

## Quantitative Analysis of Solvent Effects on the Keto–Enol Equilibrium of Pentane-2,4-dione in Aqueous Solutions

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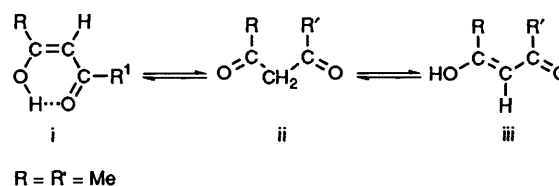
A quantitative analysis is described for solvent effects on homogeneous chemical equilibria in dilute aqueous solutions in terms of pairwise solute–solute interactions. Solvent effects of a series of monohydric alcohols on the keto–enol tautomeric equilibrium of pentane-2,4-dione (PD) have been measured in order to test the applicability of the new method. Observed medium effects could be successfully accounted for on the basis of contributions of methylene and hydroxy groups. In addition, the dependence of the equilibrium quotient on the concentration of PD has been analysed in terms of cosolvent effects.

Rate constants as well as equilibrium constants for chemical processes in dilute aqueous solutions often change significantly when organic cosolutes are added.<sup>1,2</sup> Chemical reactivity, involving organic substrates in aqueous media, is governed by non-covalent interactions between chemically inert cosolutes and both reactants and activated complex. Traditionally, important non-covalent interactions between relatively apolar organic species in dilute aqueous media have been assigned to hydrophobic forces. The molecular origin of these forces is a matter of considerable debate.<sup>3,4</sup> Recently, we developed a quantitative analysis of medium effects on organic reactions in aqueous media in terms of pairwise group interaction parameters.<sup>5–8</sup> Medium effects were attributed to 1:1 interactions of cosolutes with reactants and activated complex and were analysed by assuming additivity of group interactions based on ideas developed by Savage and Wood.<sup>9</sup> The theory was applied to medium effects on several hydrolysis reactions<sup>5–7,10–12</sup> as well as to bimolecular Diels–Alder reactions.<sup>13,14</sup> Satisfactory results were obtained in analysing medium effects of a large set of cosolute molecules, varying from alcohols,<sup>5,6,15</sup> amides,<sup>12</sup> sulfones,<sup>12</sup> sulfoxides<sup>12</sup> to carbohydrates.<sup>11</sup>

For many years, it has been recognised that equilibrium constants for homogeneous chemical equilibria in aqueous media also depend on the presence of organic cosolutes.<sup>16</sup> These medium effects have been analysed by a variety of methods, ranging from correlations with solvent-polarity scales and physical properties of the solvent to parameters derived from solubility data.<sup>16</sup> However, for relatively small solvent effects which are observed in dilute aqueous media, these methods are less appropriate. Here, we report a modification of our theoretical approach to solvent effects on reaction rate constants which is particularly suitable for a quantitative analysis of medium effects on organic equilibria in highly aqueous media. The theory has been tested by studying effects of monohydric alcohols on the keto–enol equilibrium of pentane-2,4-dione (PD) in aqueous solution.

Keto–enol equilibria are sensitive to the nature of the solvent.<sup>17–19</sup> In 1896, Claisen<sup>20</sup> commented that ‘there are compounds capable of existence in the form  $-\text{C}(\text{OH})=\text{CH}-\text{CO}-$  as well as in the form  $-\text{CO}-\text{CH}_2-\text{CO}-$ ; it depends on the nature of the substituents, the temperature and, for dissolved compounds, also on the nature of the solvent which of the two forms will be more stable’. Traditionally, solvent effects on tautomeric equilibria have been a rewarding topic for correlation analyses.<sup>16</sup> Keto–enol equilibria of 1,3-dicarbonyl

compounds, including  $\beta$ -dialdehydes,  $\beta$ -ketoaldehydes,  $\beta$ -diketones, and  $\beta$ -ketocarboxylic esters have attracted special interest because intramolecular hydrogen bonding was thought to increase the extent of enolisation of the compounds.<sup>21</sup> PD represents a prototype for the study of keto–enol equilibria of 1,3-dicarbonyl compounds. In general,  $\beta$ -diketones, both pure and in solution, exist as a mixture of three forms: (i) the *cis*-enolic form, (ii) the diketo form and (iii) the *trans*-enolic form. For PD these forms are shown in Scheme 1. The *trans*-enolic



Scheme 1

form is present for relatively few systems and therefore the keto–enol equilibrium constant  $K$  can be defined as in eqn. (1).

$$K = \frac{[\textit{cis}\text{-enol}]}{[\textit{keto}]} \quad (1)$$

Earlier studies showed that keto–enol ratios in the gas-phase approach ratios found in apolar, aprotic solvents.<sup>17</sup> Generally, the *cis*-enolic form is favoured by solvents of low polarity, whereas polar solvents displace the ratio towards the diketo form. More recently, Elmsley and coworkers<sup>22</sup> as well as Mills and Beak<sup>17</sup> have reported extensive studies of the keto–enol equilibrium of 1,3-diketones. Elmsley<sup>22</sup> showed that keto–enol equilibrium constants can be roughly correlated with the polarity of the solvent. A good correlation was found for a polarity scale advocated by Swain, which expresses the basicity  $B$  and the acidity  $A$  of the solvent. Correlations with  $E_T(30)$ , dielectric constant  $\epsilon$  and the Kamlet–Taft  $\pi^*$  were satisfactory as well and Mills and Beak<sup>17</sup> advocated the use of a multiparameter analysis, using the Kamlet–Taft approach.

Here, we show that added monohydric alcohols shift the keto–enol equilibrium in dilute aqueous media in favour of the enol form, an observation which is analysed in terms of interactions of apolar methylene moieties as well as the polar hydroxy group with the keto and *cis*-enol forms.

## Experimental

**Materials.**—Deminerilised water was distilled twice in an all-quartz distillation unit. The alcohols were used as supplied and were of highest purity available. Pentane-2,4-dione was freshly distilled from P<sub>2</sub>O<sub>5</sub> before use.

**Methods.**—The equilibrium quotient for the keto–enol equilibrium of pentane-2,4-dione (PD) was determined by <sup>1</sup>H NMR [Varian VXR-300 (300 MHz) instrument] at 25 °C. The concentration of PD was 5 × 10<sup>-3</sup> mol kg<sup>-1</sup>. The NMR tube was equipped with an external standard. In all cases non-deuteriated solvents and cosolvents were used. The equilibrium quotients were determined after allowing the equilibrium to establish during at least 4 h at 25 °C. The equilibrium quotient was determined by integrating the signals at 2.97 (diketo) and at 1.77 ppm (enol). The integration was performed after 250 pulses. The water signal did not give dynamic range problems. Each measurement was repeated several times, and the equilibrium quotients were reproducible to within 2%. The method was checked by determination of the equilibrium quotient of PD as a function of concentration and extrapolation to infinite dilution. The determined equilibrium quotients reproduced the value, obtained at high dilution, to within 3%.

## Results and Discussion

Schematically, chemical equilibria can be presented as keto(i) ⇌ enol(j), the standard Gibbs energy associated with the equilibrium being given by eqn. (2). Here, *m<sub>i</sub>* and *m<sub>j</sub>* are the

$$\Delta G^\circ = \mu_j^\circ - \mu_i^\circ = -RT \ln \left[ \frac{m_j \gamma_j}{m_i \gamma_i} \right] \quad (2)$$

molalities of, respectively, the keto and enol form. The corresponding activity coefficient are given by  $\gamma_i$  and  $\gamma_j$ . In the absence of added cosolutes and in an ideal reaction medium where compounds *i* and *j* are only present in trace amounts,  $\gamma_i = \gamma_j = 1$ . Addition of cosolutes *C* affects the activity coefficient of the compounds *i* and *j*. The standard equilibrium constant *K*<sup>°</sup> is not affected by the presence of the cosolute *C*. However, since  $\gamma_i$  and  $\gamma_j$  depend on *m<sub>c</sub>*, the equilibrium quotient *Q*, which is defined as *m<sub>j</sub>/m<sub>i</sub>*, does depend on *m<sub>c</sub>*. Hence, *Q*(*m<sub>c</sub>*) is related to *Q*(*m<sub>c</sub>* = 0; id) by eqn. (3). The

$$\ln \left[ \frac{Q(m_c)}{Q(m_c = 0; \text{id})} \right] = \ln \gamma_i - \ln \gamma_j \quad (3)$$

natural logarithm of the activity coefficient for solute *i* reflects the non-ideal behavior of the solution and can be expressed as a derivative of the excess Gibbs energy of the total reaction medium<sup>6,7</sup> [eqn. (4)]. Cassel and Wood<sup>23</sup> described how the

$$\ln \gamma_i = \frac{1}{RT} \times \frac{dG^E(\text{sln})}{dm_i} \quad (4)$$

excess Gibbs energy of a reaction mixture can be formulated for a solution containing not only the compounds that are in equilibrium but also the added alcohols. Hence, the excess Gibbs energy of the total reaction system in 1 kg of solvent, water can be given by eqn. (5); where *k*, *l* and *m* symbolise the

$$G^E(\text{sln}) = \sum_{k,l} g_{N_k, N_l} \frac{m_k m_l}{m_0^2} + \sum_{k,l,m} g_{N_k, N_l, N_m} \frac{m_k m_l m_m}{m_0^3} + \dots \quad (5)$$

solutes present in the reaction mixture. The terms  $g_{N(k), N(l)}$  and  $g_{N(k), N(l), N(m)}$  represent, respectively, the pairwise and triplet

interaction parameters involving the solute molecules including all possible cross terms. In dilute solutions in which the keto and enol form are present in trace amounts, the contributions of their mutual interactions to the overall excess Gibbs energy can be neglected. Thus, only pairwise and higher order interactions involving cosolute molecules have to be taken into account. When also the cosolutes are present in moderate concentration (*i.e.* < 1 mol dm<sup>-3</sup>), the medium effects can be accounted for on the basis of pairwise interaction terms. Under these conditions, the eqns. (6) and (7) are obtained for ln  $\gamma_i$  and

$$\ln \gamma_i = 2 \left[ \frac{1}{RT m_0^2} \right] g_{iC} m_C \quad (6)$$

$$\ln \gamma_j = 2 \left[ \frac{1}{RT m_0^2} \right] g_{jC} m_C \quad (7)$$

ln  $\gamma_j$ . Now, using eqn. (3), we find eqn. (8). Pairwise solute–

$$\ln \left[ \frac{Q(m_c)}{Q(m_c = 0; \text{id})} \right] = \frac{2}{RT m_0^2} [g_{iC} - g_{jC}] m_C \quad (8)$$

solute interaction parameters are determined by the nature of the solvent, but also by the nature of the solute. Solute–solute interactions reflect interactions between the functional groups which form the solute molecule and are able to interact with their surroundings. In 1976, Savage and Wood<sup>9</sup> introduced a concept of additivity of group interaction parameters based on empirical equations. This Savage–Wood Additivity of Groups (SWAG) model is based on the assumptions that each functional group *X* of solute *i* interacts with each group *Y* of cosolute *C* with a group-characteristic contribution independent of all other functional groups or relative positions and stereochemistry in solute *i* and cosolute *C*. The assumptions lead to an expression for the pairwise Gibbs energy interaction parameters in terms of specific group interactions [eqn. (9)]. A

$$g_{iC} = \sum_X \sum_Y n_X^i n_Y^C G_{XY} \quad (9)$$

similar equation describes the interaction between solute *j* and added solute *C*. Thus, the interaction term between brackets in eqn. (8) can be evaluated, using eqn. (9), in terms of pairwise group interaction parameters. An incremental analysis of solvent effects of a series of structurally related cosolvents, such as methanol, ethanol and propanol then yields the distinct contributions of methylene groups and hydroxy groups to the overall solvent effect.

We have determined the keto–enol equilibrium quotient of PD by <sup>1</sup>H NMR in non-deuteriated solvents, using an external standard. Following the initial work of Reeves,<sup>24</sup> <sup>1</sup>H NMR analysis has been the preferred method for the evaluation of equilibrium constants for keto–enol equilibria.<sup>25</sup> The equilibrium quotient for the keto–enol equilibrium of PD in aqueous solutions, defined as [cis-enol]/[keto], was determined at a molality of PD of 5 × 10<sup>-3</sup> mol kg<sup>-1</sup>. This solution can be considered as thermodynamically ideal and the equilibrium quotient, determined in this dilute aqueous solution, can be considered as the equilibrium *Q*(*m<sub>c</sub>* = 0; ideal). At 25 °C, the measured equilibrium constant was 0.193 ± 0.008 [literature data: 0.148 (ref. 22), 0.19 (ref. 26) and 0.23 (ref. 17)]. When the molality of PD is significant, homotactic interactions of PD cannot be neglected and PD itself will seriously affect the equilibrium quotient. Indeed, a major problem in the determination of keto–enol equilibrium constants is the fact that the *Q* depends on the concentration of the β-diketone.<sup>17,22,27</sup> The dependence of the equilibrium quotient on the mole fraction of

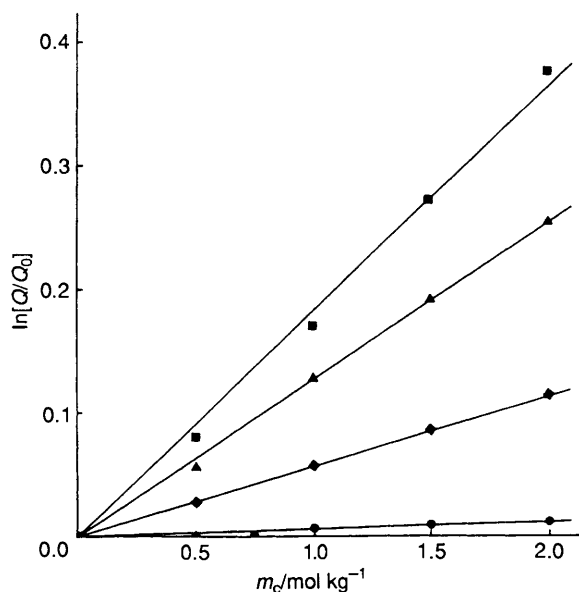


Fig. 1 Keto⇌Enol equilibrium of pentane-2,4-dione in aqueous solutions at 25 °C. Dependence of  $\ln[Q(m_c)/Q(m_c = 0)]$  on the molality of methanol, ●; ethanol, ◆; propan-1-ol, ▲ and 2-methylpropan-2-ol, ■.

Table 1 Solvent effects on the equilibrium quotient ( $[cis-enol]/[keto]$ ) of the keto-enol equilibrium of pentane-2,4-dione in mixed aqueous solutions at 25 °C

Cosolvent	$G(C)^a/J \text{ kg mol}^{-2}$	$G(C)^b/J \text{ kg mol}^{-2}$
Methanol	8 (4)	3 (16)
Ethanol	69 (8)	77 (20)
Propan-1-ol	156 (6)	151 (23)
2-Methylpropan-2-ol	228 (14)	225 (26)

<sup>a</sup> Derived from experimental data. <sup>b</sup> Calculated, assuming  $G(\text{CH}) = 37$  and  $G(\text{OH}) = -108 \text{ J kg mol}^{-2}$ .

PD appeared to be sensitive to the solvent, both in magnitude as well as in sign.<sup>22</sup> Particularly in water, the dependence on the mole fraction of PD is dramatic which accounts for the fact that reported equilibrium constants for the keto-enol equilibrium of PD in water show a larger scatter. Therefore, the equilibrium constants should be determined by extrapolation to infinite dilution.

In Fig. 1, the solvent effects of the monohydric alcohols on the equilibrium quotient of PD, expressed as  $\ln[Q(m_c)/Q(m_c = 0)]$ , are plotted as a function of the molality of the cosolvents. All plots show satisfactory linearity. The solvent effects are modest, and addition of apolar cosolvents favours the enol. For convenience,  $[g_{ic} - g_{jc}]/m_0^2$ , appearing in eqn. (8), is defined as  $G(C)$  and represents the solvent effect of cosolvent C. In Table 1, values for  $G(C)$  are given. Subsequently, by incremental analysis, the solvent effect of groups X can be determined and expressed as  $G(X)$ . Excellent additivity is observed for the methylene moieties. The analysis provides  $G(\text{CH}) = 37$  and  $G(\text{OH}) = -108 \text{ J kg mol}^{-2}$ . Hydrophobic contributions of methylene moieties clearly predominate the overall medium effects which are counteracted by the polar contribution of the hydroxy group.

Elmsley *et al.*<sup>22</sup> reported the dependence of the percentage of enol in water on the mole fraction of the carbonyl compound. In the literature, the dependence of the equilibrium quotient on the concentration of tautomers has frequently been interpreted in terms of association or stacking of the tautomers. The sol-

vent effect of PD on its tautomeric equilibrium can be expressed in terms of eqn. (8) as well, plotting  $\ln[Q(m_{\text{PD}})/Q(m_{\text{PD}} = 0)]$  versus the molality of PD. Using the data reported by Elmsley,  $G(C)$  was estimated to be  $315 \text{ J kg mol}^{-2}$ , which appears reasonable in view of the solvent effects of the monohydric alcohols.

Apparently, pairwise interactions of *cis*-enol with the monohydric alcohols as well as with the tautomers of PD itself are more favourable than those of the diketone, indicating that the *cis*-enol is the more hydrophobic isomer. Previously, direct hydrogen-bonding between the enol and the solvent has been suggested to compete with the intramolecular hydrogen-bonding in the *cis*-enolic form. Recently, however, it was shown that the intramolecular hydrogen-bonding of the enolic form remains intact in both aprotic and protic solvents.<sup>22</sup> There appears to be no convincing evidence that solvents favour either side of the equilibrium by hydrogen-bonding more strongly with either the enol or keto tautomer. Consequently, solvent effects can be rationalised by the fact that the diketone form is usually more dipolar than the *cis*-enolic form. This conclusion might seem somewhat surprising, but intramolecular hydrogen-bonding helps to reduce the dipole-dipole repulsion of the carbonyl groups, which is quite unfavourable in the diketone form.

Solvent effects on keto-enol equilibria have traditionally been analysed in terms of macroscopic properties of the solvent, such as dielectric constant or specific polarity scales. Here, we have shown that a quantitative approach in terms of pairwise group interactions does more justice to the importance of specific intermolecular interactions governing homogeneous chemical equilibria in aqueous media.

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