Tetrahedron Letters,Vol.28,No.17,pp 1889-1892,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# THERMODYNAMICS OF THE ISODESMIC ENOL-TO-METHYL ENOL ETHER EQUILIBRIUM IN WATER

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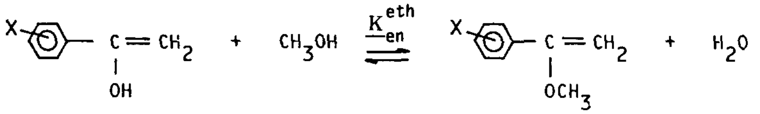
Abstract: $\Delta G°$ values for the isodesmic equilibrium between substituted acetophenone enols and the corresponding methyl enol ethers are calculated from previously reported data on equilibrium constants for keto-enol tautomerism and for enol ether formation from ketones. These values agree with those expected from literature data on analogous alcohol--ether isodesmic systems.

The determination of Gibbs free energy increments for isodesmic (real or hypothetical) alcohol-ether reactions (eq 1) has been of great help in the calculation of Gibbs free energies of unstable chemical species,

$$R^2\text{—}C(R^1)(R^3)\text{—}OH + CH_3OH \overset{\Delta G°}{\rightleftharpoons} R^2\text{—}C(R^1)(R^3)\text{—}OCH_3 + H_2O \qquad (1)$$

such as carboxylic or phosphoric esters or acid hydrates, from those of the corresponding orthoesters.[1] Such a procedure, which was also suggested by Guthrie and Cullimore[2] for evaluating keto-enol equilibrium constants when no other reliable methods were available, is based on the property that $\Delta G°$ is always close to zero and depends only slightly on polar and steric effects. Recent data on keto-enol[3,4] and ketone-to-methyl enol ether[5] equilibrium constants in water make it now possible to calculate $\Delta G°$ values for the enol-enol ether isodesmic equilibrium (eq 2), to test the coherence of the two sets of data,



(2)

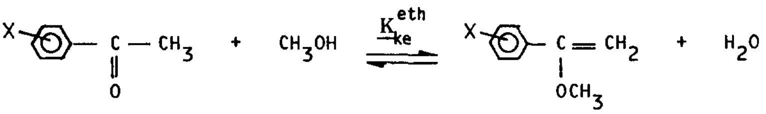
and to examine whether the previously derived equations expressing $\Delta G°$ variations in terms of polar effects or alcohol $pK'_a$s are also valid for enols.

The problem of determining stability constants for unstable enols has been solved by Kresge et al.[3] and by ourselves.[4,6] Taking advantage of the property that enol halogenation is diffusion-controlled, we deduced the keto-enol equilibrium constants from second-order rate constants observed for acid-catalyzed ketone halogenation at very low halogen concentration,[6] assuming a rate constant of 5 x $10^9$ $dm^3$ $mol^{-1}$ $s^{-1}$ for the addition process. More recently, Kresge et al. deduced more accurate absolute values by forming enols in a Norrish II type reaction, measuring enol ketonization rate constants, and combining these data with enolization rate constants.[3] Finally, following a calculation of the true diffusion-controlled rate constant (2.9 x $10^9$ $dm^3$ $mol^{-1}$ $s^{-1}$) by combining our data with those obtained by Kresge, we deduced keto-enol equilibrium constants for aliphatic ketones, cycloalkanones, and acetophenones,[4] from the previously published data.

Table I, keto-enol equilibrium constants, $K^{en}_{ke}$ (eq 3), are compared with equilibrium data for the


(3)

ketone-to-methyl enol ether process, $K^{eth}_{ke}$ (eq 4). These latter constants were obtained indirectly[5] by a combination of (i) ketone-acetal equilibrium constants in methanol, (ii) rate constants for lyonium ion-catalyzed enol ether formation from acetal in methanol, (iii) rate constants for methanol addition to enol ethers.


(4)

and (iv) Gibbs free energies of transfer of ketones and methyl ethers from methanol to water. Table I also lists the equilibrium constants for eq 2, calculated by eq 5, as well as the corresponding $\Delta G°$'s. It is noteworthy that these latter data are, as expected, close to zero.

$$K^{eth}_{en} = K^{eth}_{ke}/K^{en}_{ke} \qquad (5)$$

From data for various alcohol-methyl ether isodesmic systems, Guthrie[1,7] showed that $\Delta G°$, corrected for symmetry and steric effects, depends slightly on polar effects and can be expressed by either eq 6 or

$$(\Delta G°)_{corr} = (-0.65 \pm 0.12) + (0.48 \pm 0.04)\Sigma \sigma^*_{R_i} \qquad (6)$$

$$(\Delta G°)_{corr} = (4.78 \pm 0.28) - (0.336 \pm 0.024)pK_a \qquad (7)$$

eq 7. In these equations, which are equivalent because of the observed relationship between $pK_a$ and $\sigma^*_R$ for alcohols,[8] $\Sigma\sigma_{R_i}$ is the sum of Taft's parameters of the groups attached to the $\alpha$ carbon atom, and $pK_a$ is the acidity constant of alcohol in water.

Since it only applies to alcohols where OH is borne by a $sp^3$ carbon atom, eq 6 cannot be used to calculate $\Delta G°$ for eq 2. Therefore, we plotted the corrected literature[9] values of $\Delta G°$ against the $\sigma_I$ value of Z in hydroxy-compounds Z-OH, including alcohols but also other hydroxy-compounds, such as carboxylic acids and phenol, which exhibit similar thermodynamic behavior for isodesmic equilibria. Even though Fig.1 shows some scatter, $\Delta G°$ increases significantly with $\sigma_I$. From a least-squares treatment we obtained eq 8, which is equivalent to eq 6, but which makes it possible to calculate $\Delta G°$, provided that $\sigma_I$ for the $CH_2{=}C(Ar)$ groups are known.

$$(\Delta G°)_{corr} = -(0.08 \pm 0.12) + (4.07 \pm 0.90)\sigma_{I,Z} \qquad (8)$$

When the symmetry factor (RT Ln 2) is allowed for,[1,7] an estimation of $\sigma_{I,CH_2=C(Ph)}$ as 0.14[11] makes it possible to calculate $\Delta G°$ as 0.90 ± 0.25 kcal $mol^{-1}$, a result which is only 0.5-0.6 kcal $mol^{-1}$ larger than the experimental data. The difference, which corresponds to a factor of ca. 2 on the $K^{eth}_{en}$ value, is acceptable in view of the large uncertainty on $\Delta G°$ calculations[12] and of the indirect way of determining $K^{eth}_{en}$ in water. We conclude that there is satisfactory agreement between experimental and calculated data, and that eq 8 also accounts for the enol-enol ether equilibria.

Table I.- Calculated Constants and Standard Gibbs Energy Increments for the Isodesmic Equilibria between Substituted Acetophenone Enols and Acetophenone Enol Methyl Ethers in Water (25°C).

| X [a] | $10^8\underline{K}_{ke}^{en}$ [b] | $10^8\underline{K}_{ke}^{eth}$ ($dm^3\ mol^{-1}$) [c] | $\underline{K}_{en}^{eth}$ ($dm^3\ mol^{-1}$) [d] | $\Delta\underline{G}°$ ($kcal\ mol^{-1}$) [e] |
|---|---|---|---|---|
| 4-$OCH_3$ | 0.23 [f] | 0.15 | 0.65 | 0.25 |
| 4-$CH_3$ | 0.58 [f] | 0.29 | 0.50 | 0.41 |
| H | 1.20 [f] | 0.68 [g] | 0.57 | 0.33 |
|  | 1.08 [h] |  | 0.62 | 0.28 |
| 4-Cl | 1.66 [f] | 0.89 | 0.54 | 0.37 |
| 3-Cl | 2.70 [f] | 1.4 | 0.52 | 0.39 |
| 3-$NO_2$ | 7.4 [f] | 1.97 | 0.27 | 0.78 |

[a] X in $XC_6H_4COCH_2$, $XC_6H_4C(OH)=CH_2$ or $XC_6H_4C(OMe)=CH_2$. [b] $\underline{K}_{ke}^{eth}$ = [enol]/[ketone] . [c] From ref. 5; $\underline{K}_{ke}^{eth}$ = [enol ether]$\underline{a}_w$ / [ketone][MeOH] with $\underline{a}_w$ = 1. [d] $\underline{K}_{en}^{eth}$ = [enol ether] $\underline{a}_w$/ [enol][MeOH] with $\underline{a}_w$ = 1. [e] The standard state for solutes is an ideal 1 mol $dm^{-3}$ solution with an infinitely dilute reference state; the standard state for solvent is the pure liquid. [f] From ref. 4. [g] This value is in agreement with that derived in ref. 2 from thermodynamic considerations. [h] From ref. 3c.

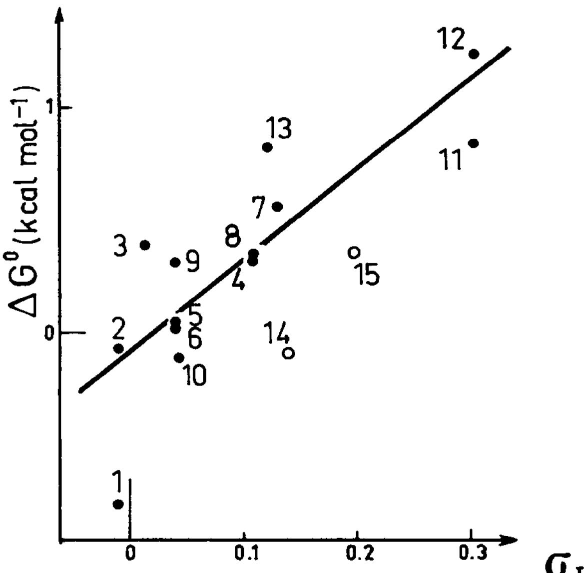


**Fig. 1**: Plot of $(\Delta\underline{G}°)_{corr}$ vs. $\sigma_{I,Z}$ for isodesmic ZOH/ZOMe equilibria. Z = Me (1), Et (2), i-Pr (3), $HOCH_2$ (4), MeCH(OH) (5), EtCH(OH) (6), (4-Pyr)CH(OH) (7), $MeOCH_2$ (8), $CH_3CH(OMe)$ (9), n-PrCH(OMe) (10), HCO (11), MeCO (12), Ph (13) (closed circles; from ref. 8); Z = $CH_2=C(Ph)$ (14), $CH_2=C(4-NO_2Ph)$ (15) (open circles; this work). $\sigma_{I,R}$ values are from ref. 10 or estimated by the equation: $\sigma_{I,R^1R^2CH}$ = 0.297 $\Sigma$ $\sigma_{I,R}$ + 0.005 (see ref. 10).

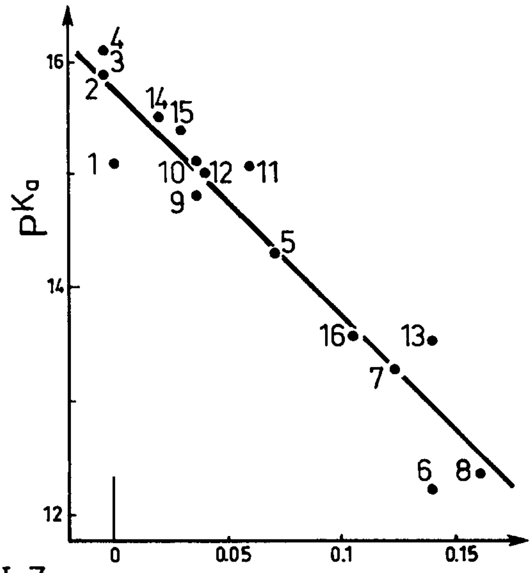


**Fig. 2**: Plot of $\underline{pK}_a$ vs $\sigma_{I,Z}$ for alcohols ZOH. Z = Me (1), Et (2), n-Pr (3), n-Bu (4), $ClCH_2CH_2$ (5), $Cl_3C-CH_2$ (6), $F_2CHCH_2$ (7), $CF_3CH_2$ (8), $MeOCH_2CH_2$ (9), $EtOCH_2CH_2$ (10), $HOCH_2CH_2$ (11), $PhOCH_2CH_2$ (12), $HC\equiv CCH_2$ (13), $CH_2=CHCH_2$ (14), $PhCH_2$ (15) (from ref. 8); Z = $HOCH_2$ (16) (data from R.P. Bell and P. Onwood, Trans.Faraday Soc. 1962, **58**, 1557). $\sigma_{I,Z}$ values are from ref. 10 or estimated by the equation: $\sigma_{I,RCH_2}$ = 0.416 $\sigma_{I,R}$ - 0.010 (see ref. 10).

Eq 7 was used by Guthrie and Cullimore[2] to calculate $\Delta G°$ values for enols from estimated $pK_a$'s. This procedure is not strictly valid because this equation was established for hydroxy compounds whose $pK_a$'s depend on polar effects only. In the case of enols it might be expected that $pK_a$ also depends on conjugative effects on enolate stability. This resonance contribution can be calculated by considering the relationship which can be derived by plotting $pK_a$ vs. $\sigma_{I,Z}$ for a variety of alcohols ZOH (Fig. 2), and the $\sigma_I$ value estimated for the $CH_2=C(Ph)$ group. The calculated $pK_a$ value for acetophenone enol, $pK_a = 13.0$, corresponds to a free-from-resonance $pK_a$ , and the difference from the experimental result (10.34)[8], to the stabilisation of the enolate by conjugation. It is noteworthy that the value obtained for $\Delta G°$ ($0.82 \pm 0.59$ kcal mol$^{-1}$) for acetophenone enol, when eq 7 is applied with $pK_a = 13.0$, is very close to that calculated from eq 8.

$K_{en}^{eth}$ values in Table I are not very substituent dependent, and, because of the uncertainty on experimental data, it is difficult to find any significant relationship with substituent parameters. However. it is interesting in this context that $K_{ke}^{en}$ and $K_{ke}^{eth}$ both follow $\sigma^+$ with $\rho$ values of $1.02 \pm 0.08$ and $0.79 \pm 0.13$, respectively,[5,6a] which account for predominant polar and conjugative effects on the initial carbonyl compound; these relationships imply that $K_{en}^{eth}$ will decrease when an electron-withdrawing substituent is introduced and that $\rho = -0.2 \pm 0.2$. Such a decrease in $K_{en}^{eth}$ is in agreement with eq 8, which indicates that $\Delta G°$ should increase with the $\sigma_I$ parameter of the $CH_2=C(Ar)$ group. However, the small variations of $K_{en}^{eth}$ show that the differences in the polar effects of PhX do not cause large variations of $\sigma_I$. Quantitatively, if one assumes eq 9 (where 6.23 is the usual factor between $\sigma_X^n$ [13] and $\sigma_{I,PhX}$[14] and $\tau$, the transmission coefficient of polar effects through the $sp^2$ carbon atom), a $\rho$ value of $-0.2$ corresponds to $\tau = 0.5$.

$$\sigma_{I,CH_2=C(Ar)} - \sigma_{I,CH_2=C(Ph)} = \tau(\sigma_{I,Ar} - \sigma_{I,Ph}) = \tau(\sigma^n/6.23) \qquad (9)$$

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12. Since the figures after the ± sign in eqs 6-8 are standard deviations, the uncertainty limits in $\Delta G°$ calculations are 2 or 3 times those indicated.
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(Received in France 6 March 1987)