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Evidence for the Effect of a Reversed Micelle on the Transition State for the Hydration of 1,3-Dichloroacetone

Summary: The transition state (TS) structure for the reversible hydration of 1,3-dichloroacetone (DCA) in the presence of bis(2-ethylhexyl)sodium sulfosuccinate (AOT) reversed micelles in hexane was inferred from a proton inventory study. In contrast to the cyclic TS structure proposed for this reaction in water–dioxane, the results indicate that the TS in question is probably acyclic and that the number of associated water molecules depends on the water/surfactant molar ratio *R*. Additional support for this dependence on *R* was obtained from the activation parameters.

Sir: Reversed micelles are surfactant aggregates in organic solvents.[1] They can catalyze diverse chemical reactions, and the origin of such catalysis has been traced to enhanced substrate reactivity and concerted proton transfer.[1,2] Micellar rate enhancement, relative to that in a reference solvent, implies different transition state (TS) structures in both cases. In the present communication direct evidence for this difference will be given, based on analysis of the solvent isotope effect for a reaction occurring inside the reversed micelles of bis(2-ethylhexyl)sodium sulfosuccinate (AOT).

The hydration of 1,3-dichloroacetone (DCA) by micellar water[3] in hexane was subjected to a proton inventory study. The dependence of the rate constant of a reaction (k^n) on the atom fraction of deuterium (n) in a solvent is given by eq 1,[4,5] where k^0 is the rate constant in water and

$$k^n = k^0[\prod_i^{\nu}(1 - n + n\phi_i^*)]/[\prod_j^{\rho}(1 - n + n\phi_j)] \quad (1)$$

ϕ_i^* and ϕ_j are the fractionation factors for the exchangeable TS and reactant-state protons, respectively. DCA does not exchange protons with micellar water, and for the latter ϕ_j is assumed to be unity, so that eq 1 becomes eq 2 and

$$k^n = k^0\ [\prod_i^{\nu}(1 - n + n\phi_i^*)] \quad (2)$$

k^n/k^0 is a polynomial in n whose order, ν, specifies the number of protons contributing to the solvent isotope effect.

Table I. Rate Constants for DCA Hydration ($k^n{}_h$) as a Function of the Atom Fraction of Deuterium (n) in the Micellar Water[a]

R	n	$10^4 k^n{}_h$, s^{-1} exptl	calcd[b,c]
1.3	0.000	6.16 ± 0.28	6.16
	0.196	5.60 ± 0.15	5.59
	0.393	5.05 ± 0.22	5.02
	0.590	4.47 ± 0.10	4.45
	0.788	3.84 ± 0.14	3.87
	0.987	3.30 ± 0.06	3.30
11.1	0.000	66.5 ± 1.7	66.5
	0.178	55.1 ± 1.1	55.6
	0.312	48.1 ± 1.0	48.2
	0.447	41.5 ± 1.1	41.3
	0.581	35.2 ± 0.3	35.1
	0.784	26.5 ± 0.4	26.8
	0.987	19.8 ± 0.4	19.7

[a] 0.2 M AOT in hexane, 25 °C. [b] Calculated rate constants, based on TS 1, assuming $\phi_a = 0.53$ and $\phi_b = 1$, for $R = 1.3$. [c] Calculated rate constants, based on eq 3, using $\phi_a = 0.49$ and $\phi_c = 0.77$, for $R = 11.1$.

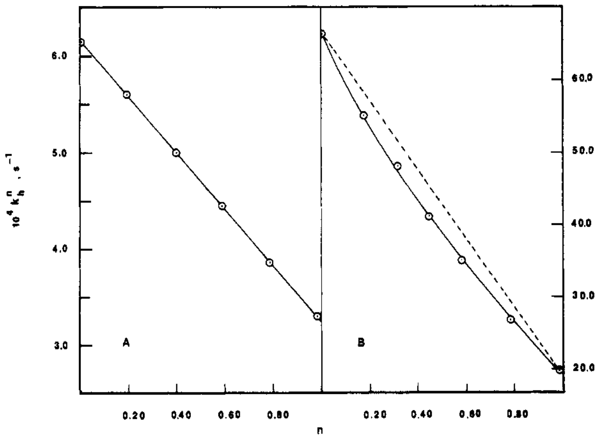
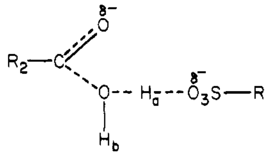


Figure 1. Dependence of the rate constant for hydration, $k^n{}_h$, on the atom fraction of deuterium (n) of the micellar water at R = 1.3 (A) and 11.1 (B) at 25 °C. Solid lines are theoretical, calculated from eq 2 and 3 for A and B, respectively.

The reaction was studied at R = 1.3 and 11.1 and the results are given in Table I.[6] A plot of $k^n{}_h$ vs. n is linear for R = 1.3 and curved upward for R = 11.1 (Figure 1). The linear dependence in the former case means that ν is unity in eq 2; i.e., only one proton is moving in the TS. Structure 1 is compatible with these results.[9] The proton "in flight", H_a,contributes to the isotope effect whereas H_b which is converted from an OH of water to an OH of the hydrate apparently does not contribute to the isotope effect; i.e., $\phi_b \simeq 1$. This proposed TS structure is different from the cyclic counterpart (TS 2, showing three protons in flight) proposed for the same reaction in water–dioxane.[11] This can be attributed to the fact that at this low



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(3) As used here, micellar water indicates water, D_2O, and/or their mixture solubilized in AOT reversed micelles.

(4) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275.

(5) Albery, W. J. In "Proton-Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman and Hall: London, 1975.

(6) Rate constants were determined spectrophotometrically at 296 nm by using 0.008 M DCA and 0.2 M AOT. The purification, drying, manipulation of the reagents, and the kinetic procedure were those given before.[7] No hydration takes place outside the AOT micelle.[7] Details of a proton inventory experiment can be found elsewhere.[8] Briefly, one determines the rate constants as a function of the deuterium content of the solvent.

(7) El Seoud, O. A.; da Silva, M. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 127.

(8) Harmony, J. A. K.; Himes, R. H.; Schowen, R. L., *Biochemistry* **1975**, *14*, 5379. Venkatasubban, K. S.; Davis, K. R.; Hogg, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 6125.

(9) Here the attacking water is drawn attached to the surfactant sulfonate group. Another possibility is that H_a is being transferred to another water molecule tightly bound to the AOT molecule. In this case, the linear dependence of k^n on n can be explained by assuming that extensive proton transfer to the second water molecule is not achieved in the TS.[10]

(10) Menger, F. M.; Venkatasubban, K. S. *J. Org. Chem.* **1976**, *41*, 1868.

(11) Bell, R. P.; Critclow, J. E. *Proc. R. S. London, Ser. A* **1971**, *325*, 35.

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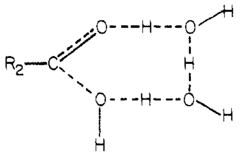

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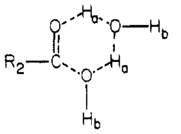
R value the interaction of water with the AOT head groups is stronger than its autoassociation.[12]

The results at $R = 11.1$ suggest that $\nu > 1$; i.e., several protons contribute to the solvent isotope effect. Curve fitting according to TS **2**, i.e., using $\nu = 3$, gave $\phi_a{}^* = 0.67$ which is outside the range expected for this type of reaction ($\phi \simeq 0.5$).[5] Additionally, the computed curvature function, γ, was different from the one derived from the experimental results.[13] A symmetrical TS containing two water molecules (**3**) gave $\phi_a{}^* = 0.53$ which is in the expected



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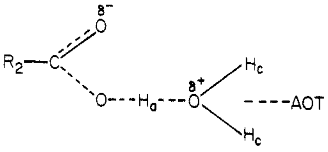
range. However, the energetically favorable linear donor–proton-acceptor arrangement cannot be accommodated in a six-membered-ring TS without considerable strain.[14] Also, the computed γ value (0.53) was not in agreement with that derived from the rate data. Analysis of the results according to a nonsymmetrical cyclic TS, hence a less strained one, using a two-term version of eq 2 gave a bad fit.[16]

In line with the TS structure proposed for $R = 1.3$, an acyclic TS containing two, or more, water molecules seems more likely. In TS **4** the proton bridge H_a contributes a



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primary isotope effect, H_b apparently does not contribute, whereas H_c of the "general base" water produces secondary effects. For this TS eq 2 becomes eq 3 and the quality of

$$k^n = k^0 (1 - n + n\phi_a{}^*)(1 - n + n\phi_c{}^*)^2 \qquad (3)$$

the fit can be seen in Figure 1. The best fit was obtained using $\phi_a{}^* = 0.49 \pm 0.02$ and $\phi_c{}^* = 0.77 \pm 0.01$, in good agreement with the values of 0.51 and 0.77 calculated based on the γ method.[5]

The reaction activation parameters[17] substantiate the change in the TS structure at the higher R value. Thus, when R was increased from 1.3 to 11.1, ΔH^* decreased from 58 to 26 kJ mol^{-1}, probably due to the participation of the "general base" water, whereas there was a large decrease in ΔS^* (from −111 to −199 J K^{-1} mol^{-1}) due to the presence of this extra water molecule. At a comparable water concentration (2.22 M, $R = 11.1$), the micellar rate constant is 266 times faster than that in water–dioxane.[11] This rate enhancement is clearly due to an entropy increase (72 J K^{-1} mol^{-1}) since ΔH^* for the reaction in AOT is 6.5 kJ mol^{-1} higher than that in water–dioxane.[18] The higher ΔS^* value for the former reaction can be easily rationalized if TS **4**, which is acyclic and contains less water molecules, is assumed.

In conclusion, differences between the structure of the TS of a micellar reaction and that occurring in a reference solvent can affect the activation parameters which, in favorable cases, entails a rate enhancement.

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[13] According to Albery,[5] γ is a function of the curvature in the ($\ln k^n/k^0$) vs. n plots. If the observed isotope effect is due to protons with the same ϕ value (e.g., the protons in flight of TS **2** designated A) γ will be given by $\gamma \simeq \Lambda_A{}^2/a$, where a is the number of the protons involved, and Λ_A is given by $\Lambda_A = (a \ln \phi_A)/\ln (k^1/k^0)$. Using $\phi_A = 0.67$ and $\ln (k^1/k^0) = -1.231$, we obtained $\gamma = 0.32$.

[14] On the other hand, a seven- or eight-membered-ring TS can support this linear arrangement.[15] At the present stage, however, we feel that more results are needed before TS **3** can be ruled out unambiguously.

[15] Gandour, R. D. *Tetrahedron Lett.* **1974**, 295. Litvinenko, L. M.; Oleinik, N. M. *Russ. Chem. Rev.* **1978**, *47*, 401.

[16] In this case the standard deviation in ϕ was equal to, or higher than, ϕ itself.

[17] At $R = 1.3$, the rate constants $k^0{}_h$ at 18, 25, 30, and 38 °C were 2.95, 6.16, 8.72, and 15.05×10^{-4} s^{-1}, and for $R = 11.1$, $k^0{}_h$ at 18, 25, and 38 °C was 51.3, 66.5, and 109.4×10^{-4} s^{-1}, giving $\Delta H^* = 58$ and 26 kJ mol^{-1} and $\Delta S^* = -111$ and −199 J K^{-1} mol^{-1}, for $R = 1.3$ and 11.1, respectively.

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(2*S*,3*S*,4*R*)-4-Amino-3-hydroxy-2-methylvalerate. Synthesis of an Amino Acid Constituent of Bleomycin from L-Rhamnose

Summary: (2*S*,3*S*,4*R*)-4-Amino-3-hydroxy-2-methylvalerate, an amino acid constituent of the antitumor antibiotic bleomycin, has been prepared from L-rhamnose. This approach to a chiral 3-hydroxy-2-methylcarboxylate constitutes an alternative to the stereoselective aldol condensation.

Sir: The bleomycins are a family of glycopeptide-derived antibiotics elaborated by *Streptomyces verticillus*.[1] A mixture of bleomycins, consisting primarily of bleomycin A_2 (**1**), is used clinically for the treatment of certain neoplasms, including squamous cell carcinomas and malignant lymphomas.[2] As part of a synthesis of the tetrapeptide S moiety of bleomycin we recently described[3] the preparation of (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvaleric acid (**2**) by modification of the method of Yoshioka et al.[4] Although affording a much higher yield of the desired isomer than the reported procedure, we noted that some

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[3] (a) Levin, M. D.; Subrahamanian, K.; Katz, H.; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1452. (b) Hecht, S. M.; Burlett, D. J.; Mushika, Y.; Kuroda, Y.; Levin, M. D. "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 48 ff.

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