325 (1976).
9. F.A. Carey and R.J. Sundberg, "Advanced Organic Chemistry," Part A, 2nd ed., New York, Plenum Press, 1984, p. 11
10. The correlation coefficients between $\Delta E^{\ddagger}$ and ΔE_R, ΔE_P, and ΔE_{av} are 0.905, 0.967, and 0.946, respectively.
11. In the CH_3Cl series, the RC is higher in energy than the PC. Therefore the TS resembles the RC in energy and structure.
12. G.S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
13. (a) W.A. Lathan and K. Morokuma, *J. Am. Chem. Soc.*, **97**, 3615 (1975) (b) H. Umeyama and K. Morokuma, *J. Am. Chem. Soc.*, **99**, 1316 (1977).
14. I. Lee and C.H. Song, *Bull. Korean Chem. Soc.*, **7**, 186 (1986).
15. J.M. Haaish, S.G. Shafer, J.R. Moffatt, and A.R. Becker, *J. Am. Chem. Soc.*, **101**, 3296 (1979).
16. Since the dissociation energy of the C-Cl bond is lower by 24 kcal/mol than that of C-F bond (Table 1), the P and D corners for X = Cl will be lower (or stabilized) by the same amount than for X = F.
17. E.R. Thorton, *J. Am. Chem. Soc.*, **89**, 2915 (1967).
18. R.P. Bell, *Proc. R. Soc. London, Ser. A*, **154**, 414 (1936).
19. M.G. Evans and M. Polanyi, *J. Chem. Soc., Faraday Trans.*, **32**, 1340 (1936).

MNDO Studies on Intramolecular Proton Transfer Equilibria of Acetamide and Methyl Carbamate[1]

Ikchoon Lee,* Chang Kon Kim, and Heon Su Seo

Department of Chemistry, Inha University, Inchon 160. *Received July 29, 1986*

Intramolecular proton transfer equilibria of acetamide and methyl carbamate have been studied theoretically by MNDO MO method. For both substrates, carbonyl-O protonated tautomer was found to be the most stable form, the next most stable one being N-protonated form. Gas phase proton transfers take place by the 1,3-proton rearrangement process and in all cases have prohibitively high activation barriers. When however one solvate water molecule participates in the process, the barriers are lowered substantially and the process proceeds in an intermolecular manner through the intermediacy of the water molecule via a triple-well type potential energy surface; three wells correspond to reactant(RC), intermediate(IC) and product complexs(PC) of proton donor-acceptor pairs whereas two transition states(TS) have proton-bridge structure. General scheme of the process can be represented for a substrate with two basic centers(heteroatoms) of A and B as,

$$\underset{}{\overset{+}{ABH}} + H_2O \rightarrow \underset{RC}{\overset{+}{ABH\cdots OH_2}} \rightarrow \underset{TS\ 1}{\overset{+}{AB\cdots H\cdots OH_2}} \rightarrow \underset{IC}{\overset{+}{AB\cdots HOH_2}}$$

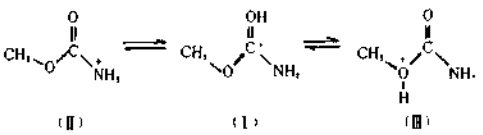
$$\underset{}{\overset{+}{BAH}} + H_2O \leftarrow \underset{PC}{\overset{+}{BAH\cdots OH_2}} \leftarrow \underset{TS\ 2}{\overset{+}{BA\cdots H\cdots OH_2}}$$

Involvement of a second solvate water had negligible effect on the relative stabilities of the tautomers but lowered barrier heights by 5~6 Kcal/mol. It was calculated that the abundance of the methoxy-O protonated tautomer of the methyl carbamate will be negligible, since the tautomer is unfavorable thermodynamically as well as kinetically. Fully optimized stationary points are reported.

Introduction

Intermolecular proton transfers[2] and proton exchanges[3] in amides and related compounds have been of considerable interest because of their widespread importance in a large number of chemical and biological processes. On the other hand, information concerning intramolecular proton transfers between functional groups within a substrate forming various protonated tautomers is essential in elucidating mechanism of the hydroiysis of amides and carbamates in acid solution.[4]

The mechanims of A2 reaction of amides and carbamates[4] in strong acidic media should depend on which protonated form(carbonyl O-, N-, or alkoxy O-protonated form) is involved in the rate-determining attack of water on the protonated substrate. Currently the addition of water to the N-protonated tautomer(II) in the rate-determining step is favored for the mechanism of hydrolysis of protonated carbamates.[4] Hence it is believed to involve two steps, the



(II) (I) (III) (1)

pre-equilibrium between the dominant carbonyl O-protonated tautomer(I) and the minor N-protonated form(II), and the rate-determining nucleophilic attack of water on (II).

In this work we investigated the proton transfer equilibria

involved in acetamide and methyl carbamate, (I), MO theoretically using MNDO method[5] in order to shed some light on the relative merits of possible mechanisms in the acid hydrolysis of the compounds.[4]

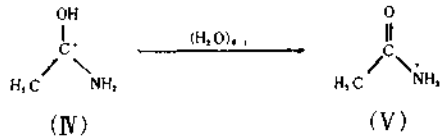
Calculations

MNDO program[5] was used throughout in the present work. All of the geometries corresponding to stationary points, *i.e.*, tautomers, intermediate complexes, and transition states(TS) were fully optimized with the energy gradient.[6] TS's were characterized by confirming only one negative eigenvalue in the Hessian matrix.[7]

Results and Discussion

Relative stabilities ($\Delta\Delta H_f$) of various protonated tautomers for acetamide and methyl carbamate are compared in Table 1. In addition to gas phase equilibria, we have also explored the equilibria involving one or two solvate water molecules, $(RCONH_2)H^+(H_2O)_n$ where R = CH_3 or CH_3O and n = 0, 1 and 2. In all cases, the carbonyl O-protonated tautomer is the most stable form, the next being the N-protonated one; the carbonyl O-protonated form will therefore be the dominant tautomer and hence will be most abundant.[4] The methoxy O-protonated form is shown to be the least stable one thermodynamically. It is notable that the N-protonated form of acetamide is slightly more favored thermodynamically than the corresponding form of methyl carbamate relative to the respective carbonyl O-protonated form; amide should have a higher equilibrium concentration of N-protonated substrate than carbamates. Reference to Table 1 also reveals that solvate molecules have negligible effect on the relative stabilities of the tautomers.

Proton Transfer Mechanism. (i) Protonated Acetamide, $(CH_3CONH_2)H^+(H_2O)_{0,1}$: We first consider the gas phase proton shift(n = 0), a 1,3-proton rearrangement process (2).[8] Fully optimized geometries of (IV) and (V)



(IV) (V) (2)

together with the TS are shown in Figure 1; the TS has a four-membered ring structure of the typical 1,3-H shift.[8] Barrier height found was 70.9 Kcal/mol which is certainly very high and gas phase proton shift seems almost impossible.

Table 1. Relative Stabilities (Kcal/mol) of Protonated Tautomers of Acetamide, $(CH_3CONH_2)H^+(H_2O)_n$, and Methyl Carbamate, $(CH_3OCONH_2)H^+(H_2O)_n$ with n = 0, 1 and 2

Protonated Atom / n	Acetamide		Methyl Carbamate		
	O*	N	Carbonyl O	N	Methoxy O
0	0.00	17.19	0.00	18.95	36.12
1	0.00	16.45	0.00	19.13	36.27
2	—	—	0.00	19.22	36.12

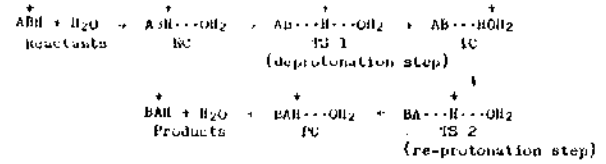
*Heat of formation, ΔH_f, for reference substrates are given in Figures showing optimized geometries.

However when we add one solvate water molecule into the reaction system, considerable lowering of the barrier is achieved as can be seen from the results presented by an energy profile in Figure 2. Now the proton transfer proceeds intermolecular way in two steps, (i) deprotonation from (IV), and (ii) re-protonation to give (V) through the intermediacy of a solvate water molecule. In addition to reactant(RC) and product complexes(PC), there is an intermediate complex(IC) formed in between the two transition states(TS) and general shape of potential surface is of a triple-well type. Optimized geometries for all of species at the stationary points are given in Figure 3. All the complexes, RC, IC and PC, are seen to consist of a pair of proton donor(protonated species) and acceptor fragments[2] separated by ~2.5A or more, whereas in the TSs the proton forms a bridge between the two fragments. These features are in good agreements with the ab initio results of proton transfer studies reported recently.[3]

Involvement of one solvate molecule causes the process to occur intermolecular manner so that a drastic lowering of the barrier height(29.1 Kcal/mol) is achieved. Thus the overall proton transfer in a substrate with two basic centers (heteroatoms) A and B involving one solvate water can be represented in a simple form of scheme I.

(ii) Protonated Methyl Carbamate, $(CH_3OCONH_2)_{0,1,2}$.

Fully optimized geometries of (I), (II), (III) and those of the TS for processes (3) and (4) where n = 0 are shown in Figure 4. Barrier heights were 71.8 and 79.0 Kcal/mol respectively for (3) and (4) with n = 0; these are prohibitively high,



Scheme I

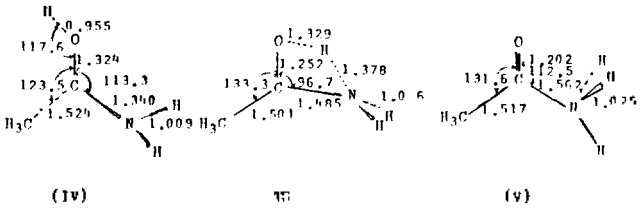


Figure 1. Geometries of species at the stationary points on the potential energy profile for the proton transfer, (IV) → (V) (bond lengths and angles are in Å and degree).

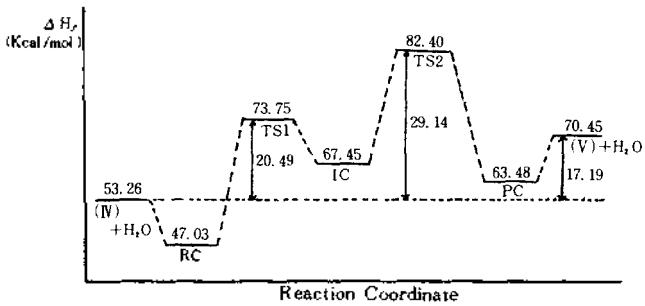


Figure 2. Potential energy profile for the proton transfer, (IV) + H_2O → (V) + H_2O.

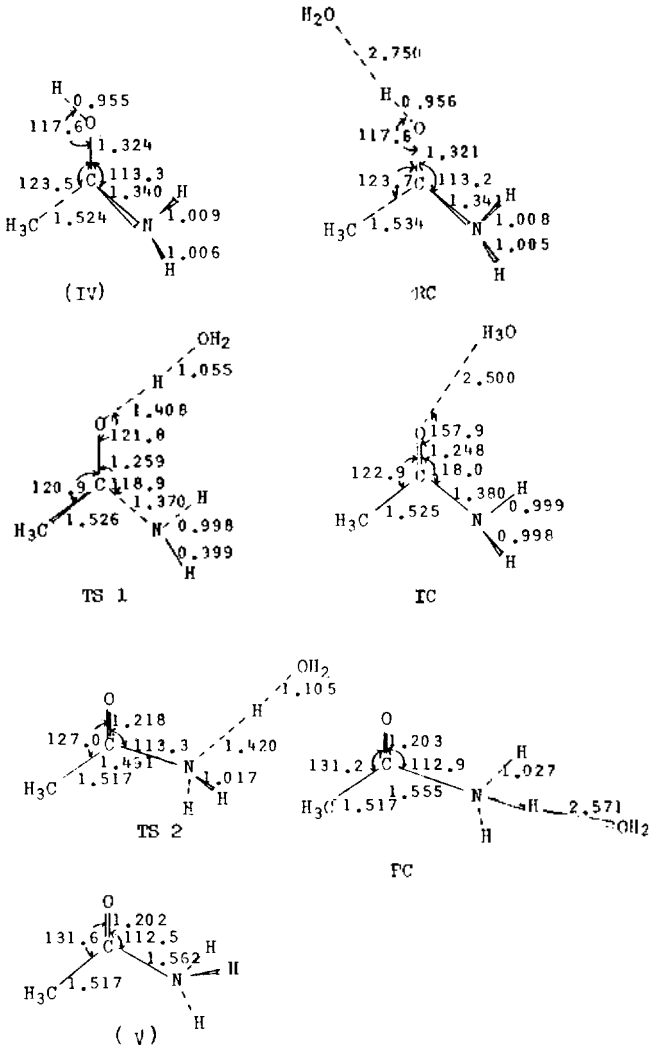


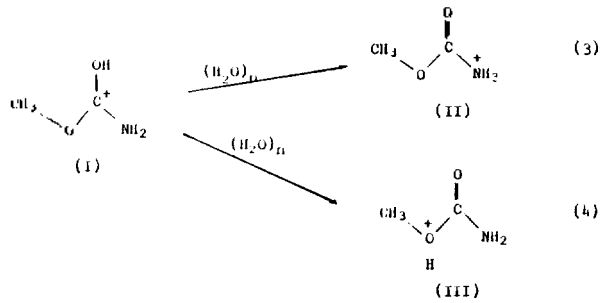
Figure 3. Geometries of species at stationary points on the potential energy profile for the proton transfer, (IV) + H_2O → (V) + H_2O (bond lengths and angles are in Å and degree).

even higher than the corresponding value for acetamide. Here also the TS's were the four-membered ring type of 1,3-H shift process.[8].

Involvement of one solvate water molecule in the intramolecular proton transfers (3) and (4) with n = 1 again causes the processes to proceed intermolecular manner in two steps and the potential surfaces become triple-well type as shown in Figure 5 and 6 respectively. The first step, deprotonation from (I), is the same for the two processes. The proton transfer to N, eq(3), is quite similar to the corresponding process for acetamide(eq(2) with n = 1) as represented by scheme I.

A notable feature in the second step of the process (4) with n = 1 is that the IC is first converted to another intermediate complex(IC*) before the TS 2 is formed; schematically it can be represented as,

$$\underset{}{\text{TS 1}} \rightarrow \underset{\text{IC}}{\text{AB}\cdots\overset{+}{\text{H}}\text{O}\text{H}_2} \rightarrow \underset{\text{IC*}}{\text{BA}\cdots\overset{+}{\text{H}}\text{O}\text{H}_2} \rightarrow \underset{\text{TS 2}}{\text{BA}\cdots\overset{+}{\text{H}}\cdots\text{OH}_2} \rightarrow \text{PC}$$



All the optimized geometries are given in Figure 7. However involvement of two solvate water molecules in the processes (3) and (4) (with n = 2 cases) little change in the shape of general potential energy profile with lowering of the barriers, TS 1 and TS 2, by only 5~6 Kcal/mol as compared with those for the corresponding n = 1 cases(Figure 8 and 9). In general, optimized structures of the species at the stationary points are similar to those of Figure 7 for n = 1 with the se-

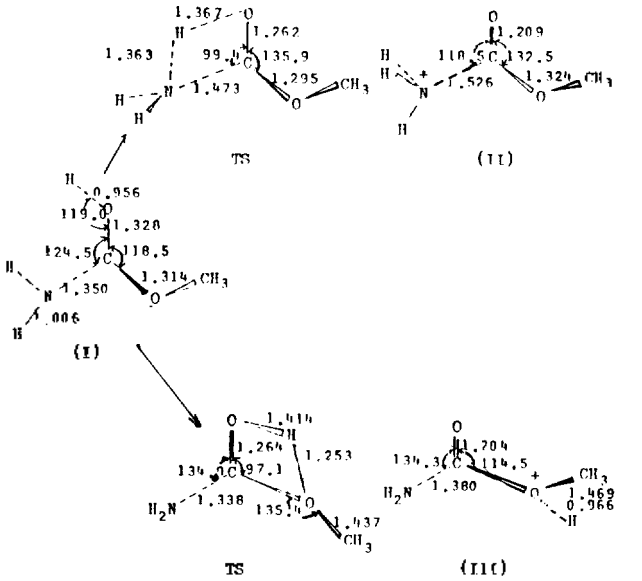


Figure 4. Geometries of species at stationary points on the pontential energy profile for the proton transfers, (I) → (II) and (I) → (III) (bond lengths and angles are in Å and degree).

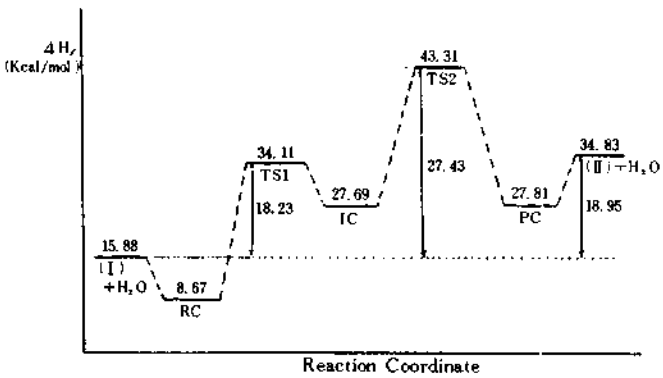


Figure 5. Potential energy profile for the proton transfer, (I) + H_2O → (II) + H_2O.

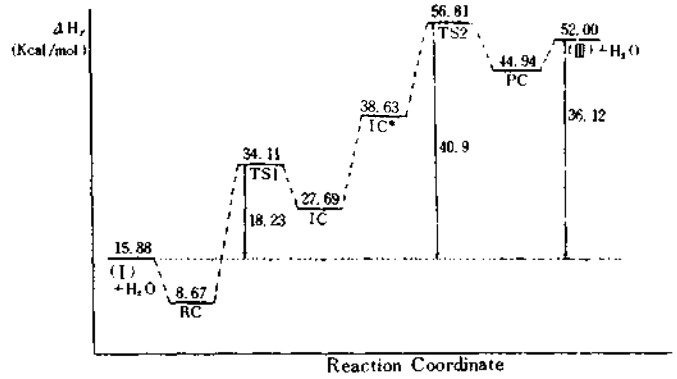


Figure 6. Potential energy profile for the proton transfer, (I) + H_2O → (III) + H_2O.

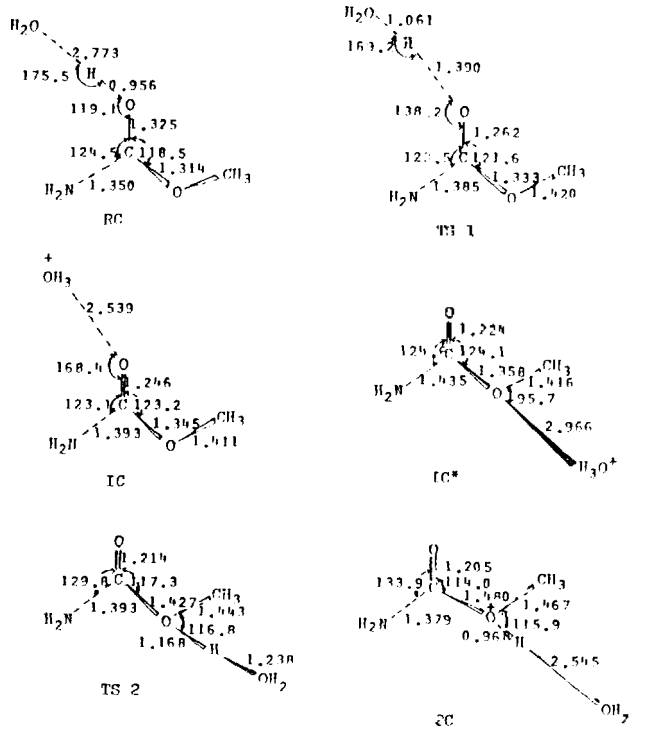


Figure 7. Geometries of species at the stationary points on the potential energy profile for the proton transfer, (I) + H_2O → (III) + H_2O (bond lengths and angles are in Å and degree).

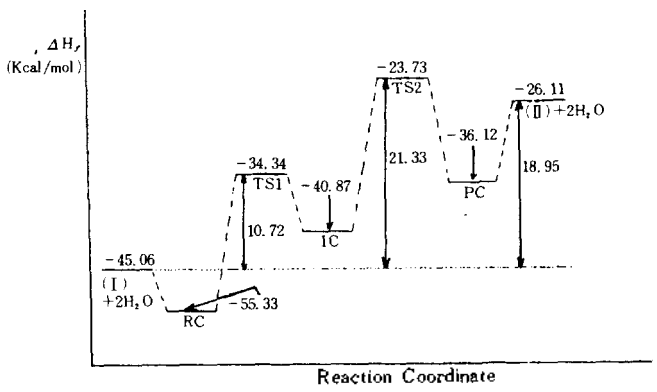


Figure 8. Potential energy profile for the proton transfer, (I) + 2H_2O → (II) + 2H_2O.

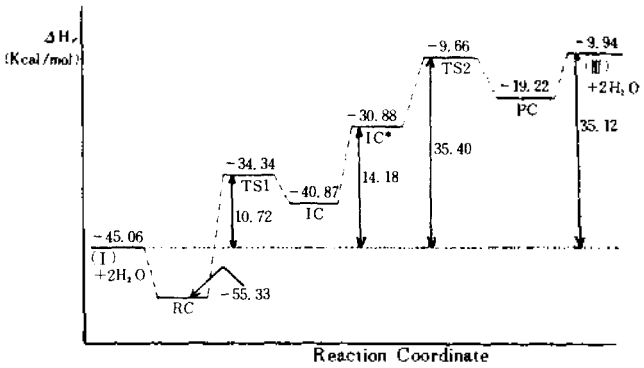


Figure 9. Potential energy profile for the proton transfer, (I) + 2H_2O → (III) + 2H_2O.

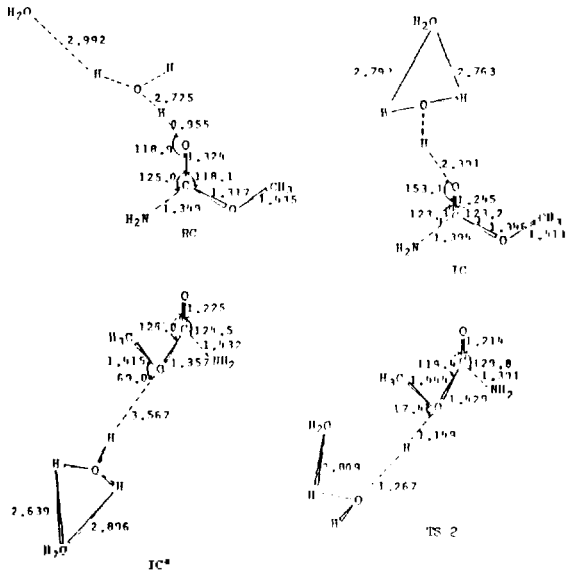


Figure 10. Geometries of some species at the stationary points on the potential energy profile for the proton transfer, (I) + 2H_2O → (III) + 2H_2O (bond lengths and angles are in Å and degree).

Table 2. Activation Barriers (Kcal/mol) to Proton Transfers from the Dominant Carbonyl O-protonated form(ground state) into other Tautomers

n	Acetamide from O- to	Methyl Carbamate from carbonyl O- to	
	N-	N-	Methoxy O-
0	70.87	71.78	79.03
1	29.14	27.43	40.93
2	—	21.33	35.40

cond water molecule solvating the first solvate water which forms a fragment in the donor-acceptor pair. Some representative optimized geometries are shown in Figure 10.

Finally we have summarized barrier heights relative to the ground state, the carbonyl O-protonated form, corresponding to the rate-determining step for the processes (3) and (4) in Table 2. Reference to Table 2 indicates that the proton transfer to the methoxy O-protonated tautomer has substan-

tially higher activation barrier compared to that for the proton transfer to the N-protonated form in methyl carbamate. Therefore we conclude that the methoxy O-protonated tautomer(III) is not only unstable thermodynamically (Table 1) but also is difficult to form kinetically so that the abundance of (III) in the acid solution will be negligible. Thus the protonation behavior of methyl carbamate will be similar to that of acetamide. This conclusion is fully consistent with experimental results of protonation equilibria of amides and carbamates.[9]

Acknowledgements. We thanks the Korea Science and Engineering Foundation and the Korea Center for Theoretical Physics and Chemistry for support of this work.

References

1. Part 43 of the series: Determination of Reactivity by MO theory.
2. (a) E.A. Hillenbrand and S. Scheiner, *J. Am. Chem. Soc.*, **106**, 6266 (1984); (b) S. Topiol, G. Mercier, R. Osman and H. Weinstein, *J. Comput. Chem.*, **6**, 581 (1985); (c) I.M. Kovach, M. Belz, M. Larson, S. Rausy and R.L. Schowen, *J. Am. Chem. Soc.*, **107**, 7360 (1985); (d) W.E. Farneth and J.I. Brauman, *ibid.*, **98**, 7891 (1976).
3. C.L. Perrin and G.M.L. Arrhenius, *ibid.*, **104**, 6693 (1982).
4. (a) V.C. Armstrong, D.W. Farlow and R.B. Moodie, *J. Chem. Soc.* (B), 1099 (1968); (b) V.C. Armstrong and R.B. Moodie, *ibid.*, 934 (1969); (c) D.W. Farlow and R.B. Moodie, *ibid.*, 407 (1971); (d) R.B. Moodie and R. Towill, *J. Chem. Soc. Perkin II*, 184 (1972); (e) L.M. Sayre, *J. Am. Chem. Soc.*, **108**, 1632 (1986).
5. (a) M.J.S. Dewar and W. Thiel *J. Am. Chem. Soc.* **99**, 4899 (1977); (b) M.J.S. Dewar and H.S. Rzepa, *ibid.*, **100**, 784 (1978).
6. (a) A. Komornicki, K. Ishida and K. Morokuma, *Chem. Phys. Lett.*, **45**, 595 (1977); J.W. McIver, Jr., and A. Komornicki, *J. Am. Chem. Soc.*, **94**, 2625 (1972).
7. I.G. Csizmadia, "Theory and Practice of MO calculations on Organic Molecules", Elsevier, Amsterdam, 1976, p. 239.
8. (a) F.M. Menger, J. Grossman and D.C. Liotta, *J. Org. Chem.*, **48**, 905 (1983); (b) K. Yamashita, M. Kaminoyama, T. Yamabe and K. Fukui, *Theoret. Chim. Acta*, **60**, 303 (1981); (c) I. Lee, J.K. Cho and B.S. Lee, *J. Comput. Chem.*, **5**, 217 (1984).
9. (a) V.C. Armstrong and R.B. Moodie, *J. Chem. Soc. (B)*, 275 (1968); (b) M. Liler *ibid.*, 334 (1971); (c) G.A. Olah and M. Calin, *J. Am. Chem. Soc.*, **90**, 401 (1958).

Studies on the Formation and Stability of Colloids (I): Perturbation of Micelle Formation of Sodium Deoxycholate by Amides

Joon Woo Park* and Hesson Chung

Department of Chemistry, Ewha Womans University, Seoul 120. *Received August 1, 1986*

The critical micelle concentration (CMC) of sodium deoxycholate (NaDC) and the effects of amides on the micellization processes have been studied by fluorometric technique using pyrene as a probe. The addition of amides as cosolvent destabilized the NaDC micelle and increased the CMC. The order of effectiveness for the perturbation of NaDC micelle was N-methylacetamide≥DMF>acetamide>formamide, which is the order of hydrophobicity of the amides. This indicated that the effect of amides on the micellization processes of NaDC arises from diminution of the hydrophobic effect. The electrostatic repulsion between ionic head groups in the NaDC micelle appeared to be much less than that in aliphatic ionic micelle. This was also revealed in the weaker dependence of the CMC on ionic strength. The premicellar association of NaDC was not significantly involved in the micellization processes of the bile salt.

Introduction

Bile salts are well known as biological surfactants and for their solubilizing action for lecithin, cholesterol and many other hydrophobic dietary lipids. The physiological role of bile salts depends mainly on their self-associating, *i.e.* micelle forming properties. Early works on the micellization and related physicochemical properties of bile salts were extensively surveyed by Small.[1]

The bile salt micelles are quite different from ordinary micelles in aggregative number and shape of the micelles. The exact nature of the driving forces for micellization of bile salts is not unequivocally explained.[2] But, several evidences suggest the presence of primary (aggregation of about 10 monomers to small micelles) and secondary (aggregation of primary micelles to large micelles) micellization phenomena for dihydroxy bile salts such as sodium deoxycholate (NaDC).[3-10,11] Generally, it is believed that the major driving force for micellization of a surfactant is hydrophobic effect, which arises from local ordering of water molecules into ice-like structure at hydrocarbon-water interface. The aggregation of hydrophobic part of surfactants results in decrease of the interfacial area, and thus, the micellization process is entropically favored.

Amides are known as a water-breaking chaotropic solutes, and they could reduce the hydrophobic interaction between water and surfactants molecules, and thus destabilize the micelles.[10b,12-14] This paper reports the effect of added amides on the critical micelle concentration(CMC) of NaDC. This is of particular interest because various compounds bearing