene (50 mL) for 1.5 h, whereupon the benzene was evaporated, the product triturated with pentane, and the pentane layer washed with aqueous $NaHSO_3$ (2 × 30 mL) and dried; evaporation of the pentane gave the product (1.5 g, 71%), which was purified for analysis by short-path distillation.

(*S*)-(+)-1-Methylheptyl Ethenesulfonate. (*R*)-1-Methylheptyl [2]-betylate ethenesulfonate (**7**, R = (*R*)-1-methylheptyl, X = $CH_2{=}CHSO_3$) (6.0 g, 15.5 mmol) was heated at reflux in toluene (50 mL) for 1 h. The toluene was evaporated and the residue triturated with CH_2Cl_2; the betaine (**16**, n = 2) was removed by filtration and the filtrate evaporated to give (*S*)-(+)-1-methylheptyl ethenesulfonate (2.46 g, 72%). The betaine **16** (n = 2) remaining on the filter was recrystallized from ethanol–water (9:1), giving white crystals: mp 357–358 °C dec; ^1H NMR (D_2O) δ 3.74 (m, 2 H), 3.45 (m, 2 H), 3.20 (s, 9 H). An authentic specimen[4a] showed the same NMR spectrum and gave no melting point depression on admixture.

(f) Reactions of [2]Norbetylates with Added Nucleophiles. (i) **Thiourea: Preparation of 1-Hexadecanesulfonyl Chloride.** *p*-Toluenesulfonic acid monohydrate (1.9 g, 2 equiv) and thiourea (1.9 g, 5 equiv) were added to a solution of hexadecyl 2-(dimethylamino)ethanesulfonate (**6**, R = hexadecyl) (5.2 g, 5 mmol) in 1,2-dimethoxyethene (DME) (75 mL) and the mixture was heated at 80 °C for 1 h. The precipitated dimethyltaurine was removed by filtration and the solvent evaporated. The residue was taken up in CH_2Cl_2–water (50 mL of each) and chlorine bubbled into the ice-cooled mixture for 1 h. The CH_2Cl_2 layer was then separated, washed with cold dilute aqueous $NaHSO_3$ (2 × 50 mL), aqueous $NaHCO_3$ (50 mL), and water (50 mL), and dried, and the solvent was evaporated to give 1-hexadecanesulfonyl chloride as a white solid (1.4 g, 86%), which on recrystallization from pentane melted at 50–52 °C and showed a ^1H NMR spectrum identical with that of the characterized sample prepared from the betylate (see Table V, supplementary material). **3-Phenylpropanesulfonyl Chloride.** The [2]norbetylate tosylate **8** (R = 3-phenylpropyl, X^- = tosylate) (4.4 g, 10 mmol) and thiourea (3.8 g, 5 equiv) in dry DME was heated at 80 °C for 0.45 h. After filtration to remove the dimethyltaurine (1.2 g, 78%), the DME was evaporated, leaving a solid residue, which was dissolved in water (75 mL) and CH_2Cl_2 (75 mL), chlorinated, and worked up as above to give 3-phenylpropanesulfonyl chloride as a liquid (1.33 g, 61%) identical in ^1H NMR spectrum with the sample prepared previously (see Table V). The dimethyltaurine was recrystallized from aqueous ethanol, mp 318–319 °C dec. Anal. Calcd for $C_4H_{11}O_3NS$: C, 31.36; H, 7.24; N, 9.14; S, 20.93. Found: C, 31.22; H, 7.17; N, 9.21; S, 20.81.

(ii) **Sodium Thiocyanate. Hexadecyl Thiocyanate.** The [2]norbetylate tosylate **8** (R = hexadecyl, X^- = tosylate) (0.55 g, 1 mmol) was suspended in water (30 mL), sodium thiocyanate (2.43 g, 30 mmol) added, and the mixture stirred at 25 °C for 2 h. Workup by extraction with CH_2Cl_2 gave hexadecyl thiocyanate as an oil (0.283 g, 99%) with the same ^1H NMR spectrum as the sample prepared before (Table V).

Comparison of the Reactions of Hexadecyl and Butyl [2]Betylates with Sodium Thiosulfate in Water. Hexadecyl [2]betylate fluorosulfate (**7**, R = hexadecyl, X = FSO_3) (1.23 g, 2.5 mmol) was suspended in an aqueous solution (50 mL) of $Na_2S_2O_3{\cdot}5H_2O$ (12 g, 48 mmol). The mixture was warmed on the steam bath for 5 min to facilitate dispersion of the betylate and then stirred at 25 °C for 2 h. The solid Bunte salt was removed by filtration and dissolved in a mixture of CH_2Cl_2 (25 mL), water (25 mL), and DME (5 mL) and Cl_2 was bubbled into the mixture for 30 min. The CH_2Cl_2 layer was washed with aqueous $NaHSO_3$ and $NaHCO_3$ solutions and dried and the solvent evaporated to leave a white solid (0.42 g) shown by NMR to be a mixture of 1-hexadecanesulfonyl chloride (total yield ~40%) and hexadecyl ethenesulfonate (**5**) (yield ~10%). (In another experiment in which the initial reaction was carried out in acetone–water at 75 °C, the chlorination of the Bunte salt quantitatively gave the sulfonyl chloride.) Butyl [2]betylate triflate (**7**, R = Bu, X = CF_3SO_3) (50 mg, 0.13 mmol) in D_2O (0.4 mL) and a solution of $Na_2S_2O_3{\cdot}5H_2O$ (635 mg, 2.6 mmol) in D_2O (0.5 mL) were mixed; the NMR spectrum after 4 min showed ~95% reaction. The same betylate (**7**, R = Bu, X = CF_3SO_3) (50 mg) in D_2O (0.4 mL) when mixed with

a solution of NaSCN (326 mg, 4.0 mmol) in D_2O (0.5 mL) showed ~66% reaction in 5 min by NMR. Hexadecyl [2]betylate (**7**, R = hexadecyl, X = FSO_3) (1.23 g, 2.5 mmol) in aqueous NaSCN (6.16 g, 75 mmol) solution (50 mL) was heated on the steam bath for 5 min and then stirred for 2 h. Workup gave hexadecyl thiocyanate (0.62 g, 88%) identified in Table V.

Variation of Partitioning of Octyl [2]Betylates with Counteranion. Samples (19 mg) of octyl [2]betylate perchlorate and fluorosulfate (**7**, R = octyl, X = ClO_4 and FSO_3, respectively) were each stirred for 15 min with a mixture of $CDCl_3$ (1 mL) and D_2O (1 mL). NMR spectra of the separated layers showed that the ratio of material in the $CDCl_3$ layer to that in the D_2O layer was >5 for the perchlorate and <0.2 for the fluorosulfate.

Reactions of Hexadecyl Trifluoroethanesulfonate (Tresylate) and Methanesulfonate (Mesylate). Standard literature methods[1h,49] starting from 1-hexadecanol, triethylamine, and the sulfonyl chloride gave hexadecyl mesylate (see Table VIII) and tresylate: ^1H NMR δ 4.34 (5, 2 H), 3.86 (quartet, J_{HF} = 9 Hz, 2 H), 1.78 (m, 2 H), 1.26 (br s, 26 H), 0.88 (t, 3 H); IR ν_{max} 1465 (m), 1380 (br s), 1320 (s), 1190 (vs), 1135 (s), 1090 (s), 950 (br s) cm^{-1}. (i) Hexadecyl tresylate (97 mg, 0.25 mmol) was stirred with an aqueous solution (5 mL) of sodium azide (162 mg, 2.5 mmol) for 28 h at 25 °C. The product obtained on workup showed in the ^1H NMR spectrum mainly the characteristic peaks at 4.34 and 3.86 ppm of the starting tresylate plus a small absorption around 3.24 ppm ascribable to less than 25% of hexadecyl azide. (ii) In a separate experiment with the same quantities and conditions except that stirring was continued for 15 days, the product (58 mg) appeared from the ^1H NMR spectrum to be entirely hexadecyl azide (87% yield) with no sign of the tresylate. (iii) The mesylate (160 mg, 0.5 mmol) was stirred at 25 °C with an aqueous solution (10 mL) of NaN_3 (325 mg, 5 mmol) for 16 days; the ^1H NMR spectrum of the product (151 mg) showed it to be almost entirely unreacted mesylate with a small amount (<10%) of 1-hexadecanol and no apparent hexadecyl azide. (iv) Hexadecyl tresylate (194 mg, 0.5 mmol) was stirred at 25 °C with a mixture of thiourea (280 mg, 5 mmol), benzene (5 mL), and water (5 mL) for 6 days; the ^1H NMR spectrum of the product showed only unreacted tresylate absorption. (v) Another experiment identical except that the mixture was stirred for 19 days gave a product which showed principally the characteristic IR bands of the tresylate listed above plus weak bands at 3150 (br), 3320 (br), and 1650 cm^{-1} ascribable to <25% of hexadecylisothiuronium tresylate. (vi) The mesylate (160 mg, 0.5 mmol) was stirred for 19 days at 25 °C with a mixture of thiourea (380 mg, 5 mmol), benzene (5 mL), and water (5 mL); the ^1H NMR spectrum of the product (136 mg) showed only unreacted mesylate plus perhaps a trace of 1-hexadecanol with no sign of the isothiuronium salt. (vii) The tresylate (194 mg, 0.5 mmol) was stirred for 19 days at 25 °C with a mixture of sodium azide (325 mg, 5 mmol), benzene (5 mL), and water (5 mL); the IR spectrum of the product showed unreacted tresylate with perhaps a trace of the azide (<5%) showing as a very weak peak at 2200 cm^{-1}.

SRIP Reaction of Hexadecyl [2]Betylate Bisulfate (**7**, R = hexadecyl, X = HSO_4). Hexadecyl [2]betylate fluorosulfate (1.5 g, 3 mmol) in CH_3OH (50 mL) was poured through a Rexyn 203 (75 mL, labeled 1.27 mequiv/mL) column in the bisulfate (and perhaps sulfate) form. (The resin had been prepared by adding excess 9 M aqueous H_2SO_4 to the resin in the OH^- form, followed by rinsing with water to neutrality and then a few times with CH_3OH). The column was washed with CH_3OH and evaporation of the solvent from the combined methanol solutions gave a solid (1.26 g). The ^{19}F NMR spectrum showed FSO_3^- to be absent. The solid was suspended in toluene and the mixture heated at reflux for 2 h; the product (0.2 g, 24%) was shown by its ^1H NMR to be dihexadecyl sulfate (see Table VIII).

Neopentyl 2-(Chlorosulfonyl)ethanesulfonate (14). Neopentyl ethenesulfonate (**5**, R = neopentyl) (0.65 g, 3.65 mmol) was added to a solution of sodium bisulfite (1.52 g, 14.6 mmol) in water (25 mL), and the mixture was stirred at room temperature for 24 h. Unreacted neopentyl ethenesulfonate was removed by washing the water layer with ether (25 mL). The water layer was separated and evaporation of water gave a solid, which was suspended in methylene chloride (25 mL), and phosphorus pentachloride was added until it stopped reacting. The reaction mixture was poured onto ice; the methylene chloride layer was separated and washed with water (25 mL). The methylene chloride layer was separated and dried, and evaporation of the solvent gave the product (0.3 g, 30%). Recrystallization with ether–pentane gave **14** as a white crystalline solid: mp 108.5–109 °C; ^1H NMR 4.11 (m, 2 H), 3.98 (s, 2 H), 3.74 (m, 2 H) and 1.01 (s, 9 H); IR ν_{max} 1382 (s), 1370 (s), 1180 (s), 1165 (s), 952 (s), 933 (s), 850 (m) cm^{-1}. Anal. Calcd for $C_7H_{15}ClO_5S_2$: C, 30.16; H, 5.42; Cl, 12.72; S, 23.00. Found: C, 30.20; H, 5.65; Cl, 12.61; S, 22.89.

4-(Hexadecyloxy)-1-butanesulfonic Acid (21, R = Hexadecyl, *n* = 4). 1-Hexadecanol (2.42 g, 10 mmol) was dissolved in dry cyclohexane (100 mL) and sodium metal (2 equiv) and 1,4-butanesultone (1.36 g, 10 mmol) added. The mixture was heated to reflux under a nitrogen atmosphere for 36 h. Unreacted sodium metal was picked out and acetone (150 mL) added. Filtration gave a solid, which was washed with ether (50 mL) and water (20 mL) and dried to give sodium 4-(hexadecyloxy)-1-butanesulfonate (1.1 g, 28% yield).

Sodium 4-(hexadecyloxy)-1-butanesulfonate (0.5 g, 1.2 mmol) was dissolved in methanol (50 mL) and passed through an ion-exchange resin (Rexyn 101 H^+ form). Evaporation of the solvent gave 4-(hexadecyloxy)-1-butanesulfonic acid hydrate (0.47 g, 95% yield). Recrystallization from hexenes–ether (20:1) gave a white crystalline solid: mp 52–54 °C dec; ^1H NMR δ 9.65 (br s, 3 H, $SO_3H{\cdot}H_2O$), 3.52 (m, 2 H), 3.09 (t, 2 H), 1.84 (m, 4 H), 1.59 (m, 2 H), 1.3 (br s, 26 H), and 0.88 (t, 3 H); IR ν_{max} 3300 (br m), 1710 (br m), 1155 (s), 1105 (s), 1035 (s), 812 (w) cm^{-1}; ^{13}C NMR δ 71.70, 70.68, 51.38, 31.94, 29.73–29.16 (complex ~11 C), 27.66, 25.92, 22.71, 21.25, 14.13. Anal. Calcd for $C_{20}H_{42}O_4S$: C, 63.45; H, 11.18; S, 8.47. Found (after sharp drying): C, 63.31; H, 11.20; S, 8.42.

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Supplementary Material Available: Four tables providing characterization of the products listed in Tables I to IV (12 pages). Ordering information is given on any current masthead page.