Amide Proton Exchange in Micelles

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Abstract: Rate constants for acid- and base-catalyzed NH exchange of long-chain amides have been measured in cationic and anionic micelles and compared with NH exchange of model amides in aqueous solution. The data show that the rates can be strongly influenced by the electrostatic environment. Anionic micelles, where k_{OH} decreases by a factor of about 2500 and where k_H increases by a factor of about 100, show the largest effects. The effects of cationic micelles are smaller: a 30-fold decrease in k_H (for ureas, or 6-fold for ordinary amides) and essentially no change in k_{OH}, which was unexpected. Other effects are negligible (less than a factor of about 2): counterion, nonionic surfactant, headgroup, chain length, etc. The data are discussed in terms of electrostatic effects, steric retardation, competition of counterions for the micellar surface, the Brønsted formulation of medium effects, charge exposure, and the nature of the transition state.

Introduction

Amide NH Exchange. Amide hydrogen exchange is the interchange of hydrogens between solvent water and an amide, peptide, or protein.[1] The rates of such exchange can provide information about biological macromolecules. These are not static structures but undergo fluctuations that can vary with the binding of other molecules and with other environmental influences. These influences affect the rates of hydrogen exchange, whose measurement then helps to elucidate the dynamic structure of the molecule.

Exchange is found to be catalyzed by acid and base, with a rate constant given by eq 1. It readily follows that the rate is minimum at a pH given by eq 2, with a rate constant k_{min} given in eq 3.[2]

$$k_{obs} = k_H[H_3O^+] + k_{OH}[OH^-] \quad (1)$$

$$pH_{min} = {}^1/_2\log(k_H/k_{OH}K_w) \quad (2)$$

$$k_{min} = (k_H k_{OH} K_w)^{1/2} \quad (3)$$

The mechanism of the base-catalyzed reaction involves removal of the amide NH (eq 4) to create the imidate anion, RC(−O⁻)═NR′.[3] The mechanism of the acid-catalyzed reaction depends on the amide.[4] For amides with electron-donating groups, the exchange occurs simply by hydronation of the nitrogen (eq 5). For amides with electron-withdrawing groups, exchange occurs by hydronation of the more basic oxygen, followed by dehydronation from nitrogen, to produce the imidic acid RC(−OH)═NR′ as intermediate (eq 6).

$$RC(=O)NHR' + OH^- \rightarrow RC(-O^-)=NR' \quad (4)$$

$$RC(=O)NHR' + H^+ \rightarrow RC(=O)NH_2R'^+ \quad (5)$$

$$RC(=O)NHR' + H^+ \rightarrow RC(-OH)=NHR'^+ \rightarrow RC(-OH)=NR' + H^+ \quad (6)$$

Electrostatic Effects. Among the strongest environmental influences are electrostatic effects of nearby charges.[5] Electrostatic interactions have long been known to have a significant effect on NH exchange.[6] The inductive effects of nearest-neighbor amino acid side chains on k_H and k_{OH} are well established.[7] Also, k_H for poly(DL-lysine) is ∼10-fold smaller than that for poly(DL-alanine), but its k_{OH} is ∼2.5-fold greater, owing to the neighboring positive charges.[8] Moreover, exchange in poly(DL-lysine) is much more sensitive to salt concentration than exchange in poly(DL-alanine).[9] One of the more interesting recent examples is the acceleration of base-catalyzed exchange

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(1) Linderstrom-Lang, K. *Spec. Publ. Chem. Soc.* **1955**, *No. 2*, 1. Leach, S. J. *Rev. Pure Appl. Chem.* **1959**, *9*, 33. Hvidt, A.; Nielsen, S. O. *Adv. Protein Chem.* **1966**, *21*, 287. Klotz, I. M. *J. Colloid Interface Sci.* **1968**, *17*, 804. Englander, S. W.; Downer, N. W.; Teitelbaum, H. *Annu. Rev. Biochem.* **1972**, *41*, 903. Otteson, M. *Methods Biochem. Anal.* **1972**, *20*, 135. Craig, L. C.; Cowburn, D.; Bleich, H. *Methods Biochem. Anal.* **1975**, *44*, 477. Englander, S. W.; Englander, J. J. *Methods Enzymol.* **1978**, *49*, 24. Woodward, C. K.; Hilton, B. D. *Annu. Rev. Biophys. Bioeng.* **1978**, *8*, 99. Barksdale, A. D.; Rosenberg, A. *Methods Biochem. Anal.* **1982**, *28*, 1. Woodward, C.; Simon, I.; Tuchsen, E. *Mol. Cell. Biochem.* **1982**, *48*, 135. Englander, S. W.; Kallenbach, N. R. *Q. Rev. Biophys.* **1984**, *16*, 521. Englander, S. W.; Mayne, L. *Annu. Rev. Biophys. Biomol. Struct.* **1992**, *21*, 243. Woodward, C. K. *Curr. Opin. Struct. Biol.* **1994**, *4*, 112. Englander, S. W.; Sosnick, T. R.; Englander, J. J.; Mayne, L. *Curr. Opin. Struct. Biol.* **1996**, *6*, 18.

(2) Leichtling, B. H.; Klotz, I. M. *Biochemistry* **1966**, *5*, 4026.

(3) Berger, A.; Loewenstein, A.; Meiboom, S. *J. Am. Chem. Soc.* **1959**, *81*, 62. Perrin, C. L.; Lollo, C. P.; Hahn, C.-S. *J. Org. Chem.* **1985**, *50*, 1405.

(4) Perrin, C. L. *Acc. Chem. Res.* **1989**, *22*, 268. Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 6693.

(5) Rajasekaran, E.; Jayaram, B.; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 8238. Bashford, D.; Karplus, M. *Biochemistry* **1990**, 29, 10219. Davis, M. E.; McCammon, J. A. *J. Comput. Chem.* **1991**, *12*, 909.

(6) Rosa, J.; Richards, F. M. *J. Mol. Biol.* **1982**, *160*, 517. Kakuda, Y.; Mueller, D. D. *Arch. Biochem. Biophys.* **1975**, *171*, 586.

(7) Molday, R. S.; Englander, S. W.; Kallen, R. G. *Biochemistry* **1972**, *11*, 150. Bai, Y.; Milne, J. S.; Mayne, L.; Englander, S. W. *Proteins* **1993**, *17*, 75.

(8) Englander, S. W.; Poulsen, A. *Biopolymers* **1969**, *7*, 379.

(9) Kim, P. S.; Baldwin, R. L. *Biochemistry* **1982**, *21*, 1.

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in diketopiperazines by the transannular dipole of the second amide group.[10]

One way to account for electrostatic effects is in terms of how the Coulombic interaction can stabilize or destabilize the charged intermediate, either cationic or anionic, and the transition state leading to it.[11] This interaction thus changes the rate constants k_H and k_{OH} in eq 1. Alternatively, electrostatic effects may be viewed as attracting or repelling H_3O^+ and OH^- and changing the local pH.[9] Equation 1 then becomes eq 7, but with rate constants that are unchanged, or nearly so. In either view a positive charge will retard the acid-catalyzed reaction, accelerate the base-catalyzed one, and shift pH_{min} to lower values. A negative charge produces the opposite effects. To a first approximation k_{min} is unchanged, and any observed reduction in k_{min} can be attributed to "steric hindrance", to internal hydrogen bonding, or to an inaccessibility to solvent, rather than to electrostatics.

$$k_{obs} = k_H[H_3O^+]_{local} + k_{OH}[OH^-]_{local} \quad (7)$$

Micelle Model. We seek to investigate further details of electrostatic effects on the rates of NH exchange. We need a model system that can provide a variable electrostatic environment for surface CONH groups. The model should satisfy the following requirements: Its structure should be similar to that of a protein, with hydrophilic residues at the surface and hydrophobic ones in the interior. The model should carry a charge on its surface. The charge type and charge density should be variable and controllable.

Micelles satisfy all these requirements.[12] On dissolving a long-chain amide in the micelle, the hydrophobic residues of both the amide and the surfactant reside in the interior. All the hydrophilic CONH groups are located at the surface, surrounded by a uniform electrostatic environment formed by the micellar head groups. Depending on the charge type of surfactants used, it is possible to create cationic, anionic, or neutral environments. The magnitude of the electrostatic interaction can be adjusted by varying the head group, the hydrophobic chain length, the concentration of surfactant, the counterion, and the type and concentration of added salt. Indeed, there have been many studies of kinetics in micelles.[13]

A few previous studies of proton exchange in ionic micelles demonstrated electrostatic effects. Menger and Lynn found that H_2O-catalyzed NH exchange of $RNH(CH_3)_2^+$ is about 30-fold greater for R = dodecyl in its own cationic micelle than for R = hexyl, which does not form a micelle.[14] Rates of photodehydronation of phenolic species in micelles are affected not only by the electrostatics but also by the details of the microenvironment, including the polarity and viscosity.[15] Accelerations and retardations have been observed for the hydrogen exchange of substituted benzoic acids, arginine, and aspartic acid.[16]

Micelles have been used to study solubilized peptides, proteins, and artificial receptors,[17] including their NH exchange.[18] In an early study of NH exchange of poly(*N*-isopropylacrylamide) in micellar sodium dodecyl sulfate (SDS), it was found that pH_{min} increases by about 1.5 and that k_{min} increases about 3-fold, relative to those in the absence of surfactants.[19] Sykes and O'Neil measured rates of NH exchange of Leu-Val-Ile-NH_2 and found that anionic micelles decrease k_{OH} and increase k_H, but that cationic and neutral micelles have little effect.[20] More recently, Spyracopoulos and O'Neil studied exchange of some amides with the NH in the middle of the amide chain, where it is positioned to probe the interior of the micelle rather than simply the electrostatic environment of the surface.[21] Again, the anionic micelle generally increases k_H and decreases k_{OH}, but the biggest effect is a 25-fold decrease in k_{min} of highly hindered amides, which was attributed to a hydrophobic effect associated with burying the NH in the interior of the micelle and excluding water from its vicinity.

Current Experiments. We now study NH exchange in three long-chain *N*-methyl amides, namely *N*-methyllauramide (MLA), *N*-methylpalmitamide (MPA), and *N*-dodecyl-*N*′-methylurea (DMU), in a wide range of micelles. We compare these with aqueous *N*-methylbutyramide (MBA) and *N*,*N*′-dimethylurea (MU) as models for nonmicellar exchange. These are convenient systems for probing micellar effects on reactivity, since the measurements are made under conditions of equilibrium, without any net chemical reaction. We expect that in anionic micelles a cationic transition state should be stabilized, thereby increasing k_H, and an anionic transition state should be destabilized, thereby decreasing k_{OH}. The effects of cationic micelles are opposite. Then pH_{min} should increase in anionic micelles and decrease in cationic ones.

Nuclear magnetic resonance (NMR) is a powerful technique for study of hydrogen exchange, and it is eminently suitable here. Each amide has an *N*-methyl that is split into a doublet by the adjacent NH. Line shape analysis of that doublet provides the rate constant for NH exchange. Since the coupling constant $^3J_{HNCH}$ is independent of magnetic field, a high-field instrument provides no advantage. Moreover, under most conditions a CW-NMR permits ready detection of the upfield *N*-methyl signal even in the presence of a large excess of H_2O, without overloading the detector of an FT-NMR and without any need for solvent suppression.

To the best of our knowledge this is the first study that covers all four combinations of acid- and base-catalyzed reactions in both anionic and cationic micelles. Some of these results were

(10) Forsyth, W. R.; Robertson, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 2694.

(11) Sheinblatt, M. *J. Am. Chem. Soc.* **1966**, *88*, 2123.

(12) Fendler, J. H. *Membrane Mimetic Chemistry*; Wiley: New York, 1982. Rosen, M. J. *Surfactants and Interfacial Phenomena*, 2nd ed.; Wiley: New York, 1989. Bunton, C. A.; Nome, F.; Quina, F. H.; Romsted, L. S. *Acc. Chem. Res.* **1991**, *24*, 357. Myers, D. *Surfactant Science and Technology*, 2nd ed.; VCH: New York, 1992.

(13) Among others: Davies, D. M.; Foggo, S. J.; Paradis, P. M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1597. Broxton, T. J.; Nasser, A. *Can. J. Chem.* **1997**, *75*, 202. Khan, M. N.; Arifin, Z. *Langmuir* **1996**, *12*, 261. Froehner, S. J.; Nome, F.; Zanette, D.; Bunton, C. A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 673. Iglesias, E.; Montenegro, L. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 1349. Marin, M. A. B.; Nome, F.; Zanette, D.; Zucco, C.; Romsted, L. S. *J. Phys. Chem.* **1995**, *99*, 10879. Rubio, D. A. R.; Zanette, D.; Nome, F.; Bunton, C. A. *Langmuir* **1994**, *10*, 1155. Germani, R.; Savelli, G.; Spreti, N.; Cerichelli, G.; Mancini, G.; Bunton, C. A. *Langmuir* **1993**, *9*, 61. Wei, L.; Lucas, A.; Yue, J.; Lennox, R. B. *Langmuir* **1991**, *7*, 1336.

(14) Menger, F. M.; Lynn, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 948.

(15) Politi, M. J.; Fendler, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 265. Einin, S. A.; Zaitsev, A. K.; Zaitsev, N. K.; Kuzmin, M. G. *J. Photochem. Photobiol.* **1988**, *A41*, 365.

(16) Isoda, T.; Yamasaki, M.; Yano, H.; Sano, T.; Harada, S. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 869. Yamashita, T.; Yamasaki, M.; Sano, T.; Harada, S.; Yano, H. *Langmuir* **1995**, *11*, 1477.

(17) Parker, W.; Song, P.-S. *Biophys J.* **1992**, *61*, 1435. Bruch, M. D.; Rizo, J.; Gierasch, L. M. *Biopolymers* **1992**, *32*, 1741. Battistutta, R.; Bisello, A.; Mammi, S.; Peggion, E. *Biopolymers* **1994**, *34*, 1535. Bonar-Law, R. P. *J. Am. Chem. Soc.* **1995**, *117*, 12397. Cerichelli, G.; Luchetti, L.; Mancini, G. *Langmuir* **1997**, *13*, 4767.

(18) O'Neil, J. D. J.; Sykes, B. D. *Biochemistry* **1988**, *27*, 2753. O'Neil, J. D. J.; Sykes, B. D. *Biochemistry* **1989**, *28*, 6736. Henry, G. D.; Sykes, B. D. *Biochemistry* **1990**, *29*, 6303. Williams, K. A.; Farrow, N. A.; Deber, C. M.; Kay, L. E. *Biochemistry* **1996**, *35*, 5145.

(19) Klotz, I. M.; Mueller, D. D. *Biochemistry* **1969**, *8*, 12.

(20) O'Neil, J. D. J.; Sykes, B. D. *Biochemistry* **1989**, *28*, 699.

(21) Spyracopoulos, L.; O'Neil, J. D. J. *J. Am. Chem. Soc.* **1994**, *116*, 1395.

presented at the 14th IUPAC Conference on Physical Organic Chemistry.[22]

Experimental Section

Chemicals. Amides and ureas were commercially available or synthesized by standard methods:[23] *N*-Methylbutyramide was prepared from butyryl chloride, aqueous methylamine, and KOH: bp 125−128 °C at 26 Torr (lit.[23a] bp 156 °C at 90 Torr); NMR (neat) δ 0.68 (t, J = 7.2 Hz, 3H), 1.40 (m, J = 7.2 Hz, 2H), 1.98 (t, J = 7.2 Hz, 2H), 2.51 (d, J = 4.8 Hz, 3H), 7.90 (s, broad, 1H). *N*-Methyllauramide was obtained similarly from lauroyl chloride: mp 67.5−68.5 °C from ethanol (lit.[23a] mp 68.4 °C); NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.24 (16H, s), 1.59 (2H, m, J = 7.2 Hz), 2.16 (2H, t, J = 7.2 Hz), 2.77 (3H, d, J = 4.8 Hz), 5.75 (1H, bs). *N*,*N*′-Dimethylurea was recrystallized from benzene. *N*-Dodecyl-*N*′-methylurea was prepared from dodecylamine and excess methyl isocyanate: mp 90−92 °C from ethanol; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.24 (brm, 18H), 1.47 (qn, J = 7.3 Hz, 2H), 2.76 (s, 3H), 3.13 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 26.8, 27.1, 29.3, 29.37, 29.49, 29.51, 29.54, 29.56, 30.1, 31.8, 40.7, 159.3.

Surfactants cetylpyridinium chloride (CPC), cetyltrimethylammonium chloride (CTAC), dodecylpyridinium chloride (DPC), lithium dodecyl sulfate (LDS), potassium deoxycholate (PDC), sodium dodecyl sulfate (SDS), and triethylene glycol monobutyl ether (TEGBE) were commercially available. Others were prepared as follows: Cetyltrimethylammonium acetate (CTAA) was prepared from equimolar aqueous cetyltrimethylammonium bromide and aqueous silver acetate, followed by addition of methanol, filtration, and evaporation of solvent.[24] The purity was 98% by titration against standard HCl, and the absence of bromide was confirmed with $AgNO_3$. Dodecylammonium chloride (DAC) solution was prepared from dodecylamine and 1 equiv of HCl. Potassium oleate (PO) and potassium deoxycholate (PDC) solutions were prepared from oleic or deoxycholic acid and 1 equiv of aqueous KOH.

Preparation of Sample Solutions. Optimal conditions for solubility and sensitivity were found to involve 0.05 M amide with 0.50 M surfactant. Most exchange samples were prepared by dissolving 0.0005 mol of amide or urea, 0.005 mol of surfactant, and 0.0015 mol of acetonitrile in deionized water. The pH was then adjusted by adding aqueous HCl, NaOH, or buffer, and the solution was diluted to 10 mL with water. The final concentrations of amide or urea, surfactant, and acetonitrile were 0.05, 0.5, and 0.15 M, respectively. Acetonitrile was used as internal standard and also to check and adjust the homogeneity of the magnetic field.

Some sample solutions were prepared by modifications of the above procedure: (1) For proton exchange in MBA or MU the concentration of amide was 0.5 M, and no surfactant was added. (2) To study the salt effect, the concentration of NaCl was varied from 0.00 to 0.25 M at 0.25 M surfactant. (3) To study the amide-to-surfactant ratio, the concentration ratio of amide to surfactant was varied from 0.05 M:0.50 M to 0.10 M:0.30 M. (4) For proton exchange in CTAA the pH was adjusted with acetic acid. (5) For proton exchange in PO or PDC the pH was adjusted with KOH. (6) To stabilize the pH near neutrality, 0.002 M phosphate or phthalate buffer was used. Independent studies of the effect of buffer concentration showed that there is no general acid or base catalysis.

Sample compositions are described in Table 1. For all micelle samples the concentrations of surfactants are far above their critical micelle concentrations.[25] Moreover, the long-chain amides partition strongly into the micelles, so that the contribution from exchange in bulk water is likely to be negligible.

pH Measurement. Measurements of pH were made at room temperature with a Corning Model 125 pH meter connected to an Ingold combination pH electrode capable of fitting inside a 5-mm NMR tube. The electrode was rinsed with deionized water and dried prior to each measurement, made at room temperature before and after the NMR experiment. To convert pH to $[OH^-]$, pK_w was taken as 13.71 at 34 °C or 14.08 at 22 °C.[26]

Table 1. Sample Solutions for Proton Exchange of Amides

expt	amide	[amide], M	surfactant	[surfactant], M	[other], M
MBA	MBA	0.50			
mba	MBA	0.0025			
MU	MU	0.50			
mu	MU	0.0025			
SDS	MLA	0.05	SDS	0.50	
sds	MLA	0.0025	SDS	0.025	
LDS	MLA	0.05	LDS	0.50	
SA5	MLA	0.05	SDS	0.25	
SA3	MLA	0.10	SDS	0.30	
SS1	MLA	0.05	SDS	0.25	0.25[a]
ST4	MLA	0.05	SDS	0.40	0.10[b]
ST1	MLA	0.05	SDS	0.25	0.25[b]
PO	MLA	0.05	PO	0.50	
PDA	MLA	0.05	PDC	0.50	
CPC	MLA	0.05	CPC	0.50	
cpc	MLA	0.0025	CPC	0.025	
CA5	MLA	0.05	CPC	0.25	
CS1	MLA	0.05	CPC	0.25	0.25[a]
CT4	MLA	0.05	CPC	0.40	0.10[b]
CT1	MLA	0.05	CPC	0.25	0.25[b]
DPC	MLA	0.05	DPC	0.50	
CTC	MLA	0.05	CTAC	0.50	
CTA	MLA	0.05	CTAA	0.50	
USDS	DMU	0.007	SDS	0.50	
UCPC	DMU	0.05	CPC	0.50	
ucpc	DMU	0.0025	CPC	0.025	
UCT4	DMU	0.05	CPC	0.40	0.10[b]
UCTC	DMU	0.05	CTAC	0.50	
UDAC	DMU	0.05	DAC	0.50	

[a] NaCl. [b] TEGBE.

NMR Experiments. The ^{1}H NMR spectra of most samples were taken on a Varian EM-390 90-MHz CW NMR spectrometer. Samples were allowed to equilibrate for 15 min to the probe temperature of 34 °C, as measured with an ethylene glycol sample.[27]

Spectra of 2.5×10^{-3} M model amides and of 2.5×10^{-3} M long-chain amide solutions in 2.5×10^{-2} M surfactants were obtained on a modified Nicolet 1180E FT-NMR spectrometer interfaced to an Oxford magnet operating at 360 MHz and a probe temperature of 22 °C. In these solutions the water peak was too intense to detect the *N*-methyl signals by CW or by normal FT-NMR, so it was suppressed with a 2−1−4−1−2 pulse sequence. The *N*-methyl resonances of the amides near δ 2.56 are approximately 765 Hz upfield of the water peak, and the spectrometer frequency was placed about 20 Hz upfield of the *N*-methyl resonances for maximum suppression.

Some spectra of 0.050 mM MU and of 0.007 M DMU in 0.50 M SDS were obtained on a 500-MHz Varian Unity spectrometer at 25 °C. Water suppression was achieved with a 1−5−10−10−5−1 hard-pulse sequence, adjusted to suppress the water peak in MU samples or to maximize the methyl peak of DMU.

Evaluation of k_{obs}. The pseudo-first-order rate constants k_{obs} and weighting factors w were calculated by line shape analysis of the *N*-methyl doublets. The coupling constant (4.8 Hz) and the natural line width (1.3−1.8 Hz) of each component of the *N*-methyl doublets in nonexchanging samples, as well as the line width of acetonitrile and the valley-to-peak intensity ratio of the *N*-methyl doublets in exchanging samples, were measured from expanded spectra. Each value was separately determined from at least five spectra and then averaged. The rate constants were then determined from a table relating them to valley-to-peak ratios.[28] The values reported are for the forward direction of

(22) Perrin, C. L.; Chen, J.-H. *Atualidades de Físico-Química Orgânica*. Submitted for publication, 1999.

(23) (a) D'Alelio, G. F.; Reid, E. E. *J. Am. Chem. Soc.* **1937**, *59*, 109. (b) Papesch, V.; Schroeder, E. F. *J. Org. Chem.* **1951**, *16*, 1879.

(24) Broxton, T. J. *Aust. J. Chem.* **1981**, *34*, 2313.

(25) Mukerjee, P.; Mysels, K. J. *Critical Micelle Concentrations of Aqueous Surfactant Systems*; National Bureau of Standards: Washington, DC, 1970.

(26) *Handbook of Chemistry and Physics*, 66th ed.; Chemical Rubber Co.: Cleveland, OH, 1985; p D-165.

(27) Raiford, D. S.; Fisk, C. L.; Becker, E. D. *Anal. Chem.* **1979**, *51*, 2050.

(28) Perrin, C. L. *Magn. Reson. Chem.* **1988**, *26*, 224.

Table 2. Rate Constants for Proton Exchange of Model Amides

soln	k_H^0, M^{-1} s^{-1}	k_{OH}^0, M^{-1} s^{-1}	k_{min}^0, s^{-1}	pH_{min}^0
MBA	$(1.03 \pm 0.03) \times 10^3$	$(1.07 \pm 0.03) \times 10^7$	1.5×10^{-2}	4.85
mba[a]	$(4.23 \pm 0.09) \times 10^2$	$(1.37 \pm 0.06) \times 10^7$	6.9×10^{-3}	4.78
MU	$(1.06 \pm 0.03) \times 10^7$			
mu[a,b]	$(3.48 \pm 0.09) \times 10^6$			

[a] 22 °C. [b] $(9.6 \pm 0.6) \times 10^6$ M^{-1} s^{-1} at 25 °C.

proton exchange and include multiplication by 2 to account for the probability that the NH spin state is reversed. No statistical correction is necessary for *N,N′*-dimethylurea, since k_{obs} is automatically per NH.

Evaluation of Rate Constants for Acid- and Base-Catalyzed Exchange. Since both H_3O^+ and OH^- may catalyze the NH exchange, k_{obs} can be expressed as eq 1. At any specific pH the contribution of either $k_{OH}[OH^-]$ or $k_H[H_3O^+]$ is negligible, so that the values of the second-order rate constants k_H and k_{OH} can be evaluated from the slopes of plots of k_{obs} vs $[H_3O^+]$ or $[OH^-]$. However, the error in k_{obs} is not constant across the plots. Therefore it is preferable to evaluate the slopes by the method of weighted linear least squares, as in eq 8. The proper weighting factors *w* were determined from Table 3 of ref 28. For each plot 10−20 data triads (k_{obs}, $[H_3O^+]$ or $[OH^-]$, *w*) were used to evaluate k_H and k_{OH} and the standard errors of these rate constants.

$$k_{cat} = \frac{(\sum w)(\sum w k_{obs}[cat]) - (\sum w k_{obs})(\sum w[cat])}{(\sum w)(\sum w[cat]^2) - (\sum w[cat])^2} \quad (8)$$

Results

The observed rate constants k_{obs} for NH exchange of short-chain amides in water and of long-chain amides in micelles were determined across a broad pH range. Typical experimental results for the acid- and base-catalyzed NH exchange of *N*-methyllauramide in SDS are shown in Figure 1, which also displays error bars to indicate both the precision of replicate measurements and the weighting scheme. The slopes, obtained by weighted linear least squares, correspond to $k_H = (1.44 \pm 0.06) \times 10^5$ M^{-1} s^{-1} and $k_{OH} = (6.6 \pm 0.4) \times 10^3$ M^{-1} s^{-1}.

Rate constants k_H and k_{OH} for NH exchange of model amides in water are listed in Table 2. The values are in good agreement with many previous determinations. The considerably faster acid-catalyzed exchange of ureas, relative to ordinary amides, is due to electron donation by the extra nitrogen, which stabilizes the *N*-protonated transition state (eq 5).[4,29] The apparent variations with temperature are artifacts of differing instrumentation, but all comparisons between solutions are consistent. Rate constants k_H and k_{OH} for NH exchange of long-chain amides in anionic and cationic micelles are listed in Tables 3 and 4. Values of k_{min} and pH_{min}, calculated from eqs 2 and 3, are also given. Tables 3 and 4 also include the micellar enhancement factors k_{cat}/k_{cat}^0 and reduction factors k_{cat}^0/k_{cat} relative to rate constants k_{cat}^0 of model amides in water from Table 2, as well as the ratio k_{min}^0/k_{min}, which measures the "steric" reduction in k_{min}, and the shift $\Delta pH_{min} = pH_{min} - pH_{min}^0$. For the long-chain urea DMU the comparison is with MU.

Electrostatic Effects. The dominant effect on k_H and k_{OH}, relative to model small amides, is due to the charge type of the surfactant. The data in Table 3 show that for anionic micelles the values of k_H are increased by factors of 50−230, and the values of k_{OH} are reduced by factors of 2000−5000. For cationic micelles the data in Table 4 show that the values of k_H are reduced by factors of 20−50 for ureas (or of 5−7 for ordinary amides), whereas the values of k_{OH} are only slightly influenced. There are also 2−6-fold reductions in k_{min}, and pH_{min} increases considerably in anionic micelles but decreases only slightly in cationic ones.

We consider ureas as providing a more trustworthy measure of the effect of cationic micelles on k_H, since they are more likely to exchange by *N*-protonation (eq 5).[4] In a cationic micelle an ordinary amide may exchange via the imidic-acid mechanism (eq 6), which is less sensitive to inductive effects. Indeed, the diminished retardation in ordinary amides is consistent with a change from the *N*-protonation mechanism in water to the imidic-acid mechanism in cationic micelles. Besides, rates for ureas are more reliable, since those for ordinary amides in cationic micelles required 0.1 M H_3O^+.

These increases and decreases are summarized in Table 5, which expresses the logarithms of all these values, averaged separately over acid- or base-catalyzed reactions in each kind of micelle. Also included are the rms variations from each average for all the rate constants in that set, as well as the averages and rms deviations of the changes in k_{min} and pH_{min}. The largest effect is that of anionic micelles, which reduce k_{OH} by an average of about 2500-fold. The smallest is that of cationic micelles, which reduce k_{OH} by an average of 34%, but the variability of this reduction is larger than the reduction itself, so that k_{OH} is not changed to any meaningful extent.

These results are consistent with the study of Klotz and Mueller[19] on the NH exchange of polyisopropylacrylamide bound by SDS, except the k_{min}. These results contrast with those of Menger and Lynn, who found a 30-fold rate increase for micellar $RNH(CH_3)_2^+$.[14] However, this is for the water-catalyzed reaction and is due to a decrease of the pK_a rather than to any effect on the local $[OH^-]$.

Other Effects. All other effects are small compared to the electrostatic one. The rms variations in Table 5 represent the average variability due to those other effects, and they are certainly small compared to the variability with catalyst and charge type. Table 6 summarizes the effects of other changes. These include the concentration of NaCl, the ratio of NaCl to surfactant (at constant concentration of counterion), the concentration of surfactant, the counterion associated with the surfactant, the head group of the surfactant, the length of the hydrophobic chain of the surfactant, dilution with nonionic surfactant, and the ratio of amide to surfactant. Almost all of these change the rate constant by less than a factor of 2. The largest exception is the 4-fold increase in k_H on replacing chloride by acetate in cetyltrimethylammonium micelles (**CTA/CTC**).

The small effect on k_H and k_{OH} of changing the surfactant concentration (**sds/SDS, cpc/CPC**) agrees with what had been observed for proton exchange in $RNH(CH_3)_2^+$.[14] The small effect on rate of changing the ratio of amide to surfactant (**SA5,3/SDS, CA5/CPC**) is consistent with the behavior observed when $RNH(CH_3)_2^+$ was diluted with $RN(CH_3)_3^+$.[14] The decrease of k_{OH} on decreasing the SDS concentration, at constant $[Na^+]$ (**SS1/SDS**), shows that all exchange is indeed micellar, since any contribution from exchange in bulk water would have permitted a rate increase.

Discussion

Errors. First-order rate constants k_{obs} determined from NMR line-shape analysis of the *N*-methyl doublets are reproducible, and the errors of reproducibility are less than 5%. Standard errors of 3−10% are observed for second-order rate constants, k_H and k_{OH}, calculated by the method of weighted linear least squares. Most of the variations detected in this study are well beyond this experimental error and thus large enough to permit conclusions to be drawn.

(29) Martin, R. B. *J. Chem. Soc., Chem. Commun.* **1972**, 793.

Table 3. Rate Constants (M^{-1} s^{-1}, s^{-1}) and Rate Ratios for Proton Exchange of Long-Chain Amides in Anionic Micelles at 34 °C

soln	$10^{-4}k_H$	k_H/k_H^0	$10^{-3}k_{OH}$	k_{OH}^0/k_{OH}	10^3k_{min}	k_{min}^0/k_{min}	pH_{min}	ΔpH_{min}
SDS	14.4 ± 0.6	140	6.6 ± 0.4	1620	4.30	3.41	7.52	2.68
sds[a]	9.6 ± 0.8	230	5.0 ± 0.3	2740	2.00	3.47	7.68	2.90
LDS	6.3 ± 0.5	61	3.5 ± 0.5	3060	2.07	7.07	7.48	2.64
SA5	13.7 ± 0.8	133	5.2 ± 0.5	2060	3.73	3.93	7.57	2.72
SA3	11.3 ± 0.5	110	2.0 ± 0.1	5350	2.10	6.98	7.73	2.88
SS1	6.1 ± 0.3	59	3.3 ± 0.1	3200	1.98	7.40	7.49	2.64
ST4	8.7 ± 0.2	84	3.7 ± 0.5	2900	2.51	5.85	7.54	2.69
ST1	5.3 ± 0.2	51	5.5 ± 0.2	1950	2.38	6.15	7.35	2.50
PDC			4.5 ± 0.7	2400				
PO			3.2 ± 0.2	3300				
USDS[b]	(2.8 ± 0.24) × 10^4	29						

[a] 22 °C. [b] 25 °C.

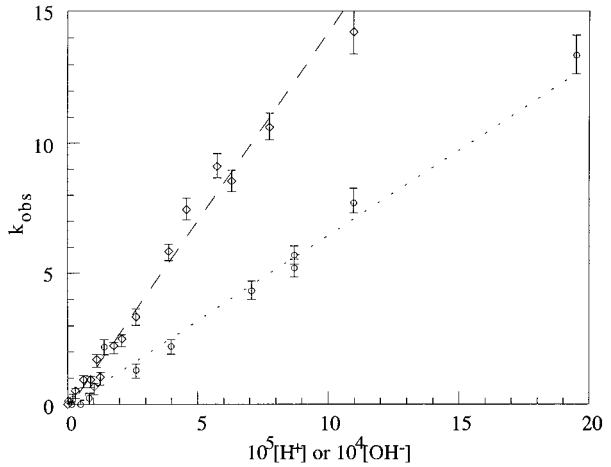

Figure 1. Weighted linear least squares analysis of acid- and base-catalyzed proton exchange of *N*-methyllauramide in SDS micelles: Upward error bars = 2σ (from reproducibility), downward error bars from Table 2 of ref 28: (− −) fit for k_H, (•••) fit for k_{OH}.

Comparison of Expected and Observed Electrostatic Effects. Rate constants for NH exchange are indeed influenced by the micellar charge (Table 5). Exchange in anionic micelles shows a higher k_H and a lower k_{OH} and, as a result, an increase of pH_{min}. Exchange in cationic micelles shows a lower k_H and a decrease of pH_{min}. These are all as expected above. However, cationic micelles do not increase k_{OH} but instead leave it essentially unchanged. This is the first of three puzzles.

The second puzzle is why the enhancement and reduction factors are greater in anionic micelles than in cationic micelles. Specifically, the average k_H/k_H^0 of 1×10^2 and the average k_{OH}^0/k_{OH} of 2.5×10^3 in anionic micelles are greater than the average k_{OH}/k_{OH}^0 of 1 and the average k_H^0/k_H in cationic micelles of 30 (for ureas, or 6 for amides). These values correspond to a >100-fold greater rate effect of anionic micelles than of cationic.

The third puzzle is why the reduction factors are greater than the enhancement factors in either anionic or cationic micelles. The values above correspond to an average reduction factor 20 times the average enhancement factor. A corollary of all of these puzzles is that the decrease of pH_{min} in cationic micelles is quite small, even though this decrease should be comparable to the increase seen in anionic micelles. Still another way of expressing these puzzles is that k_H (for ureas) is "symmetric", in that the 30-fold acceleration in anionic micelles matches the 30-fold retardation in cationic ones, whereas k_{OH} is markedly retarded in anionic micelles and not accelerated in cationic ones.

To understand these results it is necessary to recognize that three kinds of electrostatic interactions may affect the rate of NH exchange. The interaction between the micellar charge and the charge on the transition state is only the simplest. There are also interactions of the micellar charge with H_3O^+ and OH^-, which can affect the local pH and change the rates according to eq 7. Finally, it is also necessary to take into account interactions with counterions. The micelle strongly attracts counterions, which neutralize a substantial fraction of the micellar charge (ca. 60−75%, depending on counterion and concentration).[30] Consequently the counterions shield the first interaction, modify the local pH, and reduce electrostatic effects.

Steric Hindrance. According to Table 5, k_{min} in micelles is lowered an average of 3.5-fold, relative to model amides. This lowering may be attributed to a steric shielding of the NH at the micellar surface. If k_H and k_{OH} are both reduced 3.5-fold, then it follows that reduction factors would be 3.5^2-fold larger than enhancement factors. Such a 12-fold difference is close to the 20-fold difference cited above as reflective of the third puzzle above. A 3.5-fold steric reduction should be manifested regardless of micellar charge. Unfortunately, long-chain amides are insufficiently soluble in nonionic micelles to test this, but an alternative is to dilute with 50% nonionic surfactant, TEGBE (**ST1/SDS, CP1/CPC**). Yet k_{min} scarcely changes, and it certainly does not increase toward an unhindered value. This is consistent with a steric reduction, separate from any charge effect, as a resolution of the third puzzle.

Another possible form of steric hindrance is a clustering of amides within the surfactant, rendering them inaccessible to solvent. This might be due to the high proportion of amide (9%), necessitated by the insensitivity of NMR. However, there is hardly any rate effect due to increasing this percentage (**SA5,3/SDS, CA5/CPC**), except for k_{OH} at 25% amide in SDS.

Competition between Counterions and H_3O^+ or OH^-. According to eq 7, the exchange rates are proportional to the local concentrations of catalyst at the micellar surface. Although anionic micelles attract H_3O^+ and cationic ones attract OH^-, the counterion competes with these catalysts for the micellar surface.[31] Thus one reason that electrostatic interactions do not account for all the observed rate effects is that much of the surface charge on the micelle is neutralized by the counterions.

The pseudophase model permits a quantitative treatment of the distribution of ions between micelle and bulk.[32] The ratios

(30) Neves, M. de F. S.; Zanette, D.; Quina, F.; Moretti, M. T.; Nome, F. *J. Phys. Chem.* **1989**, *93*, 1502. Moroi, Y. *J. Colloid Interface Sci.* **1988**, *122*, 308.

(31) Bunton, C. A.; Savelli, G. *Adv. Phys. Org. Chem.* **1986**, *22*, 213. Quina, F. H.; Politi, M. J.; Cuccovia, I. M.; Martins-Franchetti, S. M.; Chaimovich, H. In *Solution Behavior of Surfactants*; Mittal, K. L., Fendler, J. H., Eds.; Plenum: New York, 1982; Vol. 2, p 1125. Bunton, C. A.; Ohmenzetter, K.; Sepulveda, L. *J. Phys. Chem.* **1977**, *81*, 2000.

(32) Martinek, K.; Yatsimirski, A. K.; Osipov, A. P.; Berezin, I. V. *Tetrahedron* **1973**, *29*, 963. Quina, F. H.; Chaimovich, H. *J. Phys. Chem.* **1979**, *83*, 1844. Chaimovich, H.; Bonilha, J. B. S.; Politi, M. J.; Quina, F. H. *J. Phys. Chem.* **1979**, *83*, 1851. Romsted, L. S. In *Surfactants in Solution*; Mittal, K. L., Lindman, B., Eds.; Plenum: New York, 1984; Vol. 2, p 1015. Minero, C.; Pelizzetti, E. *Adv. Colloid Interface Sci.* **1992**, *37*, 319.

Table 4. Rate Constants (M^{-1} s^{-1}, s^{-1}) and Rate Ratios for Proton Exchange of Long-Chain Amides in Cationic Micelles at 34 °C

soln	k_H	k_H^0/k_H	$10^{-6}k_{OH}$	k_{OH}/k_{OH}^0	10^3k_{min}	k_{cat}^0/k_{min}	pH_{min}	ΔpH_{min}
CPC	182 ± 5	5.7	8.3 ± 0.5	0.8	5.43	2.70	4.53	−0.32
cpc[a]	62 ± 2	6.8	16.9 ± 0.8	1.2	2.95	2.35	4.32	−0.46
CA5	198 ± 8	5.2	7.5 ± 0.7	0.70	5.38	2.72	4.57	−0.28
CS1	216 ± 6	4.8	2.5 ± 0.2	0.23	3.24	4.52	4.82	−0.02
CT4	159 ± 7	6.5	8.1 ± 0.6	0.76	5.01	2.93	4.50	−0.35
CT1	170 ± 8	6.1	7.6 ± 0.4	0.71	5.02	2.92	4.53	−0.32
DPC	197 ± 9	5.2	5.3 ± 0.7	0.50	4.51	3.25	4.64	−0.21
CTC	211 ± 9	4.9	3.9 ± 0.3	0.36	4.01	3.66	4.72	−0.13
CTA			15.9 ± 0.8	1.49				
UCPC	$(3.1 \pm 0.2) \times 10^5$	34						
ucpc[a]	$(0.97 \pm 0.09) \times 10^5$	36						
UCT4	$(5.5 \pm 0.4) \times 10^5$	19						
UCTC	$(4.7 \pm 0.7) \times 10^5$	23						
UDAC	$(2.2 \pm 0.2) \times 10^5$	48						

[a] 22 °C.

Table 5. Average Micellar Charge Effects on Rates of Amide NH Exchange

micelle	$\overline{\log(k_H/k_H^0)}$	$\overline{\log(k_{OH}/k_{OH}^0)}$	$\overline{\log(k_{min}/k_{min}^0)}$	$\overline{\Delta pH_{min}}$
anionic	2.0 ± 0.2[a]	-3.4 ± 0.2	-0.72 ± 0.14	2.71 ± 0.13
cationic	-0.75 ± 0.06[b]	-0.18 ± 0.25	-0.49 ± 0.09	-0.13 ± 0.14

[a] +1.5 for ureas (DMU/MU). [b] -1.5 ± 0.16 for ureas (DMU/MU).

Table 6. Summary of Other Micellar Effects on Rates of NH Exchange of Long-Chain Amides

change	ref → Δ	micelle	k_H^Δ/k_H^{ref}	$k_{OH}^\Delta/k_{OH}^{ref}$
[NaCl]	0 → 0.25 M	anionic	0.45	0.63
[NaCl]	0 → 0.25 M	cationic	1.09	0.33
[NaCl]/[Surf]	0 → 1	anionic	0.42	0.51
[NaCl]/[Surf]	0 → 1	cationic	1.19	0.30
[Surf]	0.5 → 0.025 M	anionic	1.62	0.59
[Surf]	0.5 → 0.025 M	cationic	0.83[a]	1.60
M^+	Na → Li	anionic	0.44	0.54
X^-	Cl → CH_3CO_2	cationic		4.1
head group	Py → NMe_3	cationic	1.16[b]	0.47
head group	NMe_3 → NH_3	cationic	0.47	
head group	SO_3 → CO_2	anionic		0.48[c]
chain length	C_{16} → C_{12}	cationic	1.08	0.64
% nonionic	0 → 20 → 50	anionic	0.60, 0.37	0.57, 0.83
% nonionic	0 → 20 → 50	cationic	0.87,[d] 0.93	0.98, 0.92
% amide	9 → 17 → 25	anionic	0.95, 0.78	0.79, 0.30
% amide	9 → 17	cationic	1.09	0.90

[a] 0.95 for DMU. [b] 1.5 for DMU. [c] 0.68 for deoxycholate. [d] 1.8 for DMU.

of local concentrations of H_3O^+ and OH^- to those in bulk are given by eqs 9−10, where K_H^M and K_{OH}^X are ion-exchange

$$\frac{[H_3O^+]_{local}}{[H_3O^+]_{bulk}} = \frac{1}{K_H^M}\frac{[M^+]_{local}}{[M^+]_{bulk}} \quad (9)$$

$$\frac{[OH^-]_{local}}{[OH^-]_{bulk}} = \frac{1}{K_{OH}^X}\frac{[X^-]_{local}}{[X^-]_{bulk}} \quad (10)$$

constants for binding to the micelle. These ratios reflect the extent to which the counterion competes with catalyst for the micellar surface. Although the surfactant increases $[H_3O^+]_{local}$ or $[OH^-]_{local}$, the increase is not as large as it would be in the absence of counterion. Thus this competition reduces the rate of acid-catalyzed exchange in anionic micelles and the rate of base-catalyzed exchange in cationic ones.

The observed effects of counterions are semiquantitatively consistent with this explanation. When the concentrations of surfactant and its counterion both decrease 20-fold (**sds/SDS, cpc/CPC**), the enhancement factors k_H/k_H^0 in SDS and k_{OH}/k_{OH}^0 in CPC increase 1.6-fold. When $[Na^+]$ and $[Cl^-]$ increase from 0.25 to 0.50 M (**SS1/SA5, CS1/CA5**), k_H in SDS and k_{OH} in CPC are reduced 0.45- and 0.33-fold, respectively. The larger reduction of k_{OH} is consistent with the observation that K_{OH}^{Cl} is ∼4, greater than K_H^{Na}, which is ∼1.[31] Indeed, quaternary chlorides were chosen over bromides because $K_{OH}^{Br} \gg 1$. Likewise, k_{OH} in cetyltrimethylammonium micelles increases 4.1-fold when the counterion is changed from chloride to acetate (**CTA/CTC**), since $K_{OH}^{OAc} < K_{OH}^{Cl}$. In contrast, k_H in anionic micelles is reduced 0.44-fold when the counterion is changed from Na^+ to Li^+ (**LDS/SDS**), even though Li^+ seems to bind less strongly to SDS micelles than does Na^+.[33] Nevertheless, most of these effects are quite small.

Consequently, the counterion effect, as expressed in eqs 9−10, does not account quantitatively for the observed rates. Since $K_H^{Na} \sim 1$, Na^+ and H_3O^+ compete equally for the micellar surface, so that $[H_3O^+]_{local}/[H_3O^+]_{bulk}$ and correspondingly k_H can be reduced only 2-fold. Likewise, since $K_{OH}^{Cl} \sim 4$, competition between Cl^- and OH^- can reduce k_{OH} only 5-fold. Thus it is unlikely that such small effects are the key to the other puzzles, namely the inability of cationic micelles to increase k_{OH} and the >100-fold greater rate enhancement and reduction factors in anionic than in cationic micelles. Indeed, it is unlikely that the counterion effect and the charge neutralization are so much greater for cationic micelles than for anionic. We therefore must consider additional explanations.

An Alternative Approach to Micellar Kinetics. Our observed rate effects cannot be interpreted simply on the basis of a change in the local pH.[9,21] Hall too had noted that the pseudophase model cannot account for all micellar effects on rates and equilibria, and he proposed an alternative based on the Brønsted formulation.[34] We now present an extension of this formulation and demonstrate its applicability to these acid- and base-catalyzed reactions.

According to the Brønsted formulation of medium effects, the rate ν is related to concentrations, activity coefficients, and activities by eq 11, where k_0 is the rate constant in bulk.[35] It is true that a change in the pH at the micellar surface changes $[cat]_{local}$, and this is the usual consideration in the pseudophase model.[9,21] However, the first form of eq 11 shows that local

(33) Romsted, L. R.; Dunlap, R. B.; Cordes, E. H. *J. Phys. Chem.* **1967**, *71*, 4581.

(34) Hall, D. G. *J. Phys. Chem.* **1987**, *91*, 4287.

(35) Hammett, L. P. *Physical Organic Chemistry*, 1st ed.; McGraw-Hill: New York, 1940; pp 127−9. Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941; p 404.

concentrations are not the only determinant of rate but that activity coefficients also contribute.

$$\nu = k_0[\text{amide}][\text{cat}]\frac{\gamma_{\text{amide}}\gamma_{\text{cat}}}{\gamma_{\ddagger}} = k_0\frac{a_{\text{amide}}a_{\text{cat}}}{\gamma_{\ddagger}} \qquad (11)$$

For reasons that will be apparent, we choose not to use the customary relative activities, but rather the absolute activities.[36a] These latter are defined by eq 12, where μ is the chemical potential. In contrast, the relative activities have an extra factor $\exp(-z_iF\psi/RT)$, where z_i is the charge, F is the Faraday, and ψ is the electrical potential. The relative activities have the advantage that activity coefficients go to unity at infinite dilution, regardless of phase. However, relative activities contain a contribution from $\Delta\psi$, the difference in ψ between two phases. The absolute activity coefficients go to unity only when all concentrations, including solvent, go to zero. The absolute activities then have no contribution from $\Delta\psi$, which is incorporated into the activity coefficients.

$$a_i = \exp(\mu_i/RT) \qquad (12)$$

The familiar requirement for equilibrium between two phases is that the chemical potential of each species must be identical in each phase.[36b] This does not hold for relative activities, since they differ by a factor $\exp(-z_iF\Delta\psi/RT)$, which accounts for micellar kinetics in the usual approach.[37] Nevertheless, it follows from eq 12 that the absolute activity of each ion, like its chemical potential, must be the same in each phase.

It is then far simpler to consider the second form of eq 11. Because equilibrium is established throughout the solution, not only the chemical potential of each ion but also its activity must be identical in every phase. Therefore, neither the pH at the micellar surface nor the activities a_{H^+} and a_{OH^-} can differ from those in bulk water, as has also been noted for the interior of a protein.[38] Indeed, because of this constancy any increase or decrease of $[\text{cat}]_{\text{local}}$ is exactly compensated by a corresponding decrease or increase in γ_{cat}. Therefore a change in $[H^+]_{\text{local}}$ or $[OH^-]_{\text{local}}$ does not itself account for the rate effects.

Since activities are constant, the rate effect can be ascribed entirely to the activity coefficient $\gamma_{\ddagger}$ of the transition state, rather than to variations of the five quantities in the first form of eq 11. This simplification is a consequence of the fact that the reaction is catalyzed by H^+ or OH^-. The activity of each of these, not only in bulk but also at the micellar surface, is what the pH meter measures. Moreover, buffering maintains the concentration of these ions, whereas other ions can be depleted from the bulk by adsorption at the micellar surface.

Thus we must consider the activity coefficient of the transition state. If a transition state is stabilized in the micelle, $\gamma_{\ddagger}$ is reduced and the rate is increased, according to eq 11. In the base-catalyzed exchange the transition state resembles the imidate anion,[3] and in the acid-catalyzed exchange it resembles the *N*-protonated intermediate or the imidic acid, depending on mechanism.[4] Then for the base-catalyzed exchange the persistent first puzzle is that cationic micelles do not stabilize a transition state that resembles the imidate anion and whose activity coefficient would be expected to be reduced. One explanation is that this transition state, with its oxyanion, also resembles OH^-, which is hydrophilic and not strongly adsorbed on the micelle, as reflected by K_{OH}^{Cl}.

We propose two further explanations, based on contrasts between the two kinds of transition states and also between the two kinds of micelles. Focusing on $\gamma_{\ddagger}$ permits us to consider specific molecular interactions, rather than continuum electrostatics or local concentrations. In the acid-catalyzed exchange of a urea the transition state resembles the *N*-protonated cation, whose positive charge is localized, whereas in the base-catalyzed exchange the transition state resembles the imidate anion, whose negative charge is delocalized between oxygen and nitrogen and thus less readily accessible than the more exposed positive charge of the *N*-protonated intermediate. As a result, stabilization of the transition state for base-catalyzed exchange by cations is less effective, simply because of the distance dependence of electrostatics.

A further difference is that the positive charge of the cationic micelles is buried within the organic head group, whereas the negative charge of the anionic micelles is exposed on sulfonate oxygens. As a result, the anionic micelles can exert a stronger electrostatic effect, again through the distance dependence of the interaction. This is analogous to the well-known inability of dipolar aprotic solvents to stabilize anions. In support, replacing the NMe_3^+ head group by the more strongly interacting NH_3^+ (**UDAC/UCTC**) does reduce k_H, but only 2-fold. The consequence of this obvious difference between cationic and anionic micelles seems not to have been explicitly recognized. Unfortunately, it is not possible to study the parallel effect of a NH_3^+ head group on k_{OH}, since it would be deprotonated.

In principle, electrostatic interactions should be symmetric with respect to positive and negative charge, like Coulomb's law. An asymmetry can be observed only through a complete study like this one, spanning the four combinations of acid- and base-catalyzed reactions in anionic and cationic micelles. The one discrepancy between expectation and observation is that cationic micelles do not increase k_{OH}, and we rationalize this in terms of the detailed structures of the transition states and of the micellar head groups. Admittedly, this rationalization alone does not account for the utter lack of acceleration of k_{OH} by cationic micelles, but the steric shielding of the NH, which reduces k_{min} in micelles, is also operative.

It should be noted that eq 11 remains consistent with the pseudophase model, as has been noted previously.[39] The transition state in the acid-catalyzed reaction is like an *N*-protonated amide, $RC(=O)NH_2R'^+$. At the acyl end this resembles the amide and at the cationic end this resembles H_3O^+. Similarly, the transition state in the base-catalyzed reaction is like an imidate anion, $RC(-O^-)=NR'$, which resembles both amide and OH^-.[3] To the extent that these resemblances extend to activity coefficients, then the ratio $\gamma_{\text{amide}}\gamma_{\text{cat}}/\gamma_{\ddagger}$ in the first form of eq 11 is approximately 1, and ν is simply proportional to $[\text{cat}]_{\text{local}}$. However, this justification of the pseudophase model does depend on an exact resemblance and an exact cancellation of activity coefficients. It is easier to focus on $\gamma_{\ddagger}$ alone.

Finally, the inability of cationic micelles to increase k_{OH} is not simply due to the low selectivity that may be expected of a rapid reaction. For an amide in water k_{OH} is high, $>10^7$ M^{-1} s^{-1}, corresponding to a free energy of activation only 4 kcal/mol above encounter control. With so low an activation energy, it is possible that the additional electrostatic stabilization from a cationic micelle would not increase the rate significantly.

(36) Guggenheim, E. A. *Thermodynamics*, 7th ed.; Elsevier: Amsterdam, 1985; (a) pp 95, 273, and 302ff, (b) p 300.

(37) Lissi, E. A.; Abuin, E. B.; Sepúlveda, L.; Quina, F. H. *J. Phys. Chem.* **1984**, *88*, 81.

(38) Perrin, C. L.; Lollo, C. P. *J. Am. Chem. Soc.* **1984**, *106*, 2754.

(39) Cornejo, P. L.; Jiménez, R.; Moyá, M. L.; Sánchez, F.; Burgess, J. *Langmuir* **1996**, *12*, 4981.

Nevertheless, an anionic micelle does increase k_H for a urea 29-fold (**USDS**), not much different from the average 100-fold increase for ordinary amides, even though the activation energy for acid-catalyzed exchange of the model urea is also quite low.

Summary/Conclusions. Rate constants for acid- and base-catalyzed NH exchange of amides can be strongly influenced by the electrostatic environment. Anionic micelles, where k_{OH} decreases by a factor of about 2.5×10^3 and k_H increases by a factor of about 10^2, show the largest effect. The effects of cationic micelles, where k_H decreases by a factor of about 30 for ureas, are smaller. Most other effects are very small (less than a factor of about 2): counterion, nonionic surfactant, head group, chain length, etc. Even the effect of cationic micelles on k_H is rather small, especially for amides, and the effect of cationic micelles on k_{OH} is undetectable. The low and variable electrostatic effect is attributed to competition by counterions, an extensive charge neutralization, the delocalized nature of the transition state for base-catalyzed exchange, and a shielding of the positive charge of cationic micelles. The Brønsted formulation, using absolute activities and activity coefficents, is a powerful method for the analysis of micellar effects on these acid- and base-catalyzed reactions.

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