Equilibrium Acidities of 2-Alkylthiazolium Cations at the C-2α Position

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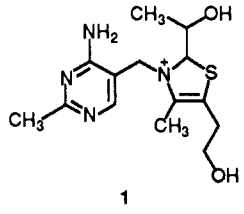
Abstract: The properties of the 2-(1-methoxyethyl)-3,4-dimethylthiazolium cation (**3**) and seven related thiazolium cations have been investigated as models for the behavior of 2-(1-hydroxyethyl)thiamin (**1**). The equilibrium acidity (pK_{HA^+}) of **3** in Me_2SO solution was found to be 14.1 ± 0.05, and evidence is presented to indicate that the value in aqueous solution is within ±1 unit of this value. These values are 3 units, or more, lower than previous estimates for the pK_{HA^+} at C-2α of the thiazolium moiety in **1**, which were based on kinetic measurements. Related thiazolium cations, where Me, RO, or Ph groups were introduced into the C-2 side chain, were found to have acidities in the 9–15 pK_{HA^+} range.

The conjugate base obtained by removing the acidic C2α hydrogen atom of 2-(1-hydroxyethyl)thiamin (**1**) is effective in both



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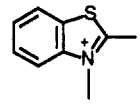

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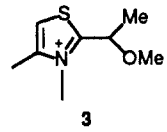

3

enzymic and nonenzymic catalysis.[1] Its acidity and the acidities of related models, such as the 2,3-dimethylbenzothiazolium cation (**2**) and the 2-(1-methoxyethyl)-3,4-dimethyl-thiazolium cation (**3**), have therefore been a matter of considerable interest for the past two decades.

A rough estimate of 17 for the pK_{HA^+} value[2] of the C2α hydrogen atom in the thiazolium moiety in **1** in aqueous solution was made early on by assuming that its rate of deprotonation could be fitted to a Brønsted plot derived for various carbonyl carbon acids.[3a] A pK_{HA^+} of about 17 was also estimated for model **2**, on the basis of the rate of deprotonation of the α-CH_3 group by water. In that study it was assumed that the rate of protonation of the conjugate base of **2** by H_3O^+ was diffusion controlled (10^{10} M^{-1} s^{-1}).[3b] This pK_{HA^+} value was believed to be an upper limit, however, because the Brønsted plot derived from rates with varied buffer bases was less than 1.0 (β = 0.63). An upper limit of the pK_{HA^+} of about this order of magnitude was also estimated recently for model **3**, based on its behavior toward bases in pyridine and dimethyl sulfoxide.[4] It was pointed out, however, that these pK_{HA^+} values are surprisingly high considering that several thiamin diphosphate-dependent enzymes must keep this C–H bond ionized at a pH near 7. On the other hand, the C-2 proton in the thiazolium moiety of thiamin itself has also been assigned an acidity in this pK_{HA^+} range (16.9–18.9).[5]

A previous attempt in our laboratory to measure the equilibrium acidity of a related model, the 2,3,4-trimethylthiazolium cation, in dimethyl sulfoxide solution gave a much lower pK_{HA^+} value (13.8).[6] This value was somewhat suspect, however, because the indicator-absorbance reading obtained on addition of the acid continued to decrease slowly after the initial drop instead of remaining constant, as in a normal titration. This required extrapolation of the absorbance reading back to zero time and limited the titration to a one-point run. The successful generation and characterization of the enamine formed by deprotonation of **3**[4] encouraged us to undertake a study of the acidity of **3** and related thiazolium cations. The successful determination of these thermodynamic acidities is reported herein.

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Results and Discussion

Preliminary Titrations and Cyclic Voltammetric (CV) Measurements. Addition of a Me_2SO solution of thiazolium nitrate **3** to Me_2SO solutions of indicator anions having pK_{HA} values of 19.9 (carbazole), 18.9 (4-chloro-2-nitroaniline), 18.1 (2-(phenylsulfonyl)fluorene), 17.9 (9-phenylfluorene), 16.8 (2,6-di-*tert*-butyl-phenol), and 15.4 (9-(phenylthio)fluorene) gave marked decreases in absorbances in every instance, showing that the pK_{HA^+} of **3** was well below any of these values. The formation of the enamine from **3** in these reactions was confirmed in two instances by the observation of the characteristic NMR peaks in Me_2SO-d_6 reported earlier.[4] On the other hand, addition of the thiazolium nitrate **3** to a Me_2SO solution containing the 9-$EtSO_2Fl^-$ ion (pK_{HA} = 12.3) caused no significant drop in absorbance, indicating that the pK_{HA^+} of **3** was several units higher than 12. These titration experiments bracketed the pK_{HA^+} of **3** between 12 and 15.4. Additional CV experiments demonstrated that a reversible acid–base equilibrium could be established.

Addition of successive aliquots of a Me_2SO solution of thiazolium nitrate **3** to a Me_2SO solution of 9-phenylfluorenide ion (pK_{HA} = 17.9) caused the CV peak at –0.123 V, characteristic of the 9-$PhFl^-$ ion, (curve 1 in A of Figure 1) to diminish progressively and a new peak at 0.266 V, characteristic of the enamine derived from **3**, to appear (curves 2 and 3 in A of Figure 1). A similar result was obtained by adding the nitrate of **3** to a solution of potassium carbazolide ion in Me_2SO, $E_{ox}(A^-)$ = 0.541 (B in Figure 1). These deprotonations could be reversed by adding 9-$EtSO_2FlH$ to the solutions containing the enamine. This caused the CV peak characteristic of the enamine (curve 1 in C of Figure 1) to be replaced by a CV peak for the 9-$EtSO_2Fl^-$ ion at 0.531 V (curve 2 in C of Figure 1). These experiments showed that acid–base equilibria between the indicators (InH), the indicator anions (In^-), cation **3**, and the enamine of **3** were being established in Me_2SO solution. Supporting evidence was obtained by determination of an acid–base-equilibrium constant by NMR.

Titration of the 2α-Carbanion–Enamine Derived from 3 with 9-(*t*-BuCO)FlH. The enamine of **3** was generated in Me_2SO-d_6 by addition of a Me_2SO-d_6 solution containing 0.5 equiv of

(1) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. (b) Krampitz, L. O. *Annu. Rev. Biochem.* **1969**, *38*, 213–240. (c) Kluger, R. *Chem. Rev.* **1987**, *87*, 863–876.

(2) In this paper we use the symbol pK_{HA} for the equilibrium acidity of a weak acid, HA, or for the acidity of its conjugate base, A^-. The symbol pK_{HA^+} is used for the acidity of a cation, such as the thiazolium ion, or the conjugate acid of an amine.

(3) (a) Crosby, J.; Stone, R.; Lienhard, G. E. *J. Am. Chem. Soc.* **1970**, *92*, 2891–2900. (b) Zoltewicz, J. A.; O'Halloran, J. K. *J. Org. Chem.* **1978**, *43*, 1713–1717.

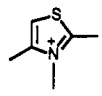
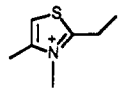
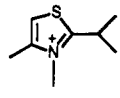
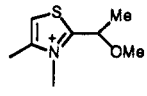
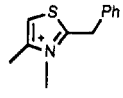
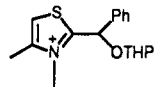
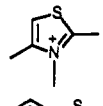
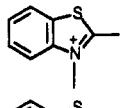
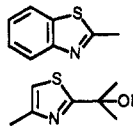
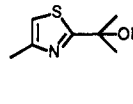
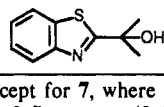
(4) Jordan, F.; Kudzin, H. Z.; Rios, C. B. *J. Am. Chem. Soc.* **1987**, *109*, 4415–4418.

(5) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674–683.

(6) Singer, D. L. Ph.D. Dissertation, Northwestern University, 1981.

0002-7863/90/1512-792$02.50/0

Table I. Equilibrium Acidities of Thiazolium Cations and Related Compounds in Dimethyl Sulfoxide at 25 °C

no.	acid (HA^+)[a]	InH (pK_{HIn})[b]	pK_{HA^+}[c]	ΔpK_{HA^+}[d]
4		HZFO2 (12.95)	13.86 (0.01)	(0.0)
5		FMY33 (13.8) HZFO2P (11.98)	12.70 ± 0.02 12.70 ± 0.02	1.4
6		FMY33 (13.8) H2FP2 (14.15)	14.85 ± 0.05 14.80 ± 0.1	−0.40
3		FSC3M7 (13.2) HZFO2 (12.95)	14.14 ± 0.02 14.15 ± 0.03	0.22
7		9-COMFH (10.35)	9.75 ± 0.04	4.3
8		HZFO2P (11.98)	12.40 ± 0.02	2.0
9		HZFO2 (12.95) FSC3M7 (13.2)	14.3 ± 0.01 14.3 ± 0.01	−0.44
10		4-NO_2-2,6-di-t-BuC_6H_3OH (7.3)	8.5 ± 0.1	5.4
11		DDH (29.4) PXH (27.9)	27.7[d] 27.5[d]	
12		MCLPH (26.6) log K_{AHA} HB1 (26.1) log K_{AHA}	25.71 ± 0.07 3.78[e] 25.69 ± 0.02 3.88[e]	
13		PXH (27.9) log K_{AHA}	26.66 ± 0.04 3.32[e]	

[a] The counterion was I^-, except for **7**, where it was NO_3^-. The pK_{HA^+} is independent of counterion. [b] The indicators are NTBUH, 4-nitro-2,6-di-*tert*-butylphenol; HZFO2P, 9-fluorenone (2,4-dichlorophenyl)hydrazone; HZFO2, 9-fluorenone (2-chlorophenyl)hydrazone; FSC3M7, 2-bromo-9-(phenylthio)fluorene; FMY33, 2-(phenylsulfonyl)-9-phenylfluorene; HZFP2, 9-fluorenone (4-chlorophenyl)hydrazone; PXH, 9-phenylxanthene; DDH, diphenyldiphenylmethane; 9COMFH, 9-carbomethoxyfluorene; MCLPH, 9-(*m*-chlorophenyl)xanthene; HB1, iminostilbene. [c] Measured by the general method described in earlier papers from this laboratory.[8] [d] Reference 6. [e] K_{AHA} is the homohydrogen-bonding constant.[9] [f] $\Delta pK_{HA^+} = pK_{HA^+}$ (**5**–**10**) − pK_{HA^+} (**4**).

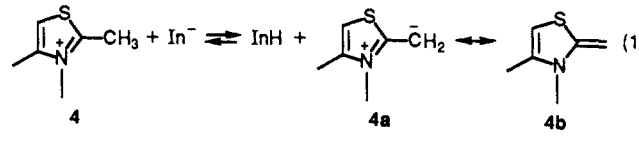
$(Me_3Si)_2NNa$ (pK_{HA} in Me_2SO = 26.1). Addition of successive aliquots of a solution of 9-(*t*-BuCO)FlH in Me_2SO-d_6 to the resulting solution gave equilibrium mixtures containing varying quantities of **3**, the enamine of **3**, 9-(*t*-BuCO)FlH, and the 9-(*t*-BuCO)Fl^- ion. The concentrations of these species were monitored by measuring the relative intensities of the following NMR peaks: CH_3N^+ for **3**, δ 4.24; CH_3N for the enamine, δ 2.82, 3.10; *t-Bu* for 9-*t*-BuCOFlH, δ 1.36; t-*Bu* for 9-(*t*-BuCO)Fl^-, δ 1.44. The pK_{HA^+} value calculated from the equilibrium constants was 13.9 ± 0.1.

Spectrophotometric Titration of 3. Experiment showed that good titrations of **3** could be obtained when indicators that were about 1 pK_{HA^+} unit more acidic than **3** were used. Under these conditions the concentration of In^- ion bases was kept relatively low during the titrations, which minimized side reactions between the In^- ions and species in solution. On addition of each aliquot of the Me_2SO solution of **3**, the absorbance dropped and then remained constant, whereas in titrations with indicators less acidic than **3** ("reaching down") the absorbance continued to decrease slowly after the initial steep drop. Titrations with indicators having pK_{HA} values of 13.2 and 12.95 gave pK_{HA^+} values for **3** of 14.14 ± 0.02 and 14.15 ± 0.03, respectively.

Equilibrium Acidities of Thiazolium Cations in Me_2SO Solution. The results of equilibrium acidity measurements on eight thiazolium cations and a few related compounds are summarized in Table I.

In considering the effects of structural changes on the acidities of thiazolium cations we will use the pK_{HA^+} for 2,3,4-trimethylthiazolium cation (**4**) as a reference point. A three-point titration gave a pK_{HA^+} of 13.86 ± 0.01 for **4**, confirming the earlier value of 13.8 obtained by two one-point titrations.[6] Dissociation of a proton from **4** gives the relatively unhindered enamine, **4a** ↔ **4b**, for which **4b** is no doubt the principal contributor.

Replacement of one or both of the hydrogen atoms in the methylene side chain of **4** by Me, Ph, or RO groups is expected to have a stabilizing electronic influence on the C=C bond, which will tend to shift the equilibrium in eq 1 to the right. From Hine's



4 **4a** **4b**

estimates of double bond stabilizing parameters,[7] the effects for

(7) (a) Hine, J. *Structural Effects on Equilibria in Organic Reactions*; Wiley-Interscience: New York, 1975; Chapter 8. (b) Hine, J.; Linden, S.-W.; Wang, A.; Thiagarajan, V. *J. Org. Chem.* **1980**, *45*, 2821–2825.
(8) (a) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
(9) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424–1427.

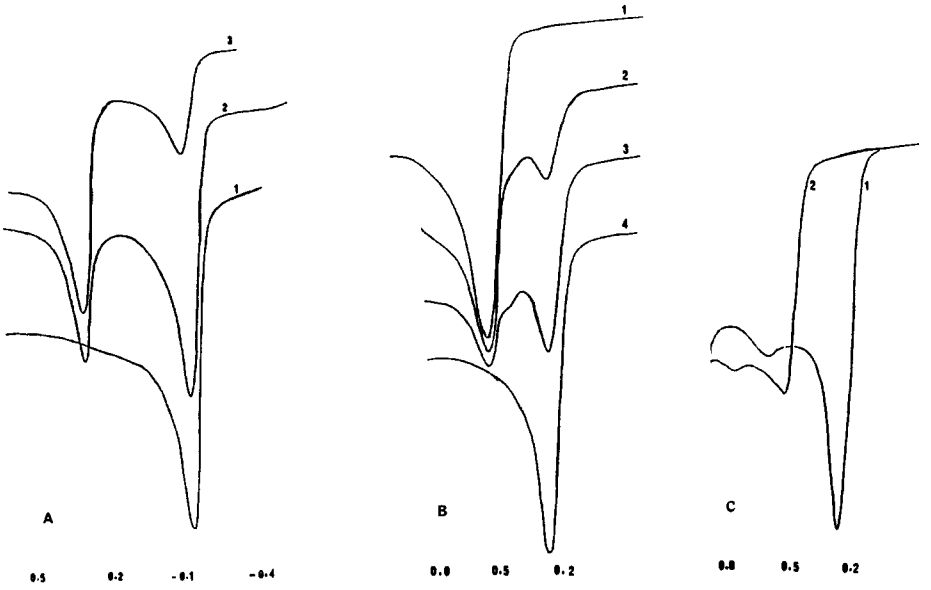


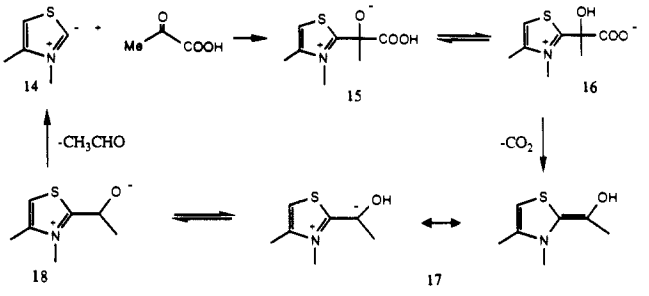
Figure 1. Cyclic voltammograms (CV tracings) showing the following: (A) the effect of adding two successive aliquots (curves 2 and 3) of a solution of thiazolium nitrate **3** to the CV recorded for a solution of 9-phenylfluorenide ion (curve 1), (B) the generation of the enamine (curve 4) by adding aliquots of a solution of thiazolium nitrate **3** to the CV recording of carbazolide ion (curve 1), and (C) formation of 9-(ethylsulfonyl)fluorenide ion (curve 2) by adding an excess of a solution of 9-(ethylsulfonyl)fluorene to a solution of the enamine (curve 1).

these groups could be as large as 3.2, 4.9, and 5.2 kcal/mol, respectively. It should be noted, however, that the S and N moieties attached to the C=C bond are already exerting strong stabilizing influences thereon (about 3.2 and 8.2 kcal/mol, respectively), so the effects of additional substituents may be moderated by saturation effects. Also, when three or four groups are attached to the C=C bond of the enamine, steric effects caused by twisting of the groups out of the C=C plane and by hindrance to solvation may counteract these acid-strengthening electronic effects to some extent. The ground-state energies of the thiazolium cations will also be influenced by these structural changes, but those effects will probably be relatively small. In any case, they are largely unknown quantities.

Examination of Table I shows that **5**, in which the 2-methyl group of **4** has been replaced by a 2-ethyl group, is 1.4 pK_{HA^+} units (1.9 kcal/mol) more acidic than **4**, which is consistent with the expected stabilization of the enamine by methyl substitution. This trend is reversed by a second methyl substitution to give **6**, presumably due to saturation and steric effects. Replacement of one of the α-Me groups in **6** by MeO, to give **3**, causes a 0.6 pK_{HA^+} unit increase in acidity, consistent with the larger stabilizing effect of MeO than Me on the C=C bond.[7] Replacement of an α-hydrogen atom in **4** by Ph, to give **7**, increases the acidity by 4.3 pK_{HA^+} units. This stabilizing effect on the enamine is 1 kcal/mol larger than predicted by Hine's double bond parameter for Ph, but smaller than most α-Ph effects in stabilizing carbanions.[10] The combined Ph and RO acidifying effect in **8** is only 2 pK_{HA^+} units, presumably due to the presence of large steric effects. The small acid-weakening effect caused by introducing a 5-Me group into **4**, to give **9**, is no doubt a consequence of stabilization of the ground state of the thiazolium ion. Fusion of a benzo group onto the 4- and 5-positions of the thiazole ring to give the 2,3-dimethylbenzothiazolium cation (**10**) increases the acidity by 5.4 pK_{HA^+} units. Here, stabilization of the enamine is effected by delocalization of the lone pair on nitrogen, rather than by stabilization of the C=C bond. We note that the pK_{HA^+} for **10** of 8.5 ± 0.1 is over 8 units lower than a previous estimate based on a kinetic analysis.[3b]

Equilibrium Acidities of Thiazolium Cations in Aqueous Solution. The thiazolium salts in Table I, with the exception of **7** and **10**, are too weakly acidic to be measured in aqueous solution. The acidities of 2-benzyl-3,4-dimethylthiazolium and 2,3-dimethyl-

Scheme I



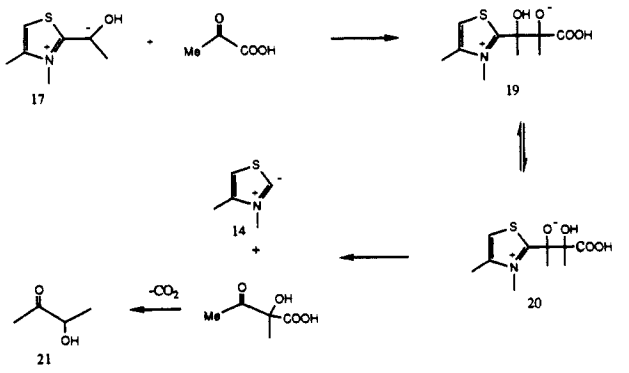
benzothiazolium iodides (**7** and **10**) were determined by adding successive aliquots of 0.02 M aqueous potassium hydroxide to the salts, and measuring the pH of the resulting solutions. For **7**, the formation of the enamine during the titration was demonstrated by visible spectroscopy, and NMR studies in D_2O showed that the thiazolium cation was regenerated by addition of trifluoroacetic acid. The pK_{HA^+} values found were 10.75 ± 0.05 and 7.5 ± 0.05 for **7** and **10**, respectively. Thus, the change from Me_2SO to H_2O causes pK_{HA^+} to increase by 1.0 unit for **7** and to decrease by 1.0 unit for **10**. The thiazolium cations are solvated in both Me_2SO and H_2O by electrostatic effects; the enamines formed on deprotonation are solvated in H_2O by hydrogen bonding, as well as by electrostatic effects. Evidently subtle changes in these solvation effects account for the differing behavior of the pK_{HA^+} values for **7** and **10** due to the change in solvent. A somewhat similar behavior has been observed for the conjugate acids of primary amines vs those of secondary and tertiary amines. In changing from Me_2SO to H_2O, the pK_{HA^+} values for $R_2NH_2^+$ and R_3NH^+ cations were found to increase by 0.5–1.5 units, whereas those for RNH_3^+ cations decreased by 0.5–1.5 units.[11] We conclude from a consideration of these data that we can expect the pK_{HA^+} values for thiazolium cations in aqueous solution to be within ±1 unit of those in dimethyl sulfoxide solution.

Mechanisms of Catalytic Action of 2-(1-Hydroxyethyl)thiamin (1). The enamine derived from 2-(1-hydroxyethyl)thiamin (**1**) by deprotonation of the C-2α position is believed to play important catalytic roles when enzyme-bound in all thiamin-dependent enzymatic processes such as (a) the decarboxylation of pyruvic acid and (b) the formation of acetolactate. These functions are illustrated in Schemes I and II with conjugate bases derived from

(10) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *12*, 321–325.

(11) Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23–28.

Scheme II



3,4-dimethylthiazolium and 2-(1-hydroxyethyl)-3,4-dimethylthiazolium cations, **14** and **17**, respectively, serving as models for the conjugate bases derived from thiamin and 2-(1-hydroxyethyl)thiamin.

In Scheme I, the carbanion ylide **14** effects an addition to the highly electrophilic carbonyl group of pyruvic acid to give **15**. Tautomerism of **15** to **16** is exothermic and is expected to occur rapidly. Loss of carbon dioxide from **16** gives enamine **17**, the conjugate acid of which has a pK_{HA^+} of about 14 in Me_2SO (based on that of its Me ether, **3**, in Table I) and is estimated to have a pK_{HA^+} of 14 ± 1 in water. Since the pK_{HA} of zwitterion **18** can be expected to be in about the same range (see below), tautomerism of **17** to **18** will also occur readily. Finally, loss of acetaldehyde from **18** gives ylide **14**. (This moiety in thiamin has been reported to have a pK_{HA} of 16.9–18.9.[5]) Crosby, Stone, and Lienhard found that the decarboxylation **16** to **17** is strongly accelerated in Me_2SO solution where solvation of the negative charge on oxygen of the carboxylate ion is greatly reduced, and have suggested that enzymic reactions may occur in a similar relatively hydrophobic environment.[3a]

Compound **12** is an unquaternized model for the conjugate acid of **18** wherein the hydroxyl group is tertiary, rather than secondary. We were unable to measure a pK_{HA^+} value for 2-(1-hydroxy-1-methylethyl)-3,4-dimethylthiazolium iodide (N-methylated **12**), because rapid deprotonation and elimination occurred in the presence of indicator bases in the pK_{HA} 14–16 region, as evidenced by a rapid drop in absorbance. The drop in absorbance was slow, however, when the thiazolium ion was added to a Me_2SO solution of In^- ion having a pK_{HA} of 13.2. Less basic In^- ions caused no reaction, presumably because they failed to deprotonate the alcohol. These results point to a pK_{HA^+} for N-methylated **12** about 3 units higher than 13.2, i.e., ~16. (The corresponding secondary alcohol, the conjugate acid of **18**, would be expected to have a pK_{HA^+} value 1 or 2 units lower.) The pK_a of **12** itself is about 10 units higher. Comparison of the pK_{HA^+} value of 27.6 for **11** with that of 8.5 for **10** shows that quaternization by N-methylation in this instance caused an increase in acidity of 19 pK_{HA^+} units (26 kcal/mol). For **12**, the effect of quaternization by N-methylation is smaller because the acidic proton is one atom further removed from the quaternary nitrogen atom. If we assume a transition coefficient of 0.5, the effect of quaternization on **12** would be expected to be about half that for **10** vs **11**, as observed.

In Scheme II, enamine **17** initiates a benzoin-type condensation with pyruvic acid to give **19**. Proton transfer gives **20**, which undergoes an elimination reaction to generate **14** and acetolactic acid. The latter may then undergo thermal decarboxylation to form acetoin (**21**). In an aqueous environment the tautomers **17** and **18** should be present in about equal concentration, but the greater nucleophilicity of the carbanionic site toward the carbonyl group dictates the observed course of the condensation.

Summary and Conclusions

The establishment of an acid–base equilibrium between the 2-(1-methoxyethyl)-3,4-dimethylthiazolium cation (**3**) and its conjugate base, an enamine, has been demonstrated by NMR and cyclic voltammetry. The equilibrium acidity of **3** in Me_2SO has been determined by NMR and measured precisely by spectrophotometric titrations using appropriate indicators. The values of pK_{HA^+}, 14.1 ± 0.05, found in Me_2SO solution, and that of 14 ± 1 estimated for aqueous solution are about 3 units lower than that for 2-(1-hydroxyethyl)thiamin estimated previously by kinetic measurements in aqueous solution. The lower value is more in line with the function of **1** in enzymic catalysis at physiological pH's. We will refrain from speculation as to how the enzyme can effect such catalysis, however, until detailed kinetic information on proton transfers between model **3** (and/or **1**) and the corresponding enamine becomes available. Equilibrium acidities for seven other thiazolium ions structurally related to **3** were found to be in the range of pK_{HA^+} = 8.5–14.8 in Me_2SO. Two of the more acidic thiazolium ions were found to have acidities in aqueous solution that were within ±1 unit of that in Me_2SO. The effects of structural changes on acidities in Me_2SO were shown to be consistent with stabilization of the C=C bonds in the enamine by donor groups, as predicted by Hine's double bond stabilization parameters.

Experimental Section

Synthesis. Materials. 2,4-Dimethylthiazole was purchased from Kodak, Rochester, NY; 2-methylbenzothiazole, 4-methylthiazole, and 2,4,5-trimethylthiazole were purchased from Aldrich, Milwaukee, WI; 2-ethylthiazole and 2-isopropylthiazole were purchased from Pyrazine Specialties, Atlanta, GA. 9-Pivaloylfluorene was a gift from Prof. C. Y. Meyers, University of Southern Illinois, Carbondale, IL. The preparation of indicators not commercially available has been described earlier.[12] 2-(2-Hydroxyisopropyl)benzothiazole (**13**) was prepared by the method of Corey.[13]

2,3,4-Trimethylthiazolium Iodide (4).[14] 2,4-Dimethylthiazole (1.0 g, 8.8 mmol) was mixed with excess methyl iodide (1.0 mL) in a sealed tube for 5 h during which time crystals formed. The product was recrystallized from ethanol (1.9 g, 7.5 mmol, 85%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.6 (s, 1 H, C5-H), 3.80 (s, 3 H, NCH_3), 2.80 (s, 3 H, C2-CH_3), 2.46 (s, 3 H, C4-CH_3). Anal. Calcd for $C_6H_{10}NSI$: C, 28.25; H, 3.95; N, 5.49; I, 49.74. Found: C, 28.25; H, 3.90; N, 5.57; I, 49.33.

2-Ethyl-3,4-dimethylthiazolium Iodide (5). 2-Ethyl-4-methylthiazole (1.0 g, 7.1 mmol) was mixed with excess methyl iodide (3 mL) for 24 h at 40 °C. The crystals formed were recrystallized from ethanol (1.0 g, 3.7 mmol, 52%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.5 (s, 1 H, C5-H), 3.8 (s, 3 H, NCH_3), 3.15 (q, 2 H, J = 6.5 Hz, C2-CαH_2), 2.45 (s, 3 H, C4-CH_3), 1.43 (t, 3 H, J = 6.5 Hz, C2-CβH_3). Anal. Calcd for $C_7H_{12}NSI$: C, 31.24; H, 4.50; N, 5.20; S, 11.91; I, 47.15. Found: C, 31.02, H, 4.50; N, 5.30; S, 10.89; I, 48.30.

2-Isopropyl-3,4-dimethylthiazolium Iodide (6). 2-Isopropyl-4-methylthiazole (1.0 g, 7.1 mmol) was mixed with excess methyl iodide (3 mL) for 4 h at 35 °C. The crystals formed were recrystallized from ethanol (1.1 g, 3.8 mmol, 55%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.65 (s, C5-H), 3.85 (s, 3 H, NCH_3), 3.65 (sept, 1 H, J = 6.1 Hz, C2-CαH), 2.45 (s, 3 H, C4-CH_3), 1.40 (d, 6 H, J = 6.1 Hz, C2-CβH_3). Anal. Calcd for $C_8H_{14}NSI$: C, 33.93; H, 4.98; N, 4.95; I, 44.82. Found: C, 33.88, H, 4.91; N, 4.88; I, 45.06.

2-(1-Hydroxyethyl)-4-methylthiazole.[15] *n*-Butyllithium (6.0 mL, 10.0 M, 60 mmol) was dissolved in THF (20 mL) and cooled in a dry ice/acetone bath at −77 °C. 4-Methylthiazole (5.9 g, 60 mmol) dissolved in THF (15 mL) was added portionwise via a syringe through a septum under argon. The reaction mixture was stirred for 45 min. Acetaldehyde (9.25 g, 210 mmol) dissolved in THF (15 mL) and chilled to 0 °C was next added portionwise via the same device. The reaction mixture was stirred under the same conditions for an additional hour, after which a mixture of ethanol and water was added between −4 and 0 °C. The solvent was removed and the residue was extracted with ether and water. The ether layer was dried ($MgSO_4$) and upon removal of solvent the crude product was purified by chromatography, yielding an oil (5.15 g, 36 mmol, 60%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 6.8 (s, 1 H, C5-H), 5.0 (q, 1 H, J = 6 Hz, C2-CαH), 3.5 (s, 1 H, OH), 2.3 (s, 3 H, C4-CH_3), 1.55 (d, 3 H, J = 6.7 Hz, C2-CβH_3). Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; S, 22.39. Found: C, 49.8; H, 6.30; N, 9.80; S, 21.70.

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2-(1-Methoxyethyl)-4-methylthiazole.[16] Sodium hydride (1.15 g, 80% in oil, 38.5 mmol) was washed with anhydrous hexane and was suspended in anhydrous THF (40 mL) under argon at 0 °C. 2-(1-Hydroxyethyl)-4-methylthiazole (5.0 g, 35 mmol) dissolved in 20 mL of THF was added dropwise into the NaH suspension over a period of 30 min. The reaction mixture was stirred under the same conditions for 1 h until all of the NaH reacted. Methyl iodide (5.7 g, 40 mmol) dissolved in 10 mL of THF was added portionwise to the reaction mixture over a period of 20 min, and the resulting reaction mixture was stirred for 1.5–2 h until the reaction was completed. The reaction mixture was treated with methanol (5 mL), and the solvent was evaporated. The residue was extracted with ether and water, and the ether extract dried ($MgSO_4$). The solvent was removed, yielding an oil which was purified by column chromatography (2.86 g, 18 mmol, 52%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 6.8 (s, 1 H, C5-H), 4.6 (q, 1 H, J = 6.4 Hz, C2-CαH), 3.34 (s, 3 H, OCH_3), 2.37 (s, 3 H, C4-CH_3), 1.46 (d, 3 H, J = 6.4 Hz, C2-CβH_3). Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91; S, 20.39. Found: C, 53.13; H, 7.10; N, 9.02; S, 19.8.

2-(1-Methoxyethyl)-3,4-dimethylthiazolium Iodide (3).[16] 2-(1-Methoxyethyl)-4-methylthiazole (1.5 g, 9.5 mmol) was mixed with excess methyl iodide (3 mL) in a sealed tube at approximately 60 °C for 3–4 h. The crystals formed were isolated, washed with ether, and recrystallized from ethanol (2.5 g, 8.4 mmol, 87%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.65 (s, 1 H, C5-H), 5.47 (q, 1 H, J = 6.4 Hz, C2-CαH), 4.20 (s, 3 H, NCH_3), 3.46 (s, 3 H, OCH_3), 2.60 (s, 3 H, C4-CH_3), 1.59 (d, 3 H, J = 6.4 Hz, C2-CβH_3). Anal. Calcd for $C_8H_{14}NOSI$: C, 32.23; H, 4.39; N, 4.70; I, 42.56. Found: C, 31.89; H, 4.76, N, 4.67; I, 42.55.

2,3,4,5-Tetramethylthiazolium Iodide (9). 2,4,5-Trimethylthiazole (1.0 g, 7.9 mmol) was reacted with excess methyl iodide (1.0 mL) in a sealed tube for 5 h. The crystals thus formed were recrystallized from ethanol (1.8 g, 6.3 mmol, 80%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 3.80 (s, 3 H, NCH_3), 2.89 (s, 3 H, C2-CH_3), 2.50 (s, 3 H, C4-CH_3), 2.26 (s, 3 H, C5-CH_3). Anal. Calcd for $C_7H_{12}NSI$: C, 31.12; H, 4.49; N, 5.20; I, 47.15. Found: C, 31.24; H, 4.43; N, 5.23; I, 46.88.

2-Benzyl-4-methylthiazole.[17] Benzyl cyanide (20.3 g, 173.4 mmol), pyridine (20 mL), and triethylamine (20 mL) were mixed together. Dry hydrogen sulfide (Matheson) was bubbled through the reaction mixture with vigorous stirring. After the mixture was allowed to react overnight, water was added, forming phenylthioacetamide.[18] After recrystallization from benzene, the phenylthioacetamide was dissolved in ethanol, and an equimolar amount of chloroacetone added. The reaction mixture was stirred and refluxed overnight. The reaction mixture was cooled to room temperature and acidified with hydrochloric acid to pH 4, and the solvent was removed at a rotary evaporator. Sodium carbonate was added to raise the pH to 8 and the aqueous solution was extracted with ether (3 × 50 mL). The ether layer was dried ($MgSO_4$), and the ether was removed at a rotary evaporator. The remaining liquid was distilled under reduced pressure (75 °C, 2 mm), yielding a colorless liquid (19.3 g, 102.0 mmol, 59%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.31 (m, 5 H, C_6H_5), 6.72 (s, 1 H, C5-H), 4.29 (s, 2 H, C2-CαH_2), 2.43 (s, 3 H, C4-CH_3).

2-Benzyl-3,4-dimethylthiazolium Iodide (7). 2-Benzyl-4-methylthiazole (1.0 g, 5.3 mmol) was dissolved in excess methyl iodide (3 mL) at room temperature. After 5 h the crystals formed were filtered and washed with ether (1.5 g, 4.4 mmol, 83%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.39–7.52 (m, 6 H, C_6H_5 and C5-H), 4.65 (s, 2 H, C2αH_2), 3.95 (s, 3 H, NCH_3), 2.42 (s, 3 H, C4-CH_3). Anal. Calcd for $C_{12}H_{14}NI$: C, 43.52; H, 4.26; N, 4.23; I, 38.31. Found: C, 43.37; H, 4.24; N, 4.29; I, 36.75.

2-(1-Hydroxybenzyl)-4-methylthiazole.[19] n-Butyllithium (6.0 mL, 10.0 M, 60 mmol) was dissolved in THF (20 mL), and the solution was cooled in a dry ice/acetone bath at −77 °C. 4-Methylthiazole (5.9 g, 60 mmol) dissolved in THF (15 mL) was added portionwise via a syringe through a septum under argon. The reaction was stirred for 45 min, and benzaldehyde (6.36 g, 60 mmol) dissolved in THF (20 mL) was added portionwise via the same device. The mixture was reacted for 1.5–2 h after which a mixture of ethanol/water was added at −4 to 0 °C. The solvent was removed and the residue was extracted with ether and water. The ether layer was dried ($MgSO_4$), the solvent was evaporated, and the crude product was purified by chromatography on silica gel, yielding a solid (7.8 g, 38.4 mmol, 64%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.35 (m, 5 H, C_6H_5), 6.82 (s, 1 H, C5-H), 6.00 (s, 1 H, C2-CαH), 2.39 (s, 3 H, C4-CH_3). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 63.92; H, 5.41; N, 6.90; S, 15.32.

2-[1-(Tetrahydropyranyloxy)benzyl]-4-methylthiazole (Two Diastereomeric *d,l* Mixtures). 2-(1-Hydroxybenzyl)-4-methylthiazole (2.0 g, 9.6 mmol), dihydropyran (1.6 g, 19.27 mmol), and p-toluenesulfonic acid (92 mg, 0.48 mmol) were dissolved in THF (50 mL). The solution was heated at reflux for 1–1.5 h. The solvent was removed, and the oily residue was dried. The residue was extracted with anhydrous hexane and was further treated with anhydrous $MgSO_4$. The solvent was removed and the resultant oil was purified by silica gel (60–200 mesh) chromatography eluting with a mixture of hexane/ether (2.53 g, 8.74 mmol, 90.7%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.5–7.2 (m, 10 H, C′$_6H_5$/C_6H_5), 6.83 (s, 1 H, C5′-H), 6.81 (s, 1 H, C5-H), 6.1 (s, 1 H, C2α-H), 6.0 (s, 1 H, C2′α-H), 4.9 (t, 1 H, THP′), 4.7 (t, 1 H, THP), 4.0–3.75 (m, 2 H, THP), 3.6–3.4 (m, 2 H, THP′), 2.4 (s, 3 H, C4′-CH_3), 2.37 (s, 3 H, C4-CH_3), 2.0–1.5 (m, 12 H, THP/THP′). Anal. Calcd for $C_{16}H_{20}NO_2S\cdot{}^1/_2H_2O$: C, 64.19; H, 6.73; N, 4.68; S, 10.71. Found: C, 64.41; H, 6.88; N, 3.98; S, 9.58.

2-[1-(Tetrahydropyranyloxy)benzyl]-3,4-dimethylthiazolium Tetrafluoroborate (8) (Two Diastereomeric *d,l* Mixtures). 2-[1-(Tetrahydropyranyloxy)benzyl]-4-methylthiazole (250 mg, 0.86 mmol) was dissolved in methylene chloride (5 mL). Trimethyloxonium tetrafluoroborate (127 mg, 0.86 mmol) was added to the solution at 0 °C under argon. The mixture was stirred at 0–4 °C under an argon-purified atmosphere for 16–20 h. The solution was then filtered, and the solvent was removed. The dried residue was washed with anhydrous ether several times and dried to give a white solid which was recrystallized from EtOH (yield: 285 mg, 0.73 mmol, 85%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.7 (s, 1 H, C5-H), 7.45 (m, 5 H, C_6H_5), 6.25 (s, 1 H, C2α-H), 5.0 (t, ca. 0.4 H, THP-H), 4.6 (t, ca. 0.6 H, THP-H), 3.85–3.4 (m, 2 H, THP), 3.7 (s, ca. 1.8 H, NCH_3 isomeric mixture), 3.65 (s, ca. 1.2 H, N′CH_3 isomeric mixture), 2.45 (s, 3 H, C4-CH_3), 1.8–1.4 (m, 6 H, THP). Anal. Calcd for $C_{17}H_{23}NO_2SBF_4\cdot{}^1/_2H_2O$: C, 50.89; H, 6.03; N, 3.49; S, 7.99. Found: C, 50.91; H, 5.53; N, 3.72; S, 8.44.

2-(1-Hydroxy-1-methylethyl)-4-methylthiazole (12). n-Butyllithium (6.0 mL, 10.0 M, 60 mmol) was dissolved in THF (20 mL) and was cooled in a dry ice/acetone bath at −77 °C. 4-Methylthiazole (6.0 g, 60 mmol) dissolved in THF (15 mL) was added portionwise via syringe through a septum under argon. The reaction was stirred for 45 min. Acetone (3.5 g, 60 mmol) dissolved in THF (10 mL) was then added portionwise via the same device. The mixture was reacted for 1.5–2 h after which a mixture of ethanol/water was added at −4 to 0 °C. The solvent was removed and the residue was extracted with ether and water. The ether layer was dried over anhydrous $MgSO_4$ and upon removal of solvent yielded a crystalline solid which was recrystallized to give pure product (3.9 g, 25.2 mmol, 42%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 6.8 (s, 1 H, C5-H), 3.0 (s, 1 H, OH), 2.45 (s, 3 H, C4-CH_3), 1.65 (s, 6 H, isopropyl-CH_3). Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91; S, 20.39. Found: C, 52.61; H, 7.13; N, 8.63; S, 19.71.

2-(1-Hydroxy-1-methylethyl)-3,4-dimethylthiazolium Iodide. 2-(1-Hydroxy-1-methylethyl)-4-methylthiazole (1.5 g, 9.5 mmol) was reacted with excess methyl iodide (2.0 mL) in a sealed vessel for 3–4 h at 30 °C. The reaction mixture was diluted with ether, and the volatile materials were removed. The solids obtained were washed with ether and recrystallized from ethanol (1.5 g, 5.0 mmol, 53%). ^1H NMR (200 MHz, CD_3CN/TMS): δ 7.61 (s, 1 H, C5-H), 5.15 (s, 1 H, OH), 4.01 (s, 3 H, NCH_3), 2.44 (s, 3 H, C4-CH_3), 1.76 (s, 6 H, isopropyl-CH_3). Anal. Calcd for $C_8H_{14}NOSI$: C, 32.12; H, 4.72; N, 4.68; S, 10.72; I, 42.19. Found: C, 32.01; H, 4.69; N, 4.48; S, 9.86; I, 43.30.

Titration Using ^1H NMR. Solutions of thiazolium salt, sodium bis(trimethylsilyl)amide and pivaloylfluorene in DMSO-d_6 were prepared in cells pump purged at least three times with argon (prepared as in the case of spectrophotometric titrations but at higher concentration). The NMR tube was flushed with argon and additions were made under an argon screen. The amount of reagents added was measured gravimetrically. From the ratio of the integration of =N$^+$—Me (δ 3.93) and —N—Me (δ 3.10 and 2.98), the concentrations of thiazolium and enamine were calculated. Subsequently, as aliquots of pivaloylfluorene solution were added, the ratio of salt to enamine changed. From the changes in these concentrations, the ratios of [9-RFlH] to [9-RFl$^-$] were deduced. The deduced ratios were in agreement with the ratios of signals at δ 1.36 and 1.44. pK_{HA} values were calculated from the following equations:

$$K_{eq} = [HIn][A^-]/[In^-][HA] \qquad pK_{HA} = pK_{HIn} - \log K_{eq}$$

Electrochemical Measurements. Electrochemical measurements were performed by using a Bioanalytical Systems Inc. CV-27 instrument equipped with a three-electrode assembly. A platinum auxiliary electrode and a platinum working electrode were used. The latter was polished with Buehler alumina water emulsion micropolish II between runs and

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wiped with Kimwipe between scans. A Ag/AgI reference electrode was made by dipping a silver wire coated with AgI by anodic deposition into a saturated solution of $Et_4N^+I^-$ in DMSO and sealed by a VYCOR membrane.

An amount of the neutral compound sufficient to make 5 mL of 3.0 mM solution was weighed into the electrochemical cell and placed on the cell holder. Tetraethylammonium tetrafluoroborate (electrometric grade from Southwestern Analytical Chemicals Inc., dried under vacuum at 70 °C for 48 h, 0.108 mg) was placed in the cell and 5 mL of purified DMSO was added. Pure argon was bubbled through the solution constantly except while recording the scan, at which time the solution was blanketed with argon. About 0.3 equiv of CH_3SOCH_2K (150–200 mM solution) was added in aliquots and the cyclic voltammogram recorded after each addition. In the case of thiazolium salts, the neutral solution was scanned under argon to ensure that the oxidation of the counterion would not cause interference. Cyclic voltammograms were recorded at a scan rate of 100 mV/s on a Houston 100 X-Y recorder. The ferrocenium/ferrocene redox couple (0.875 mV vs Ag/AgI) was used as a standard. The redox couple of ferrocenium/ferrocene was checked against the reference electrode before and after the measurements.

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Stabilization of Crown Ether Containing Supported Liquid Membranes

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Abstract: Lipophilic ionophores, synthesized by coupling crown ethers 18-crown-6 and 12-crown-4 at the termini of polysiloxane backbones, have been tested as carriers in the transport of potassium perchlorate through a supported (Accurel) liquid membrane that contains *o*-nitrophenyl *n*-octyl ether (NPOE) as the membrane phase. The polysiloxane-coupled crown ethers are able to facilitate the ion transport. The stability of the membrane is enhanced in comparison with that of simple crown ethers like dibenzo-18-crown-6 by at least a factor of 25, because of the high partition coefficient (log P_{CE} = 4.7–27) of the carrier for which the contribution of one siloxane moiety to the value of log P_{CE} is 0.6. Experiments with polysiloxane-coupled crown ethers in poly(dimethylsiloxane) as the membrane phase showed a large decrease of the flux, probably due to the unfavorable partition of the salt between water and poly(dimethylsiloxane). The transport through these membranes can be described by a model, assuming thermodynamic equilibrium at the interfaces and linear concentration gradients of both complex and free crown ether. The experimental relation between the flux and the initial carrier concentration can only be explained when the transport takes place via 2:1 (crown ether:cation) complexes for both polysiloxane-coupled 12-crown-4 and polysiloxane-coupled 18-crown-6.

Conventional mass separation techniques are currently supplemented by processes that utilize semipermeable membranes. Disadvantages of solid (micro)porous polymer membranes are the often insufficient transmembrane flux or an insufficient selectivity. Liquid membranes with carrier molecules offer a possible solution for both problems.

So far most of the work in this area has been carried out with bulk liquid membranes composed of a hydrophobic organic solvent which separates two aqueous phases.[1-5] The disadvantage of bulk liquid membranes is the large quantity of carrier relative to the effective area where phase transfer can take place. Consequently, supported liquid membranes have been developed. These are composed of solutions of a carrier in hydrophobic organic solvents, immobilized in thin porous microfiltration films, that separate two aqueous phases. These systems resemble biological membranes in which carrier molecules such as valinomycin facilitate selective transport of potassium ions. Previously, we have reported the mechanism of transport of potassium and guanidinium salts through supported liquid membranes.[6,7]

In order to create a stable supported liquid membrane, the carriers in the membrane phase must possess a high lipophilicity. In a previous paper, we reported the influence of the lipophilicity of the crown ether on the flux of guanidinium thiocyanate through a supported liquid membrane.[7] The experimental results were described in terms of a general model. This model includes as parameters the partition of both the crown ether and the salt, electroneutrality, the complexation constants in both the membrane and the aqueous phases, and the concentration gradients of the crown ether, complex, and salt in the membrane phase. We concluded that with increasing lipophilicity of the crown ether the membrane stability is enhanced while the diffusion coefficient of the carrier molecule hardly decreases. The increased lipophilicity was accomplished by introduction of alkyl or aryl functional groups, but the lifetime of these membrane systems is still limited. An alternative approach would be to bind the carrier molecules to a polymeric support such as liquid polysiloxanes that possess better diffusion properties than solid polymeric materials. Bradshaw et al. have used such polysiloxane-coupled crown ethers as a stationary phase in capillary

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