

## On the Mechanism of Keto—Enol Tautomerization for Acetylacetone and 2-Carboethoxycyclohexanone

N. C. SØNDERGAARD, P. E. SØRENSEN and J. ULSTRUP

Chemistry Department A, The Technical University of Denmark, Building 207, DK-2800 Lyngby, Denmark

The keto—enol tautomerization reactions of acetylacetone and 2-carboethoxycyclohexanone in mixtures of water and dioxan has been investigated and the rate constants and activation parameters obtained for both the ketonization and enolization reactions. The transition states are found to contain several water molecules. Analysis of the activation parameters on the basis of recent quantum theories of proton transfer reactions in polar media suggests that the proton transfers in the water-substrate chain involve at least one step in which a separate  $H_3O^+$  unit is formed (step-wise mechanism), and that the main contribution to the high negative entropies of activation observed is the loss of translational degrees of freedom.

There is good evidence that the hydration of carbonyl compounds in general proceeds by a "cooperative" mechanism, in which the transition state contains the substrate and several water molecules organized in a ring structure,<sup>1-5</sup> and in which an important step is the synchronous or step-wise transfer of protons in this ring. We present here experimental data, which suggest that also the reversible keto-enol transformation for acetylacetone (*acac*) and 2-carboethoxy-cyclohexanone (*cc*) in water and water/dioxan mixtures probably proceeds by such a mechanism.

### EXPERIMENTAL

**Materials.** Doubly distilled water was used throughout. Acetylacetone, *purum* (E. Merck, Darmstadt) and 2-carboethoxycyclohexanone (kindly supplied by Dr. D. W. Earls, Stirling University, UK) were purified by distillation *in vacuo*, and the middle fraction collected and stored for no longer than one week. Dioxan,

*technical* (BASF) was purified according to literature procedures.<sup>6</sup>

**Kinetic and equilibrium measurements.** The pure substrates are predominantly in the enol form, stabilized by intramolecular hydrogen bonds. In water containing solutions the enol form is partly converted to keto form. The kinetics of the keto—enol conversions were determined in two ways: (a) the equilibration of a solution of substrate (usually  $6 \times 10^{-4}$  M) was followed spectrophotometrically (on a Beckman DB GT spectrophotometer) at 274 nm (*acac*) or 260 nm (*cc*), where the enols have maximum absorption; or (b) the enolization rate was determined by adding excess bromine to a solution of substrate (*acac* only) and following the decay of bromine spectrophotometrically at 410 nm.

Equilibrium constants were determined in several ways: (1) by extrapolation of kinetic plots to zero time. The optical density thus obtained was combined with the one measured at "infinite" time (equilibrium value); (2) by combination of rate constants from bromination and equilibration experiments; (3) by a titration procedure,<sup>7</sup> where added bromine reacts immediately with all enol present in an equilibrated solution, and the excess bromine is quenched rapidly with allyl alcohol.

### RESULTS AND DISCUSSION

The equilibration rates were strictly first order in substrate concentration. The measured  $k_{obs}$  is a sum of the first order enolization ( $k_e$ ) and ketonization ( $k_k$ ) rate constants, and from a knowledge of the equilibrium constant  $K_E = k_e/k_k$  the rate constants could be determined separately at each water concentration and temperature. Fig. 1 shows the measured dependence of  $K_E$  on the water concentration, and Fig. 2 the dependence of  $\log_{10} k_e$  and  $\log_{10} k_k$  on  $\log_{10} [H_2O]$ . The figures also include

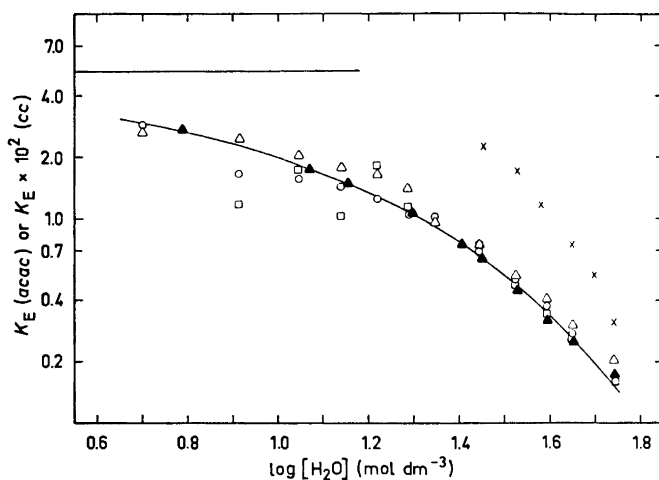


Fig. 1. Dependence of  $K_E$  on water concentration in the dioxan mixtures; 298.2 K. The horizontal line shows the value of  $K_E$  obtained for pure dioxan.<sup>8</sup>  $\Delta$  Titration (*acac*).  $\blacktriangle$  NMR (*acac*) Ref. 8.  $\circ$  Extrapolation (*acac*).  $\square$  Bromination (*acac*).  $\times$  Extrapolation (*cc*).

recent data by Watarai and Suzuki<sup>8</sup> for acetylacetone in water/dioxan mixtures. Reaction orders with respect to water are shown in Table 1, and Table 2 shows the formal activation and thermodynamic parameters determined from equilibration experiments in the temperature interval 15–45 °C.

Since  $K_E$  for *cc* is very small at the water concentration used (Fig. 1), it could not be obtained with the desired accuracy, but the ketonization activation parameters could be

estimated without large error by directly using  $k_{\text{obs}}$  values for  $k_k$ . For *acac* it is seen from Fig. 1 that the agreement between  $K_E$  values determined by different experimental techniques is good at high water concentrations but rather poor at lower concentrations. The values obtained by titration are in general too high, which is perhaps not surprising, since it is difficult to quench the excess bromine by allyl alcohol sufficiently rapidly. The  $K_E$  values determined by bromination experiments are consistent with the others at the higher water concentrations, even though the kinetic bromination curves are treated as pure first order plots. This has been shown by Bell and Crooks<sup>9</sup> not to be strictly correct, but analysis of the present data showed that the expected deviation is small.

We believe that the most accurate way of determining  $K_E$  is by NMR techniques as done by Watarai and Suzuki.<sup>8</sup> The solid curve in Fig. 1 is an exponential least squares fit using their results, and interpolated values from this curve have been used for separating our  $k_{\text{obs}}$  into  $k_e$  and  $k_k$ .  $K_E$  values for *acac* in pure water (15.0 %) and dioxan (84.0 %) were also taken from Ref. 8. These values are required in the extrapolation method mentioned earlier. For *cc* only pure dioxan stock solutions were used, and the value 76 % was applied for the equilibrium percentage in this solvent.<sup>9</sup>

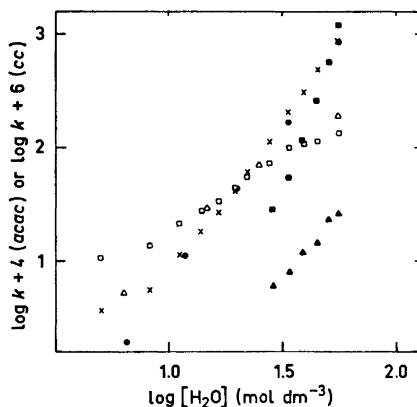


Fig. 2. Dependence of  $k_e$  and  $k_k$  on water concentration in dioxan mixtures; 298.2 K.  $\Delta$   $k_e$  (*acac*) Ref. 8.  $\bullet$   $k_k$  (*acac*) Ref. 8.  $\square$   $k_e$  (*acac*).  $\times$   $k_k$  (*acac*).  $\blacktriangle$   $k_e$  (*cc*).  $\blacksquare$   $k_k$  (*cc*).

Table 1. Reaction orders with respect to water. The numbers in parenthesis refer to the range of water concentration in mol dm<sup>-3</sup>.

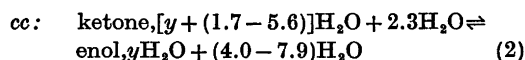
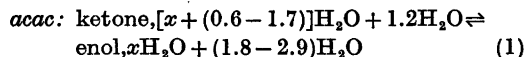
Compound	Acetylacetone		2-Carboethoxy-cyclohexanone This work
	Ref. 8	This work	
Enolization	2.3-0.7 (6.4-55.5)	1.2 (5.0-55.5)	2.3 (28.5-55.5)
Ketonization	1.7-3.2 (6.4-55.5)	1.8-2.9 (5.0-55.5)	4.0-7.9 (28.5-55.5)

Table 2. Activation and thermodynamic parameters. [H<sub>2</sub>O] in mol dm<sup>-3</sup>. ΔH‡ and ΔH in kJ mol<sup>-1</sup>, ΔS‡ and ΔS in J K<sup>-1</sup> mol<sup>-1</sup>.

Compound	Acetylacetone Ref. 8 <sup>a</sup>				This work				2-Carboethoxy-cyclohexanone This work		
	[H <sub>2</sub> O]	ΔH‡	ΔS‡	ΔH	ΔS	ΔH‡	ΔS‡	ΔH	ΔS	ΔH‡	ΔS‡
Enolization					41 ± 2	-143 ± 4	-8 ± 2	-42 ± 6			
	55.5										
Ketonisation					49 ± 2	-101 ± 4	8 ± 2	42 ± 6	53 ± 2	-123 ± 4	
Enolization	40.0	-168	-8.2	-23	42 ± 2	-149 ± 4	-6 ± 2	-21 ± 6			
	19.4										
Ketonization	48.2	-145	8.2	23	48 ± 2	-128 ± 4	6 ± 2	21 ± 6			<sup>b</sup>

<sup>a</sup> Water concentration 9.6 mol dm<sup>-3</sup>. <sup>b</sup> The reaction was extremely slow at this water concentration.

Our value,  $k_{\text{obs}} = 1.02 \times 10^{-1} \text{ s}^{-1}$  for *acac* in pure water at 25 °C is directly comparable and agrees well with that of Watarai and Suzuki, who found  $k_{\text{obs}} = 1.01 \times 10^{-1} \text{ s}^{-1}$ . Both values disagree with that estimated by Ahrens *et al.*<sup>11</sup> ( $k_{\text{obs}} = 2.5 \times 10^{-3} \text{ s}^{-1}$ ), who, however, used an indirect method. The data suggest that the reversible keto-enol conversions can be represented schematically as



where  $x$  and  $y$  are the hydration numbers for the enol forms of *acac* and *cc*, respectively.

Care must of course be exercised in coming to conclusions from rate data, for which the reaction medium is changed as much as in the present (and previous) investigation. However, both the reaction order with respect to water and the large negative activation entropies

strongly suggest that several water molecules form part of the activated complex, as also found previously for carbonyl hydration reactions. The difference in the number of water molecules entering the transition state in the two systems and the slightly (numerically) higher values of ΔS‡ for the ketonization of *cc* than for *acac* can be understood, if  $x$  is larger than  $y$ . This seems reasonable in view of the hydrophobic character of *cc* compared with *acac* and implies that the transition states for the two systems are more similar than suggested by the different reaction orders with respect to water. Previous investigations of the keto-enol conversion of *acac*<sup>8</sup> and of the hydration of 1,3-dichloroacetone<sup>5</sup> furthermore show that the reaction order with respect to water is very little dependent on the nature of the less polar medium component (dioxan or acetonitrile), whereas if alcohols are the second medium component, the reaction order is lower. This is probably due to a partial replacement of water by hydroxylic solvents in the activated complex

The large negative activation entropies for hydration and keto-enol reactions have been ascribed to the formation of a cyclic transition structure,<sup>4,8</sup> *i.e.* to the loss of translational entropy, when water enters the activated complex. In this complex protons are believed to migrate by a Grotthus-like mechanism. However, the relatively small difference in  $\Delta S^\ddagger$  for *acac* and *cc*, in spite of the difference in the number of water molecules entering, suggests that intramolecular reorganization entropy might also be of importance.

An estimate of this contribution can be made on the basis of recently developed theories of electron and proton transfer in polar media.<sup>12,13</sup> Since the characteristic proton frequency  $\Omega_p \gg kT/\hbar$  at room temperature, the proton movement in the transition complex is of sub-barrier nature, and all proton reorganization terms therefore appear in the pre-exponential factor of the reaction probability. Using 0.35 Å for the proton shift distance<sup>14</sup> and  $\Omega_p = 3.8 \times 10^{14} \text{ s}^{-1}$ <sup>15</sup> a value of  $-29 \text{ J K}^{-1}$  per proton is obtained for a harmonic potential, whereas  $-8 \text{ J K}^{-1} \text{ mol}^{-1}$  per proton is found, if a Morse potential is used for the proton bond. This suggests that proton reorganization in the water chain is of some importance, but the dominating contribution is the translational entropy.

The proton transfer was previously suggested to proceed by a stepwise mechanism,<sup>16</sup> forming a separate intermediate  $\text{H}_3\text{O}^+$ . This point can be further illustrated in the following way. For reactions of the kind investigated the solvent reorganization energy  $E_s$  is quite small, being of the order of  $50 \text{ kJ mol}^{-1}$ .<sup>17</sup> From the pK values of *acac* (=9.0) and *cc* (=11.0) the free energies of formation of  $\text{H}_3\text{O}^+$  in a step-wise mechanism are found to be  $60 \text{ kJ mol}^{-1}$  and  $75 \text{ kJ mol}^{-1}$ , respectively. Within the framework of the theories mentioned this gives  $60 \text{ kJ mol}^{-1}$  and  $75 \text{ kJ mol}^{-1}$  for the activation energies for *acac* and *cc*, respectively, corresponding to effectively "barrierless" reactions.<sup>12</sup> This agrees quite well with the experimentally observed  $\Delta H^\ddagger$  values (the intrinsic  $\Delta S^\ddagger$  was seen to be small). On the other hand, a concerted mechanism has an initial and a final state only and a free energy of reaction given by the keto-enol equilibrium constant. From the reported values of the latter (for pure dioxan) the calculated activation energies for

this mechanism would be approximately  $10 \text{ kJ mol}^{-1}$  and  $11 \text{ kJ mol}^{-1}$  for *acac* and *cc*, respectively, *i.e.* substantially less than observed experimentally. Since the theoretical energy of activation is only weakly dependent on the equilibrium constant,<sup>12,13</sup> the order of the values estimated would refer to a considerable range of water concentrations. The analysis of the rate data thus suggests that protons migrate in a transition complex chain or ring structure with several water molecules in such a way that the chain is "broken" in at least one link, forming a separate  $\text{H}_3\text{O}^+$  entity.

*Acknowledgement.* We thank Mrs. A. M. Kjær for technical assistance.

## REFERENCES

1. Eigen, M. *Discuss. Faraday Soc.* 39 (1965) 7.
2. Dahn, H. and Aubort, J.-D. *Helv. Chim. Acta* 51 (1968) 1348.
3. Bell, R. P. and Critchlow, J. E. *Proc. Roy. Soc. (London) Ser. A* 325 (1971) 35.
4. Bell, R. P. and Sørensen, P. E. *J. Chem. Soc. Perkin Trans. 2* (1972) 1740.
5. Bell, R. P., Millington, J. P. and Pink, J. M. *Proc. Roy. Soc. (London) Ser. A* 303 (1968) 1.
6. Bell, R. P. and Jensen, M. B. *Proc. Roy. Soc. (London) Ser. A* 261 (1961) 38.
7. Bell, R. P. and Lidwell, O. M. *Proc. Roy. Soc. (London) Ser. A* 176 (1940) 88.
8. Watarai, H. and Suzuki, N. *J. Inorg. Nucl. Chem.* 36 (1974) 1815.
9. Bell, R. P. and Crooks, J. E. *Proc. Roy. Soc. (London) Ser. A* 286 (1965) 285.
10. Dieckmann, W. *Ber. Deut. Chem. Ges.* 55 (1922) 2470.
11. Ahrens, M.-L., Eigen, M., Kruse, W. and Maass, G. *Ber. Bunsenges. Phys. Chem.* 74 (1970) 380.
12. Levich, V. G., Dogonadze, R. R. and Kuznetsov, A. M. *Elektrochim. Acta* 13 (1968) 1025.
13. Dogonadze, R. R., Ulstrup, J. and Khar-kats, Yu. I. *J. Chem. Soc. Faraday Trans. 2* 70 (1974) 64.
14. Conway, B. E. In Bockris, J. O. M. and Conway, B. E., Eds., *Modern Aspects of Electrochemistry*, Butterworths, London 1974, Vol. 3.
15. More O'Ferrall, R. A., Koepl, G. W. and Kresge, A. J. *J. Amer. Chem. Soc.* 93 (1971) 1.
16. Jaffe, M. R., Fay, D. P., Cefola, M. and Sutin, N. *J. Amer. Chem. Soc.* 93 (1971) 2878.
17. Kresge, A. J. *J. Chem. Soc. Rev.* 2 (1973) 475.
18. Pearson, R. G. and Dillon, R. L. *J. Amer. Chem. Soc.* 75 (1953) 2439.

Received March 20, 1975.