NMR (100 MHz, δ, $CDCl_3$) 2.6 (2 H, d, J = 5.8 Hz), 3.6 (2 H, s), 3.9 (2 H, d, J = 6.2 Hz), 5.1-5.2 (1 H, m), 7.0-7.4 (5 H, m), 7.7-7.9 (4 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 21.08, 36.20, 39.47, 67.72, 115.39, 123.63, 127.00, 129.03, 129.81, 131.58, 134.36, 167.93, and 168.82 ppm; IR (KBr disk) 3060, 2950, 2250, 1780, 1710, 1400, 1270, 1120, 895, 715, 690 cm^{-1}.

Lipase Resolution. A solution of nitrile **1d** (100 mg, 0.578 mmol) in 0.1 M phosphate buffer (pH 7.2, 3.0 mL) and acetone (0.1 mL) was incubated with lipase P (50 mg) at 40 °C for 3 h. The mixture was extracted with ethyl acetate and separated by silica gel TLC. The optical purity of the alcohols produced and the remaining ester, which was converted into the alcohol by LAH reduction, were determined by the ^1H NMR analysis of the corresponding (+)-MTPA esters, respectively. To hydrolyze the (phenylthio)acetoxy group of **1s**, only the enzymatic reaction using lipase MY (*Candida* sp.) was successful.

Absolute Stereochemistry of 2b, 2c, 2d, and 2e. Authentic (*R*)-(-)-epoxystyrene was converted to (*S*)-3-hydroxy-3-phenylpropionitrile via reaction with KCN.[4c] The product had $[\alpha]^{25}_D$ -45.3° (*c* 1.91, EtOH, 94% ee) and had the reverse optical rotation as **2b**. Therefore, **2b**, which was produced by lipase-catalyzed hydrolysis of **1k**, was established to have the *R* configuration. Authentic (*S*)-(+)-epichlorohydrin (>98% ee) was converted to (*S*)-1-chloro-4-phenyl-2-butanol via reaction with $PhCH_2MgBr$ (THF solution) at -40 °C in the presence of 10 mol % of CuI,[14] and then the chloride was treated with KCN in MeOH to produce (*S*)-3-hydroxy-5-phenylpentanenitrile; $[\alpha]^{25}_D$ -19.7° (*c* 1.45, EtOH, 96% ee). Consequently, **2c**, which was produced by lipase-catalyzed hydrolysis of **1n**, was established to have the *S* configuration. The absolute configuration assignment of **2d** and **2e** was performed by the ^1H NMR analysis of the corresponding (+)-MTPA esters using reference products (*R*)-**2a**, (*R*)-**2b**, (*S*)-**2c**, and (*S*)-**4**. From the diastereomeric differences in chemical shifts made by the methoxy group in (+)-MTPA esters, the configuration was theorized. Since the signal due to the methoxy group of the (+)-MTPA ester of the racemic **2e** split into two peaks (δ 3.58 and 3.49) in the ^1H NMR spectra, the enantiomeric excess of **2e** was calculated by comparison with the intensity of the two peaks. The absolute configuration of **2e**, which was produced by lipase-catalyzed hydrolysis of **1s**, was presumed as *R* of 78% ee because this ratio was just the same tendency of the chemical shift of the methoxy group of the (+)-MTPA ester of 75% ee of (*S*)-*N*-[3-(phenylthio)-2-hydroxypropyl]phthalimide (**4**). Following the same method described as above, the absolute configuration of **2d** was presumed as *R*.

(2*S*)-*N*-[3-(Phenylthio)-2-hydroxypropyl]phthalimide (4). A solution containing 105 mg (0.7 mmol) of phtalimide and (*S*)-glycydyl sulfide[14] (100 mg, 0.61 mmol, 75% ee) in 5 mL of DMF was heated at 140-150 °C for 3 h under argon. The reaction mixture was cooled to room temperature and dissolved in ethyl acetate. The organic layer was washed with water and dried. Evaporation and purification using silica gel TLC (Wako gel B5-F, hexane/ethyl acetate, 2:1), gave **4** (40 mg, 0.143 mmol, 23%): $[\alpha]^{21}_D$ -3.4° (*c* 2.0, THF); R_f 0.5, hexane/ethyl acetate (2:1); mp 38-40 °C; ^1H NMR (100 MHz, δ, $CDCl_3$) 2.9 (2 H, dd, J_1 = 16.8 Hz, J_2 = 8.4 Hz), 3.9-4.1 (3 H, $RNCH_2CHOH$, m), 7.0-8.0 (9 H, m); ^{13}C NMR (50 MHz, δ, $CDCl_3$) 39.54, 42.83, 68.64, 123.41, 123.59, 123.98, 126.85, 129,12, 130.36, 131.86, 132.60, 134.16, 134.24, 134.30, 134.91, 167.95, and 168.70 ppm; IR (KBr disk) 3450, 3200, 2950, 1780, 1710, 1470, 1310, 1050, 790, 710, and 690 cm^{-1}.

(+)-MTPA Ester of (2*S*)-4: ^1H NMR (200 MHz, δ, $CDCl_3$) 3.10 (1 H, dd, J_1 = 7.0 Hz, J_2 = 14.17 Hz), 3.24 (1 H, dd, J_1 = 6.0 Hz, J_2 = 14.18 Hz), 3.44 (O*Me*, d, J = 1.14 Hz), 3.53 (O*Me*, d, J = 1.2 Hz), 4.12 (1 H, dd, J_1 = 7.30 Hz, J_2 = 14.5 Hz), 5.44-5.56 (1 H, m), 7.19-7.90 (14 H, m). The ratio of the peak intensity of two signals due to the methoxy group at δ 3.44 and 3.53 was 87.6 to 12.4

Acknowledgment. We are grateful to Professor Masanori Utaka of the Faculty of Engineering of Okayama University for the helpful discussions throughout this work. We are also grateful to Mr. Eiichiro Amano of the Faculty of Engineering for elemental analyses and the SC-NMR Laboratory of Okayama University for the NMR measurements. We thank Amano Pharmaceutical Co., Ltd., for providing lipases.

Supplementary Material Available: ^1H NMR of compounds **1a-t**, **4**, and the (+)-MTPA ester of (*S*)-**4** and ^{13}C NMR of compounds **1a-t** and **4** (29 pages). Ordering information is given on any current masthead page.

(14) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771.

Lipophilic Derivatives of [2.2.1]- and [2.2.2]Cryptands: Thermodynamics of Micellization of Their Alkali and Alkaline Earth Cryptates[1]

Toni L. Lauricella, Manuel López, Steven R. Miller, Lourdes E. Echegoyen, George W. Gokel,* and Luis Echegoyen*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received February 27, 1990

Critical micelle concentrations (cmc's) were measured at several temperatures in the range 8-32 °C for previously unknown 2-*n*-$C_{14}H_{29}$-[2.2.1], cryptand **1**, in the presence of 1 equiv of either Na^+ or Ca^{2+}. Thermodynamic parameters for micelle formation by the complexes were assessed by using the cmc dependence on temperature, $\Delta H°_{mic}$, which was found to be 3.5 kJ/mol (0.84 kcal/mol) for Na^+·**1**, (cmc at 26 °C = 0.092 mM), and 8.4 kJ/mol (2.0 kcal/mol) for Ca^{2+}·**2** (cmc at 26 °C = 0.583 mM). $\Delta S°_{mic}$ was 0.09 kJ/mol K for both complexes. The overall micellization process is entropy driven (large $T\Delta S°$) while the major difference between the two complexes is of enthalpic origin. These results are compared to the ones observed for the K^+ and Ba^{2+} complexes of known 2-*n*-$C_{14}H_{29}$-[2.2.2]cryptand. These observations help quantitate the problem of micellar surface charge.

Introduction

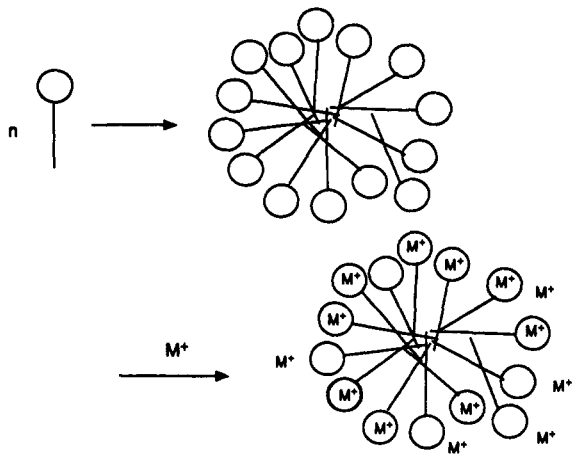
The effect of surface charge on micellar structure, aggregation number, and stability is a subject of considerable current interest and debate. Theoretical, as well as experimental, models have been developed to explain charge effects on amphiphile head groups and the counteranions associated with them in micelles.[2] Macrocyclic polyethers

* Address correspondence concerning the synthetic aspects of this work to G.W.G. and concerning the physical aspects to L.E.

(1) Portions of this work were presented in preliminary form at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (Orange Beach, Alabama, Sept 1988).

0022-3263/91/1956-1524$02.50/0

Scheme I

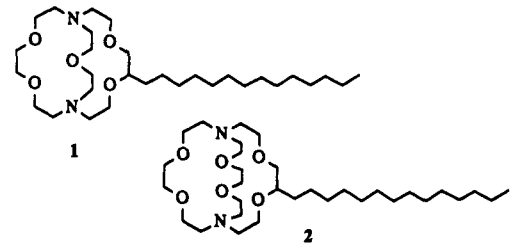


(crown ethers) have been used as model systems to study these phenomena quantitatively.[3] The cation binding abilities of cyclic polyethers have been used in two general ways.

In one case, the macrocyclic polyether group is covalently linked to a hydrophobic residue. The crown serves as the polar head group in the resulting amphiphile due to its strong hydrophilic character.[3] The resulting nonionic surfactants are capable of associating into micelles[4] and/or vesicles,[5] depending on the structures of the head group and lipophilic tail. Since these polyethers, which are sometimes bicyclic (cryptands), are often strong cation binders, complexation may lead to charge modification at the aggregate surface. The concept is illustrated in Scheme I. Grätzel et al.[6] have used [tetraaza-12-crown-4]-$C_{14}H_{29}$ as an electron storage system when it is complexed to Cu^{2+}. Others, notably Okahara et al.[7] and Turro et al.,[8] have reported similar experiments. The work of D'Aprano and Sesta[9] is especially relevant to the present report and is described in more detail later.

In the second group of aggregation-related experiments utilizing cation–macrocycle complexation, the polyether or cryptand is added separately to anionic micelles. The crown or cryptand complexes the positive counterions associated with these anionic micelles.[10,11] Although decreased cmc values were observed in both types of studies, different explanations were offered to account for them.[10,11] In one case, it was argued that addition of [2.2.2]cryptand to sodium dodecyl sulfate (SDS) micelles led to complexation and charge neutralization at the surface, thus increasing negative charge repulsions between the head groups, and decreasing critical micelle concentrations (cmc's).[10] The same experimental observations were explained by Quintela et al.[11] as resulting from incorporation of the alkali metal cryptate just under the micellar surface.

Our own efforts in this area may be useful in the context of this problem. Previously communicated work from our laboratories involved the thermodynamic parameters for micellization of compound **2**, when complexed with K^+ or Ba^{2+}.[1] We now report the complete results of studies for both compounds **1** and **2**. Monovalent sodium and divalent calcium were selected for complextation studies of **1**. Ionic radii of 0.95 and 0.99 Å for the latter cations, respectively, are suited for complexation within the [2.2.1]cryptand cavity of **1**. Monovalent potassium and divalent barium were selected for complexation with **2** because of the close correspondence of their ionic radii (1.33 and 1.35 Å, respectively) to the [2.2.2]cryptand cavity. These two lipophilic cryptands thus offer a convenient set to quantitatively probe the effect of surface charge upon micellization.



1

2

Results and Discussion

A large number of amphiphilic cation binders can easily be imagined. Indeed we have previously prepared a number of systems containing both macrocyclic polyether rings and hydrophobic tail(s). For the present purpose, however, we hoped to ensure maximum binding and therefore to observe the maximum effect in the systems studied. Fortunately, the ideal system for our purposes had been prepared by Montanari and his co-workers a number of years ago as part of an interesting phase transfer catalysis study.[12]

Cryptand Syntheses. Two cryptands were required for this study. The [2.2.2]cryptand derivative, **2**, was prepared and reported by Montanari and his co-workers.[12] The approach is illustrated below and described in detail in the Experimental Section. We used the Montanari approach to prepare **2** although we modified the experimental procedure and report those modifications herein. This new procedure could also be applied to the synthesis of the hitherto unknown [2.2.1]cryptand derivative, **1**. Note that both cryptands have identical chain lengths and are therefore comparable to the greatest extent possible. Syntheses and complete characterization are presented in the Experimental Section.

Solution Studies. The cmc values were obtained directly from plots of the apparent surface tension (γ) measured for solutions of **1** and **2** at different temperatures vs the logarithm of the concentration. All solutions studied contained either the free ligand (**1** or **2**) or their corre-

(2) Fendler, J. H. *Membrane Mimetic Chemistry*; Wiley: New York, 1982.

(3) (a) Doscher, T. M.; Myers, G. E.; Atkins, D. C. *J. Colloid Sci.* **1951**, *6*, 223. (b) Okahara, M.; Kuo, P.-L.; Yamamura, S.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1980**, 586. (c) Gould, I. R.; Kuo, P.-L.; Turro, N. J. *J. Phys. Chem.* **1985**, *89*, 3030. (d) Shinkai, S.; Nakamura, S.; Manabe, O.; Yamada, T.; Nakashima, N.; Kunitake, T. *Chem. Lett.* **1986**, 49. (e) Moroi, Y.; Pramauro, E.; Gratzel, M. *J. Colloid Interface Sci.* **1979**, *69*, 341. (f) Le Moigne, J.; Gramain, P. H. *J. Colloid Interface Sci.* **1977**, *60*, 565.

(4) (a) Maclay, W. N. *J. Colloid Sci.* **1956**, *11*, 272. (b) Schick, M. J. *J. Colloid Sci.* **1962**, *17*, 801. (c) Schott, H. *J. Colloid Interface Sci.* **1972**, *43*, 150.

(5) (a) Okahata, Y.; Tanamachi, S.; Nagai, M.; Kunitake, T. J. *Colloid Interface Sci.* **1981**, *82*, 401. (b) Baillie, A. J.; Florence, A. T.; Hume, L. R.; Muirhead, G. T.; Rogerson, A. *J. Pharm. Pharmacol.* **1985**, *37*, 863. (c) Echegoyen, L. E.; Hernandez, J. C.; Kaifer, A. E.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc., Chem. Commun.* **1988**, 836. (d) Fasoli, H.; Echegoyen, L. E.; Hernandez, J. C.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc., Chem. Commun.* **1989**, 578–580.

(6) Monserrat, K.; Gratzel, M.; Tundo, P. *J. Am. Chem. Soc.* **1980**, *102*, 5527.

(7) Okahara, M.; Kuo, P.-L.; Yamamura, S.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1980**, 586.

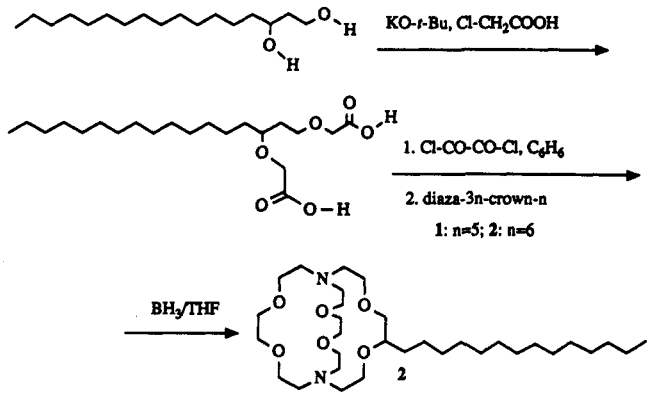
(8) Gould, I. R.; Kuo, P.-L.; Turro, N. J. *J. Phys. Chem.* **1985**, *89*, 3030.

(9) Sesta, B.; D'Aprano, A. *J. Phys. Chem.* **1988**, *92*, 2992.

(10) Evans, D. F.; Sen, R.; War, G. G. *J. Phys. Chem.* **1986**, *90*, 5500.

(11) Quintela, P. A.; Reno, R. C. S.; Kaifer, A. E. *J. Phys. Chem.* **1987**, 3582.

(12) (a) Cinquini, M.; Montanari, F. *J. Chem. Soc., Chem. Commun.* **1975**, 393. (b) Cinquini, M.; Montanari, F.; Tundo, P. *Gazz. Chim. Ital.* **1977**, *13*, 11–14.



sponding 1:1 L:M^{n+} (n = 1 or 2) complexes. Note that the 1:1 ratio refers to the stoichiometric amounts of ligand and salt added, not to the actual species present in the system. This is an important qualification since the stability constants, K_s, for the lipophilic cryptands with these cations are not known in water, although they may be estimated with reasonable accuracy (see below). Further, the equilibrium constants after the formation of the micelles are also unknown. All cmc values are presented in Table I, along with the calculated surface excess concentrations, Γ_{max}, and the minimum areas per surfactant molecule, A_{min}.

The calculated values derived from the cmc's were obtained from the Gibbs adsorption equation[13] as described elsewhere.[1,9] Activity coefficients were assumed to be unity at the relatively low concentrations used in these studies. Therefore,

$$\Gamma_{max} = [d\gamma/d \log c]/2.3RTB$$

where $d\gamma/d \log c$ values were obtained directly from the slopes in the γ vs log c plots below the cmc's, and $B = 2$. The minimum areas were calculated from the equation

$$A_{min} = 10^{14}/N\Gamma_{max}$$

where N is Avogadro's number. The general trend of decreasing Γ_{max} and increasing A_{min} with increasing temperatures is evident from the data in Table I.

The free energies for the micellization process of these complexes, $\Delta G°_{mic}$, were determined from

$$\Delta G°_{mic} = RT \ln (cmc)$$

$\Delta S°_{mic}$ values were determined from $\Delta G°_{mic}$ vs T plots, as the negative of the slopes. Five measurements were made for each solution at each temperature. Reproducibility was typically ±0.2 dyn/cm. These plots are shown in Figure 1 for the Na^+ and Ca^{2+} complexes of 1 and for K^+ and Ba^{2+} complexes of 2. Enthalpy values, $\Delta H°_{mic}$, were calculated from these parameters using $\Delta G°_{mic} = \Delta H°_{mic} - T\Delta S°_{mic}$. The thermodynamic parameters are summarized in Table II.

Cmc Values. Several observations can be made directly from these results. In general, cmc values for the complexes decrease with increasing temperature. Similar results have been previously reported for other surfactant systems,[14] particularly by D'Aprano and Sesta[9] and ourselves.[1] This is mainly a reflection of the favorable entropic contribution ($T\Delta S$) which results in a more negative ΔG. Another striking observation is the difference observed between the cmc value of the monovalent cation complexes when compared to those for the corresponding divalent

(13) Gibbs, J. W. *Collected Work*; Longmans Green: New York, 1928; Vol. 1, pp 218–237.
(14) Schick, M. G. *J. Phys. Chem.* **1963**, *67*, 1976.

Table I. Temperature-Dependent Surface Properties for Aqueous Solutions of 1 and 2[a]

compd	salt added	T, °C	10^4·(cmc),[b] mol/L	$10^{10}\Gamma_{max}$,[c] mol/cm^2	$100A_{min}$,[d] nm^2
1	none	8	3.81	2.42	68.8
1	NaCl	8	0.99	2.74	60.7
1	NaCl	14	0.97	3.03	54.8
1	NaCl	20	0.94	2.86	58.2
1	NaCl	26	0.92	2.78	59.8
1	NaCl	32	0.88	2.54	65.4
1	$CaCl_2$	8	7.40	1.39	119.9
1	$CaCl_2$	14	7.15	1.49	111.3
1	$CaCl_2$	20	6.73	1.28	129.1
1	$CaCl_2$	26	5.83	1.43	116.5
1	$CaCl_2$	32	5.76	1.15	144.5
2	none	10	1.40	3.10	53.6
2	KCl	10	0.93	3.77	44.1
2	KCl	18	0.82	3.30	50.3
2	KCl	25	0.82	2.76	60.2
2	KCl	32	0.82	2.26	73.5
2	KCl	40	0.71	1.77	93.8
2	$BaCl_2$	10	6.52	2.05	81.0
2	$BaCl_2$	18	6.13	1.80	92.3
2	$BaCl_2$	25	5.52	1.71	97.1
2	$BaCl_2$	32	4.74	1.58	105.1
2	$BaCl_2$	40	3.93	1.53	108.5

[a] In water. [b] Critical micelle concentrations (cmc's). [c] Surface excess concentrations (Γ_{max}). [d] Minimum areas per surfactant head group (A_{min}).

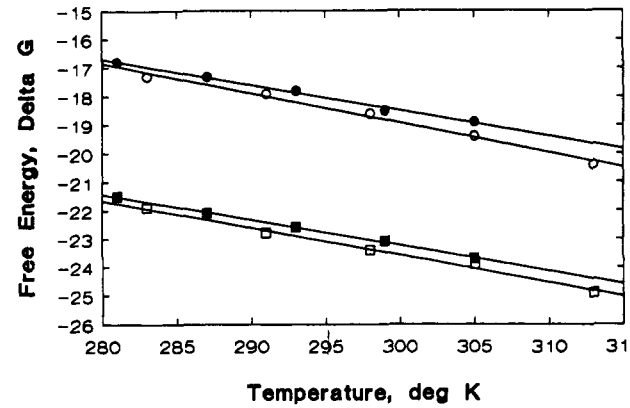


Figure 1. Temperature dependence of free energy. Salt added to cryptands 1 or 2: (●) Ca^{2+}/1, (■) Na^+/1, (○) Ba^{2+}/2, (□) K^+/2.

cases. Thus, (1·Na^+) and (2·K^+) have much lower cmc values (~0.1 mM at low temperatures) than the corresponding (1·Ca^{2+}) and (2·Ba^{2+}), ~0.6–0.7 mM.

Thermodynamic Parameters. Two observations derived from the data in Table II are particularly striking. First, the thermodynamic parameters appear to be more closely controlled by the charge on the cation complexed than by the size of the cryptand. The second important observation is the consistency of the entropic term for all the systems studied. All values fall between 90 and 100 J/mol K, which corresponds to a $T\Delta S°$ contribution of about 25–30 kJ/mol. This large entropic contribution controls the overall free energy of the micellization process. The process is thus entropy driven and, as evident from the data, mainly controlled by desolvation of the lipophilic chain. Since the chain is the same for all of the complexes, the positive entropy contribution upon desolvation and micellization is expected to be similar. Entropy changes associated with the head groups are either very small for the micellization process or similar for all the complexes studied. We judge the latter to be unlikely. That the values are somewhat lower for the complexes of 1 than those of 2 may have some significance, but the differences

Table II. Thermodynamic Parameters for the Micellization of 1•Na^+, 1•Ca^{2+}, 2•K^+, and 2•Ba^{2+} [a]

complex	$\Delta G°_{mic}$, 25 °C		$\Delta H°_{mic}$		$\Delta S°_{mic}$	
	kJ/mol	kcal/mol	kJ/mol	kcal/mol	J/mol K	cal/mol K
1·Na^+	−23	−5.5	3.5	0.84	89	21
1·Ca^{2+}	−18	−4.4	8.4	2.0	90	22
2·K^+	−23	−5.6	5.5	1.3	100	24
2·Ba^{2+}	−19	−4.5	12.6	3.0	97	23

[a] In water at 25.0 ± 0.1 °C; values for ΔG are ±1 kJ/mol.

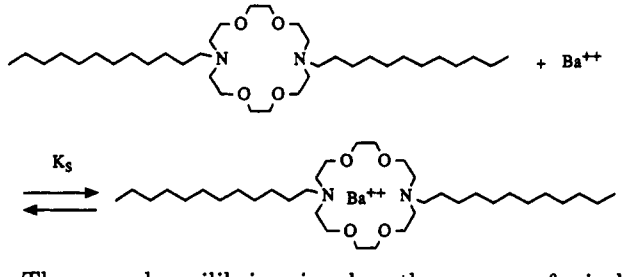
are so small that an explanation does not seem warranted.

The overall micellization process for the present systems may be represented, if in a somewhat oversimplified way, by three basic equilibria. Equation 1 represents the complexation between the monomeric ligand and the cation below the cmc. Although stability constant values have

$$L + M^{n+} \rightleftharpoons [LM^{n+}] \qquad K_s \qquad (1)$$

not been determined for these complexes, alkali metal NMR experiments with some of them suggest that the values are very large. One experiment involved the dissolution of 1·Na^+ (1:1) in D_2O, at 0.08 mM concentration. This concentration, which is below the value of the cmc (~0.09 mM), insures that most of the ligand is monomeric. The ^{23}Na NMR spectrum of this sample exhibited a very small signal at 105.8 MHz after 5000 scans. Thus, essentially all the Na^+ is bound to the ligand and the correlation time of the complex is sufficiently long to afford pronounced broadening of the resonance. All of this indicates a relatively large K_s value.

The value reported in the literature for [2.2.1]cryptand (no side chain), is log K_s = 5.4.[15] Assuming that this K_s value is similar for the lipophilic monomeric ligand 1, a reasonable assumption based on our experience with lipophilic crown ether compounds, and assuming that the initial complex concentration present is 0.08 mM, one obtains a value of ~78% for the complexed fraction. The 22% calculated for the uncomplexed fraction correlates well with the qualitative NMR observations described above. Similar calculations for the Ca^{2+} complex, based on a K_s value[15] of $10^{6.95}$, results in a calculated bound fraction of ~99%. Additional indirect evidence to support these conclusions comes from the observed decrease in stability constant between *N,N'*-bis(*n*-dodecyl)diaza-18-crown-6 (see illustration) and Ba^{2+}, when compared with the value for the unsubstituted diaza ligand.[16,17] The stability constant decreases from 955 to 158 upon lipophilic substitution. This indicates only a 6-fold decrease in binding ability, which would not significantly alter the binding characteristics of the ligands discussed here.



The second equilibrium involves the process of micellization from m molecules of the complex, eq 2. This

$$m[LM^{n+}] \rightleftharpoons [LM^{n+}]_m \qquad (2)$$

process must necessarily be accompanied by another reaction, partial dissociation of some metal cations due to surface electrostatic repulsions (eq 3).

$$[LM^{n+}]_m \equiv [L_mM^{n+}{}_m] \rightleftharpoons [L_mM^{n+}{}_{m-s}] + sM^{n+} \qquad (3)$$

^{23}Na NMR studies of 1·Na^+ (1:1) above the cmc (3 mM) clearly show a strong signal for hydrated Na^+ corresponding to ~33% of the total [Na^+] present in the system. Addition of Ag^+ (K_s for the complex 1·Ag^+ has a reported value[15] of $>10^{10}$) results in an approximately 3-fold increase in signal strength. These NMR results indicate that the extent of cation dissociation from the micellar aggregate is not much larger than from the more dilute monomeric complex, at least not for the Na^+ complex of 1. Although this has not been fully investigated for the other cases, we assume in the discussion below that a similar situation prevails for all the complexes.

Numerical values of the cmc's for the divalent cation cases are in good agreement with those reported for analogous systems.[16,17] The corresponding ones for the monovalent cation complexes are substantially smaller, typically by about 7-fold. It could be argued that these reduced cmc values result from salting-out due to the presence of the water structuring by Cl^-. However, such an explanation would predict a more pronounced effect for the divalent cation cases, based simply upon stoichiometric considerations, since chloride salts were used in all cases reported here. A competing process that results in "salting-in" is the strong complexation of the cation with the cryptand groups. A competition between these two effects has been used to explain the behavior of some crown ether substituted surfactant solutions.[9] While at low salt concentrations the cmc's are actually lower than for the pure compound, they are higher at larger concentrations. The explanation is that salting-out by Cl^- dominates at low salt concentrations where salting-in via strong complex formation with the cation is very low. As the salt concentration increases, so does the fraction of bound ligand, and salting-in predominates. The latter results in more stable monomeric complexes and consequent increases in cmc values.

Since the complexes studied here contain bicyclic cryptand head groups instead of monocyclic crown rings, much higher stability constants prevail. This means that even at low salt concentrations salting-in must be the dominant factor. These complexes thus reflect the differences between monovalent and divalent cation complexation on the process of micellization. When the thermodynamic parameters reported in Table II are examined closely, enthalpic differences account for all observed charge effects. It has already been pointed out that, as expected, entropic contributions are almost the same for mono- and divalent complexes of 1 and 2. Free energy differences are thus the result of enthalpy differences upon micellization. For a particular ligand, the enthalpy change is typically twice as unfavorable for binding a divalent cation compared to the monovalent cation case. Thus, 2·Ca^{2+} has a $\Delta H°_{mic}$ of 8.4 kJ/mol vs 3.5 kJ/mol for the

(15) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.
(16) Anderegg, G. *Helv. Chim. Acta* **1975**, *58*, 1218.
(17) Le Moigne, J.; Simon, J. *J. Phys. Chem.* **1980**, *84*, 170.

corresponding Na^+ complex. Similarly, $2{\cdot}Ba^{2+}$ has a value of 12.6 kJ/mol while the K^+ complex has a value of 5.5 kJ/mol. That the enthalpy changes associated with ligand 2 are always about 50% larger than the corresponding values with ligand 1 may be a reflection of the larger cryptate in the former, with a consequent larger repulsive force on the micellar surface and a more pronounced curvature.

Conclusion

When [2.2.1]- (1) or [2.2.2]cryptands (2) are used as polar head groups with $C_{14}H_{29}$ lipophilic tails to form amphiphilic compounds, controlled charge effects are observed upon micelle formation. These amphiphiles, 1 and 2, are able to complex strongly with monovalent and divalent cations. In the case of 2, K^+ and Ba^{2+} were selected for complexation due to their optimal ionic radii, while Na^+ and Ca^{2+} were selected in the case of 1. The cmc values are always much larger in the case of the divalent cation complexes than for the corresponding monovalent ones. Entropy changes upon micellization were essentially identical for all four complexes. Overall micellization is entropy driven, while enthalpy differences account for the charge effects.

Experimental Section

Melting points are uncorrected. TLC analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Rotating disk chromatography was performed on 2-mm circular plates prepared from Kieselgel 60 PF-254. All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate, unless otherwise described below. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. High-resolution mass spectra were obtained from the Florida State University Mass Spectra facility, Tallahassee, FL.

The chloroacetic acid was purified by subliming commercially available chloroacetic acid in a sublimator (0.1 mm, 40 °C). Sodium chloride (certified ACS reagent) and calcium chloride (analytically pure reagent) were dried overnight in a vacuum oven just prior to use. Water used in all solution preparations was distilled and deionized to a minimum resistance of 18 MΩ.

Surface tension measurements as a function of the concentration of surfactant were used to determine the cmc's of these complexes. Stock solutions of 10 mM 1:1 [ligand]:[metal cation] were prepared and allowed to stand overnight before used; 13 solutions were made via dilution of the stock to cover a wide range of concentrations above and below the cmc. The free ligand was studied in an identical manner. Surface tension measurements were made at five different temperatures ranging between 8 and 32 °C, using a tensiometer based on the du Nuoy ring method. Temperatures were controlled to within ±0.1 °C using a jacketed solution beaker through which thermostated water was circulated. Five measurements were obtained for each solution at each temperature. Reproducibility was typically within ±0.2 dyn/cm.

Synthesis of Cryptand 1. (a) (1,2-Hexadecanediyldioxy)diacetic Acid, A. Potassium metal (31.3 g, 0.800 mol) was dissolved in 1000 mL of dry *t*-BuOH. 1,2-Hexadecanediol (41.4 g, 0.160 mol) was added and was followed by the slow addition of a solution of sublimed chloroacetic acid (38.0 g, 0.402 mol) in 100 mL of *t*-BuOH. The reaction mixture was heated at reflux temperature for 2 days. The reaction mixture was cooled to room temperature, 73 mL of 12 M HCl was added, and the reaction mixture was evaporated in vacuo. The residual water was removed as the benzene–water azeotrope, the benzene solution was filtered, and the filtrate was evaporated in vacuo. The resulting white solid was recrystallized from hexanes (150 mL) to give A (37.9 g, 63%) as a white powder: mp 72–77 °C (lit.[12b] mp 74–77 °C); ^1H NMR ($CDCl_3$) 0.86 (t, 3 H, CH_3), 1.25 (s, broad, 26 H, aliph CH_2), 3.62 (m, 3 H, OCH_2CHRO), 4.17 (s, 2 H, $COCH_2O$), 4.2 (s, 2 H, $COCH_2O$), 10.72 (s, 2 H, COOH).

(b) (1,2-Hexadecanediyldioxy)diacetic Acid Chloride, B. Oxalyl chloride (3.8 g, 30.0 mmol), 4.1 (3.7 g, 9.9 mmol), and 1 drop of pyridine were combined in 50 mL of dry benzene. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was evaporated in vacuo, and the crude yellow oil (4.0 g, 98%) was carried on to the next step.

(c) 2,9-Dioxo-4,7,13,16,21-pentaoxa-1,10-diaza-5-*n*-tetradecylbicyclo[8.8.5]tricosane, C. This cyclization was carried out according to a procedure developed by Lehn.[18] 4,10-Diaza-15-crown-5 (1.33 g, 6.1 mmol) and triethylamine (0.617 g, 6.1 mmol) were dissolved in dry benzene (90 mL). A solution of 4.2 (2.5 g, 6.1 mmol) in dry benzene (90 mL) was prepared. The solutions were added to a reaction flask, containing 500 mL of dry benzene, over 4 h, under an atmosphere of nitrogen, using syringe pump. The reaction mixture was allowed to stir for 12 h, filtered through a pad of Celite, and evaporated in vacuo. The crude oil was filtered through alumina (50 g, EtOAc/hexane, 1:1) to give 1.74 g (51%) of a clear oil: ^1H NMR 0.88 (t, 3 H, CH_3), 1.11 (s, 2 H, CH_2), 1.25 (s, broad, 24 H, CH_2), 3.30–4.40 (m, 31 H, cryptand); IR (neat) 3500 (b, w), 2950, 2900, 1650 (s), 1480, 1350, 1110 cm^{-1}; high-resolution mass spectrum calcd for $C_{30}H_{56}N_2O$ 556.4088, found 556.4091.

(d) 2,9-Dioxo-4,7,13,16,21,24-hexaoxa-1,10-diaza-5-*n*-tetradecylbicyclo[8.8.8]hexacosane, D. 4,13-Diaza-18-crown-6 (2.5 g, 9.5 mmol) and triethylamine (2.1 g, 20.9 mmol) were dissolved in 170 mL of dry benzene. A solution of B (4.0 g, 9.5 mmol) in dry benzene (170 mL) was prepared. The solutions were added to a reaction flask, containing 1000 mL of dry benzene, over 9 h, under N_2, using a syringe pump. The reaction mixture was allowed to stir for 12 h, filtered through a pad of Celite, and evaporated in vacuo. The crude oil was filtered through alumina (50 g) to give 4.75 g (83%) of a clear oil which had spectral properties identical with those reported:[12b] ^1H NMR ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.11 (s, 2 H, CH_2), 1.25 (s, broad, 24 H, CH_2), 3.30–4.40 (m, 31 H, cryptand); IR (neat) 3500 (b, w), 2950, 2900, 1650 (s), 1480, 1350, 1110 cm^{-1}.

4,7,13,16,21-Pentaoxa-1,10-diaza-5-*n*-tetradecylbicyclo[8.8.5]tricosane, 1. A solution of C (1.74 g, 3.1 mmol) in THF (25 mL) was prepared. Borane–THF (8 mL, 1M, 80 mmol) was added, and the reaction mixture was heated at reflux temperature for 16 h. The reaction mixture was cooled and concentrated in vacuo. A 3 M HCl solution (40 mL) was added, and the reaction mixture was heated at reflux temperature for 4 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (200 mL) and 1 M HCl (700 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The aqueous layer was basified to pH 10 with 15 M NH_4OH and was extracted with CH_2Cl_2 (5 × 100 mL). The CH_2Cl_2 portions were filtered through Celite and concentrated in vacuo. The residue was distilled (bp 205–210 °C, 0.01 mm) to give 1.0 g (60%) of a yellow oil: ^1H NMR 0.88 (t, 3 H, CH_3), 1.05–1.65 (m, 26 H, aliph CH_2), 2.75 (b s, 12 H, CH_2N), 3.60 (m, 19 H, CH_2O); IR (neat) 3450 (b), 2950, 2850, 1480, 1370, 1300, 1120 (b), 980, 940, 750, 720 cm^{-1}; high-resolution mass spectrum: calcd for $C_{30}H_{60}N_2O_5$ 528.4502, found 528.4470.

Synthesis of Cryptand 2: 4,7,13,16,21,24-Hexaoxa-1,10-diaza-5-*n*-tetradecylbicyclo[8.8.8]hexacosane. A BH_3–THF solution (30 mL, 1 M, 30 mmol) was added to D (4.6 g, 7.7 mmol), and the reaction mixture was stirred at room temperature for 24 h. Water (3.5 mL) was added during 1 h, and the reaction mixture was concentrated in vacuo. A 1 M HCl solution (30 mL) was added, and the solution was heated at reflux temperature for 1 h. The reaction mixture was basified to pH 10 with 15 M NH_4OH and extracted with CH_2Cl_2 (200 mL, 2 × 100 mL). The combined organic portions were concentrated in vacuo and dried under high vacuum. The residue was filtered through alumina (40 g) and then distilled (bp 215–220 °C, 0.01 mm) to give 2.3 g (52%) of a pale yellow oil which had spectral properties identical with those reported: ^1H NMR ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.05–1.65 (m, 26

(18) Lehn, J.-M. U.S. Patent number 3,888,877, June 10, 1975.

H, aliph CH_2), 2.68 (t, 12 H, CH_2N), 3.30–3.90 (m, 23 H, CH_2O).

Acknowledgment. We thank the National Institutes of Health for grants GM 33940 (physical studies) and GM 36262 (syntheses) which supported this work.

Supplementary Material Available: 60-MHz ^1H NMR spectra of compounds A, C, D, 1, and 2; infrared spectra for compounds C, D, and 1; and 100-MHz ^{13}C NMR spectra for compound 1 (9 pages). Ordering information is given on any current masthead page.

Reactions and Diastereoselectivity of N^2-Arylsulfonyl Amidine Anions

Philip Magnus*[,1] and John Moursounidis

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received July 11, 1990

Cyclic N^1-alkyl-N^2-sulfonyl amidine anions undergo stereoselective aldol reactions to give the syn diastereoisomer as the major product. The ratio of syn to anti aldol products decreases as the size of the N^1-alkyl increases. This is interpreted as a change in the transition state from an open-aldol to a closed-Zimmerman–Traxler-type transition state.

Compared to the extensive investigations of the alkylation and aldol chemistry of cyclic ketones, cyclic amides (lactams) have received considerably less attention.[2] Part of our alkaloid research program required alkylation of the amide enolate (endo-*E* enolate) **2** derived from the tetracyclic amide **1**.[3] While we could not successfully alkylate **1**, the derived thioamide **3** underwent thio-Claisen rearrangement, as described by Takano[4] to give **4**. Thioamides exhibit increase diastereoselectivity in the aldol reaction compared to amides. For example, *N*-methylthiopyrrolidone **5** gave the syn and anti aldol products **5a** and **5b**, respectively, in a 19:81 ratio, whereas *N*-methylpyrrolidone **6** gave the syn and anti aldol products **6a** and **6b**, respectively, in a 1:1 ratio (Scheme I).[5]

If the oxygen atom of an amide is replaced by a functional group that could exert either a steric or electronic effect, or a combination of both, changes in the diastereoselectivity might result. With this in mind we have examined some reactions of N^1-alkyl-N^2-*p*-tolylsulfonyl amidine anions (Scheme II). It is somewhat surprising that the chemistry of these anions has not been previously explored.

For Scheme II, *N*-Ts geometry in **7** is *E* (X-ray crystallographic structural data on aldol adducts **51**, **52**, and **65**). The *N*-lithio derivative **8** should undergo C-alkylation to give **9**. The alkyl group R in **9** should assume an axial conformation, at least for a six-membered ring ($A^{1,3}$ strain).[6] It is difficult to predict the diastereoselectivity of the reaction between the lithio derivative **8** and an aldehyde. On the one hand the prior literature shows that cyclic ketone enolates react with aldehydes under kinetic control (no demonstrable equilibration) to give the anti aldol product as the major diastereoisomer.[2] As mentioned above, the same situation is true for lactam enolates. A *Zimmerman–Traxler*-type transition state for an *E* enolate (cyclic amidine) predicts the anti diastereoisomer, whereas the so-called open transition state for an *E* enolate leads to the syn diastereomer.[7] The *N*-lithio derivative **8**, in a conformation where the N^1-alkyl group and N^2-Ts group are *Z* (syn), in a *Zimmerman–Traxler* transition state **11**, leads to the anti diastereoisomer **12**, and the rotamer **13** leads to the syn diastereoisomer **14** (Scheme III).

An open transition state such as shown in Scheme IV leads to a reversal of the diastereoisomers for a particular orientation of the aldehyde. This simple analysis is severely complicated by the various steric interactions of the NTs group with the NR group and the R group in the aldehyde. These various manifestations of $A^{1,3}$ steric strain will no doubt play important roles in transition states such as **11**/**13** (NTs, NR $A^{1,3}$ strain) and **15** (NTs, R $A^{1,3}$ strain), but before the fact it is difficult to make significant predictions regarding the preferred, if any, diastereoselectivity. Although two reasonable predictions are possible, the newly formed carbon–carbon bond in either *syn*-**10** or *anti*-**10** should be axial (for a six-membered ring) and remain axial **17**. Conformational relaxation to the equatorial conformer **18** should be prevented by the $A^{1,3}$ strain that develops when, and if, the stereochemical relationship between the NR and NTs functionality is *E*. This will depend upon the size of R, and as a consequence, there should be a trend in the extent of diastereoselectivity as a function of the bulk of R. There should also be a change in the diastereoselectivity as the size of the Ts group is altered (trisyl, for example). We have not examined this possibility.

The synthesis of N^1,N^1-dialkyl-N^2-*p*-tolylsulfonyl amidines **7** was accomplished in a straightforward manner, using a reaction described in 1960 by King.[8] Treatment

(1) Address correspondence to this author at The Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712.

(2) Evans, D. A. Stereoselective Alkylation Reactions of Chiral Metal Enolates In *Asymmetric Synthesis*: Morrison, J. D., Ed.; Academic Press Inc.: 1984; Vol. 3, p 1. Heathcock, C. H. The Aldol Addition Reaction In Morrison, J. D., Ed.; *Asymmetric Synthesis*; Academic Press Inc.: 1984; Vol. 3, p 111.

(3) Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* **1989**, *28*, 951. Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518.

(4) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153. Takano, S.; Hirama, M.; Araki, T. K.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084.

(5) Tamura, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7808.

(6) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(7) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(8) King, C. *J. Org. Chem.* **1960**, *25*, 352.

0022-3263/91/1956-1529$02.50/0