Tetrahedron Vol. 44, No. 10, pp. 2997 to 3004, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00
Pergamon Press plc

SUBSTITUENT EFFECTS IN KETO-ENOL TAUTOMERISM. PART 3.[1] INFLUENCE OF SUBSTITUTION ON THE EQUILIBRIUM COMPOSITION OF β-DICARBONYL COMPOUNDS.

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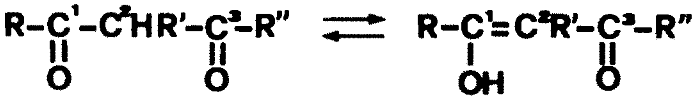
(*Received in UK* 25 *March* 1988)

ABSTRACT: The enol content and equilibrium free energies for the keto-enol tautomerism have been determined for a series of 1,3-diketones, at 40 °C, in deuterochloroform and dimethylsulfoxide-d_6 (DMSO), by ^1H n.m.r.. Compounds containing methyl, phenyl, t-butyl, 2-thienyl, trifluoromethyl and ethoxy groups have been examined. The equilibrium free energies in DMSO are characterized by a linear additivity effect, and substituent parameters, representing the variation produced by the substituent, have been calculated. Equilibrium enthalpy and entropy have been obtained in the range of temperature 20-60 °C. A correlation between enolic $^1J_{-CH=}$ coupling constants and equilibrium free energies in DMSO is discussed in terms of substituent effects on the energy of the enol.

The tautomeric equilibrium of simple enols[2] as well as of β-diketones[3] has been the subject of continuos interest in chemistry. In the latter system, the position of the keto-enol equilibrium is affected by the presence of substituent groups at the three carbon atoms of the diketone frame (Equation 1).



$$\underset{\displaystyle O}{\underset{\|}{R-C^1}}-C^2HR'-\underset{\displaystyle O}{\underset{\|}{C^3}}-R'' \rightleftharpoons \underset{\displaystyle OH}{\underset{|}{R-C^1}}=C^2R'-\underset{\displaystyle O}{\underset{\|}{C^3}}-R'' \qquad (1)$$

Interpretation of substituent effects is complicated by the fact that the influence on the stability of each of the two tautomers cannot be established unambiguously.[4]

It is known that electron withdrawing groups increase the content of the enol form.[5] Alkyl groups produce a decrease of enol percent when attached to the central carbon atom[5] and an increase when bonded to the 1 and 3 positions.[6a] However, only scattered data are available on the effect of β-substituents on the tautomeric equilibrium,[5,6] and the phenomenon is not well understood, whereas solvent effects have been investigated in detail.[7]

We report a systematic investigation on the equilibrium composition for a series of β-diketones. carried out by ^1H n.m.r. in $CDCl_3$ and DMSO-d_6 solutions. The results are reported in Table 1.

Table 1

Data for the Tautomeric Equilibrium of β-Diketones, R-COCHR'CO-R", at 40 °C.[a]

	Compound	Substituent			$CDCl_3$		DMSO	
		R	R'	R"	% enol[b]	$-\Delta G^o$ (kcal/mol)	%enol[b]	$-\Delta G^o$ (kcal/mol)
1	2,4-Pentanedione	CH_3	H	CH_3	83.5	1.01	55.7	0.14
2	3-Methyl-2,4-pentanedione	CH_3	CH_3	CH_3	40.0	-0.25	21.5	-0.80
3	1-Phenyl-1,3-butanedione	Ph	H	CH_3	91.0	1.44	77.1	0.76
4	1,3-Diphenyl-1,3-propanedione	Ph	H	Ph	95.8	1.94	91.5	1.48
5	5,5-Dimethyl-2,4-hexanedione	Bu^t	H	CH_3	88.5	1.27	68.2	0.47
6	2,2,6,6-Tetramethyl-3,5-heptanedione	Bu^t	H	Bu^t	92.0	1.52	77.2	0.75
7	1-(2-Thienyl)-1,3-butanedione	Thi[c]	H	CH_3	82.0	0.94	61.0	0.28
8	1,3-bis(2-Thienyl)-1,3-propanedione	Thi	H	Thi	81.5	0.92	68.0	0.47
9	1,1,1-Trifluoro-2,4-pentanedione	CF_3	H	CH_3	>99.5	>3.3	88.1	1.24
10	1,1,1,5,5,5-Hexafluoro-2,4-pentanedione	CF_3	H	CF_3	>99.5	>3.3	97.0	2.16
11	1,1,1-Trifluoro-5,5-dimethyl-2,4-hexanedione	CF_3	H	Bu^t	>99.5	>3.3	92.2	1.54
12	Ethyl 3-oxobutanoate	CH_3	H	OEt	8.0	-1.52	4.0	-1.98

a) Keto $\rightleftharpoons$ Enol

b) ±1%

c) Thi = 2-thienyl

Among the β-diketones, each replacement of the methyl groups of 2,4-pentanedione increases the enol percent, which varies between 83.5% (1) and 100% for the trifluoromethyl derivatives (9, 10 and 11) in $CDCl_3$. The enol percent is lowered in DMSO solution for all compounds. In fact, the higher polarity of DMSO shifts the equilibrium toward the keto form[7a] and the enol content varies in a larger range, between 56% for (1) and 97% for the hexafluoroderivative (8). Therefore, measurement of enol percent and evaluation of substituent effects are facilitated in this solvent.

Despite the different electronic characteristics of trifluoromethyl, phenyl, thienyl and t-butyl groups, the enol percent in the corresponding β-diketone derivatives is always higher than that in 2,4-pentanedione. The only exception is represented by the two 2-thienyl derivatives (7 and 8), the enol content of which, in $CDCl_3$, is similar to that of 2,4-pentanedione (1). Alkyl substitution at the central carbon atom causes a drop of the enol content, in agreement with the previous findings (entry 2).[4,7a] The presence of the ester functionality also decreases drastically the enol percent (12). The trifluoromethyl derivatives (9, 10, 11) in $CDCl_3$ show only the peaks due to the enol form, whereas, in DMSO, the peak from the keto $-CH_2-$ group is clearly observed (see Experimental).

The results show the additive character of substituent effects on the tautomeric equilibrium. The influence of a group on the equilibrium free energy of the monosubstituted derivative, with respect to 2,4-pentanedione, is reproduced by the same extent, within the experimental error, in the disubstituted compound. For instance, the equilibrium free energy in DMSO varies from -0.14 kcal/mol for 2,4-pentanedione, (1), to -0.76 kcal/mol for 1-phenyl-1,3-butanedione, (3), and to -1.48 kcal/mol for 1,3-diphenyl-1,3-propanedione, (4). Substitution of methyl by phenyl group produces a change of 0.62 kcal/mol in the first case and of 0.72 kcal/mol in the second one. A similar additive character of substituent effects was observed by Shapet'ko for ^1H and ^{13}C n.m.r. chemical shifts of the α and β carbon atoms in the enol form of β-diketones.[8] An analogous additive effect has been found by us for the corresponding keto tautomers.[1] A linear equation was used to represent the variation produced by the β-substituents and to calculate chemical shift values. In a similar fashion, substituent parameters, calculated from the equilibrium measurements, can represent the increment apportioned to each of the β-substituents in terms of equilibrium free energy in DMSO, according to equation 2:

$$\Delta G^o = -0.14 + \Delta(X) + \Delta(Y) \qquad (2)$$

where -0.14 is the ΔG^o value for 2,4-pentanedione and $\Delta(X)$ and $\Delta(Y)$ are the substituent factors attributable to group X and Y, respectively. The average Δ values are -0.67 kcal/mol for R = phenyl, -0.30 kcal/mol for R = t-butyl, -1.0 kcal/mol for R = CF_3, and -0.16 kcal/mol for R = 2-thienyl. Thus, ΔG^o calculated for $CF_3COCH_2COC(CH_3)_3$ is -1.44 kcal/mol which compares very well with the experimental value of -1.54 kcal/mol.

A similar treatment can be extended to the data from the $CDCl_3$ solutions and the substituent parameters obtained are -0.46 kcal/mol for R = phenyl and -0.25 kcal/mol for

R = t-butyl. The 2-thienyl derivatives have about the same enol content of 2,4-pentanedione and the trifluoromethyl derivatives are about 100% enol.

It is quite remarkable that a linear additivity observed for physical parameters, such as chemical shifts of single species, applies in the case of a chemical phenomenon involving two equilibrating species.

The spectra were recorded at different temperatures in the case of 2,4-pentanedione (1), the two phenyl (3 and 4) and the two t-butyl (5 and 6) derivatives, between 20 and 60 °C. The actual variation of composition with temperature[9] and the thermodynamic parameters for enolization, keto $\rightleftharpoons$ enol, are listed in Table 2. The results are consistent with data available in the literature.[3,10,7b] The enol is energetically more stable than the keto form, by ca. 2 kcal/mol for most compounds. The negative values of the equilibrium entropy are in agreement with the more rigid structure of the enol, as expected for the presence of an intramolecular hydrogen bond.[11] Although only five compounds, and therefore two substituents, have been examined, the thermodynamic parameters do not seem to vary in a predictable way.

Table 2

Variations of Enol Content with Temperature and Thermodinamic Parameters for the Equilibrium Keto $\rightleftharpoons$ Enol, in DMSO.

Compounds			Enol Percent[a]			ΔH^o	ΔS^o
	R	R''	21 °C	40 °C	60 °C	(kcal/mol)	(eu)
(1)	CH_3	CH_3	59.8	55.7	51.1	-1.75	-5.2
(3)	Ph	CH_3	80.4	77.1	74.1	-1.89	-3.6
(4)	Ph	Ph	93.7	91.5	87.8	-3.59	-6.8
(5)	Bu^t	CH_3	72.9	68.2	63.4	-2.18	-5.5
(6)	Bu^t	Bu^t	80.6	77.2	74.1	-1.85	-3.5

a) ± 0.5%

We searched for possible correlations between electronic parameters, like chemical shifts and/or coupling constants, and equilibrium free energies, in order to obtain clues about relative importance of substituent effects on the two tautomeric species. On examination of ^{13}C n.m.r. data for both keto and enol species in the same series of β-diketones,[1] only the coupling constants, $^1J_{-CH=}$, for the enol form seem to vary along with equilibrium free energies, in DMSO, according to a well defined trend (Figure 1a). The point obtained from the $^1J_{-CH=}$ coupling constant for enolic $CH_3COCH_2CO_2Et$ (12) and its

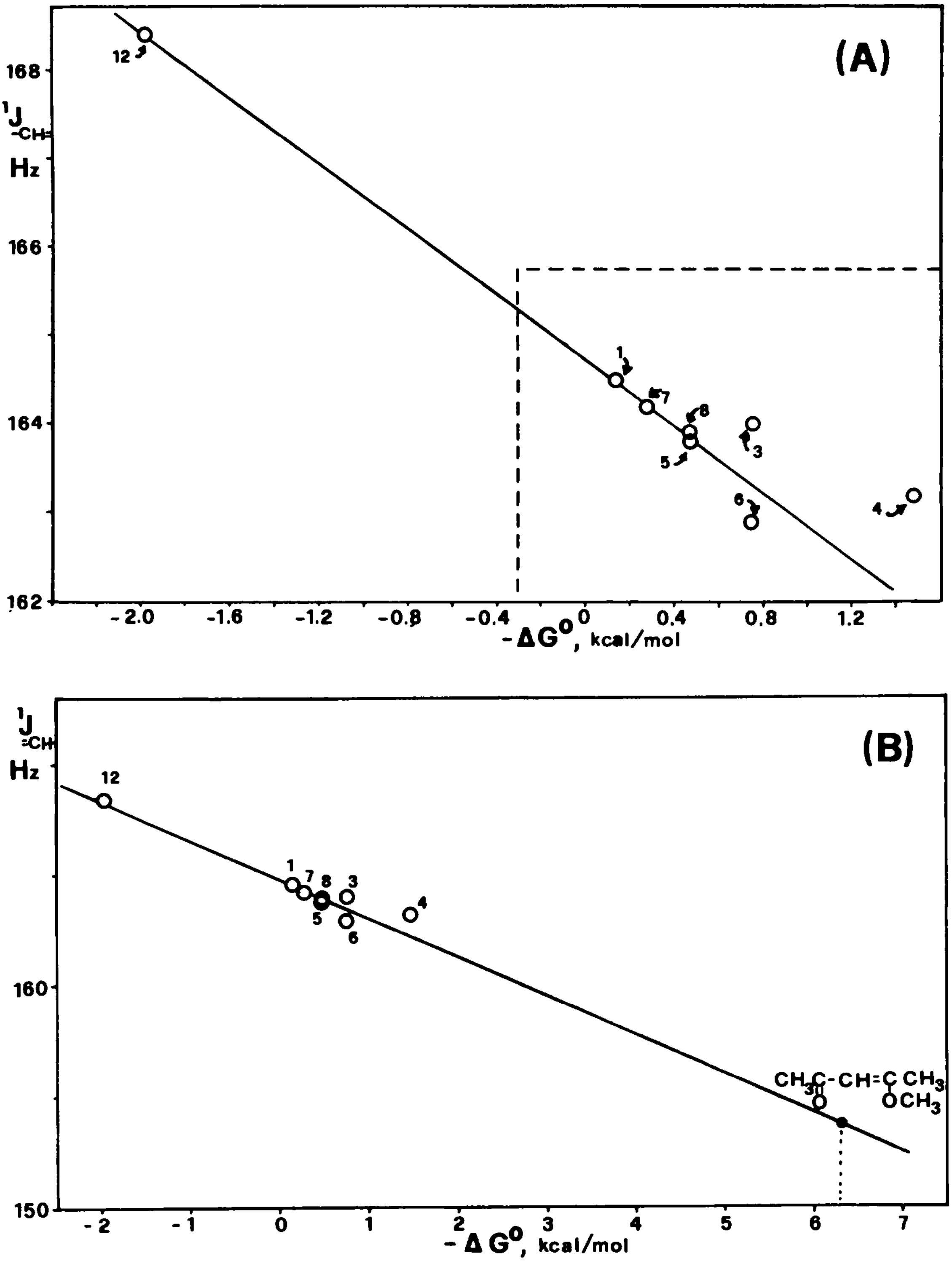


Figure 1

Plot of enolic $^1J_{-CH=}$ coupling constants of the β-diketones vs equilibrium free energies (ΔG^o at 40 °C) in DMSO (A).
Extrapolation of the equilibrium free energy (ΔG^o = -6.3 kcal/mol, corresponding to 99.996% enol) from the $^1J_{-CH=}$ coupling constant (153.9 Hz) of the pure enolic species, 4-methoxy-3-penten-2-one (B).

equilibrium free energy (1.98 kcal/mol, 4% enol) also lies on the straight line obtained by least square treatment of the corresponding points from the β-diketones.

Moreover, entering the graph with the $^{1}J_{-CH=}$ coupling constant for the ether MeCOCHC(OMe)Me (153.9 Hz in $CDCl_3$), which is a pure enol species, gives on the abscissa scale an extrapolated value of 6.3 kcal/mol for the equilibrium free energy, corresponding to a theoretical 99.996% enol (Figure 1b).

The trifluoromethyl derivatives 9 and 10 did not fit into the correlation obtained for the other compounds, probably because of the strong electronic perturbation produced by the substituents. However, a straight line can be drawn with the points from compounds 1, 9 and 10.

A similar graph obtained from the $^{1}J_{-CH_2-}$ coupling constants of the keto species, all of them laying between 126 and 128 Hz,[1] shows only scattered points.

Since the coupling constants reflect the bond sp character, the plot shows that higher enol content is associated with increasing p character of the -CH= linkage (i.e.: values of ^{1}J decreasing toward the typical values of sp_3 C-H bonds).[12] The ibridization of the central carbon atom is quite likely related to the overall thermodynamic stability of the molecule. In this respect, the energies of the keto species appear to be less and randomly dependent on structural variations than those of the enol, if coupling constants may be taken as sort of energy probes. It may therefore be suggested that changes in the equilibrium composition as a function of structure are caused by variations in the energy of the enol rather than of the ketone.

EXPERIMENTAL

The compounds were either commercially available or prepared as previously described,[13] according to literature methods.

^{1}H n.m.r. spectra were recorded on a Bruker Spectrospin WP 80 SY pulsed FT spectrometer operating at 80.13 MHz, with the probe thermostatted at 313 °K. Samples were in 0.05 molar solutions of chloroform-d_1 ($CDCl_3$) or dimethylsulfoxide-d_6 (DMSO). ^{13}C n.m.r. data for 4-methoxy-3-penten-2-one, $CH_3COCHC(OCH_3)CH_3$, were obtained with the same instrument. The solvents were dried over molecular sieves and all manipulations were carried out under argon atmosphere. The solvents were used for both internal ^{2}H lock and internal reference (peak at 7.25 ppm for $CHCl_3$ and 2.49 ppm for DMSO, downfield from Me_4Si). The samples were thermostatted at 40 °C, at least for three days for the $CDCl_3$ solutions, before recording the spectra. Equilibrium constants were obtained by integration of keto and enol resonance peaks, generally $-CH_2-$ and -CH=, respectively, and the measurements were accurate within 1%. ^{1}H n.m.r. chemical shifts for the compounds in $CDCl_3$ have been previously reported,[13] and those recorded in DMSO solutions are listed in Table 3. Up to ten fold dilutions of 0.12 molar 1,3-diphenyl-1,3-propanedione showed no change in enol percent or chemical shifts.

Table 3

^1H n.m.r. Chemical Shifts (δ, ppm) of β-Diketones, in DMSO-d_6

Compound	Substituents			Enol Tautomer		Keto Tautomer
	R	R'	R"	OH	$-C^{2}H=$	$-\underset{\vert}{C}^{2}H-$
1	CH_3	H	CH_3	15.48	5.66	3.66
2	CH_3	CH_3	CH_3	16.44	-	3.85[a]
3	Ph	H	CH_3	16.1	6.52	4.26
4	Ph	H	Ph	17.1	7.32	4.86
5	Bu^t	H	CH_3	15.87	5.81	3.76
6	Bu^t	H	Bu^t	16.27	5.86	3.86
7	Thi	H	CH_3	15.6	6.36	4.20
8	Thi	H	Thi	15.9	7.08	4.73
9	CF_3	H	CH_3	10.3	5.94	2.74
10	CF_3	H	CF_3	11.6	6.62	3.22
11	CF_3	H	Bu^t	9.2	6.31	4.35
12	CH_3	H	OEt	11.98	5.08	3.56

a) Center of a quartet

Partial financial support from Ministero della Pubblica Istruzione (M.P.I.) is acknowledged.

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