Tetrahedron Letters,Vol.29,No.43,pp 5541-5544,1988	0040-4039/88 $3.00 + .00
Printed in Great Britain	Pergamon Press plc

ACIDITY CONSTANTS OF PROTONATED SIMPLE CARBONYL COMPOUNDS: COMMENTS ON LITERATURE DATA AND INDIRECT ESTIMATES

by Jean Toullec

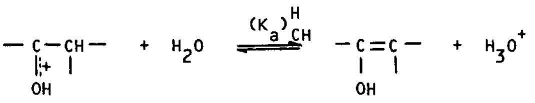
Institut de Topologie et de Dynamique des Systèmes de l'Université Paris 7,
associé au C.N.R.S., 1, rue Guy de la Brosse, 75005 PARIS, France

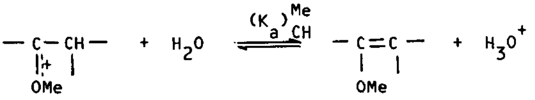
Abstract : The pK_a values for OH-acidity of protonated simple carbonyl compounds (oxocarbenium ions) are estimated from keto-enol equilibrium constants combined with CH-acidity constants of the ions, calculated by application of the Marcus equation to the ketonisation process.

Since the acidity constants of the conjugate acids of very weak bases are fundamental data, a great many studies have been devoted to their determination.[1] The usual method consists of measuring the acid/base concentration ratios in strong acid media and of calculating pK_a by one of the procedures based on the use of acidity functions. Whereas consistent data have been obtained for many organic bases, there are still disagreements for simple carbonyl compounds (e.g., for acetone: -2.72,[2] -5.37,[3] and -3.06[1]). These may be due to the occurence of side reactions[1] and/or to the presence of intermediates between the free carbonyl compounds and the fully protonated ones.[3,4] In this paper I show: (i) that the reported pK_a's are in most cases some units less negative than those expected on the basis of different comparisons, and (ii) that more realistic values can be estimated from kinetic and equilibrium data for keto-enol tautomerisation.

Acidity constants of protonated carbonyl compounds (OH-substituted carbenium ions) are expected to depend mainly on the polar and resonance effects of the groups attached to the carbonyl. Since σ^+ parameters have been used to account for the rate constants for carbenium ion-yielding proton addition to various olefinic compounds,[5] pK_a can be plotted against the sum of σ^+. Figure 1 shows that the points for amides, carboxylic acids and esters fall relatively close to a straight line, whose slope ($\rho^+ = -8.6$, $r = 0.93$) is in agreement with that expected for the effects of substituents directly attached to the carbenium centre. In contrast, the points corresponding to literature data for benzaldehyde and various ketones lie some pK_a units above the line, suggesting some failure in pK_a determination.

A further piece of evidence that most literature pK_a values for simple carbonyl compounds are too high comes from a comparison of the CH-acidity constants of the oxocarbenium ions (eq 1) with the acidity constants of the corresponding methyl derivatives (eq 2). The former can be determined from the


$$-\underset{\overset{\|+}{OH}}{C}-\underset{|}{CH}- \;+\; H_2O \;\xrightleftharpoons{(K_a)^H_{CH}}\; -\underset{\overset{|}{OH}}{C}=\underset{|}{C}- \;+\; H_3O^+ \qquad (1)$$


$$-\underset{\overset{\|+}{OMe}}{C}-\underset{|}{CH}- \;+\; H_2O \;\xrightleftharpoons{(K_a)^{Me}_{CH}}\; -\underset{\overset{|}{OMe}}{C}=\underset{|}{C}- \;+\; H_3O^+ \qquad (2)$$

the keto-enol equilibrium constants, which are now known with accuracy,[9] combined with literature data on OH-acidity; the latter can, as previously shown,[10] be derived from data on acetal-to-oxocarbenium ion[11] and ketone-to-enol equilibrium constants.[12] The large differences between the two sets of CH-acidity constants (Table 1) are far larger (5-6 units) than those expected (ca. 2 units) if one considers the relatively small differences in charge-delocalisation abilities of the OH and OMe groups.[13]

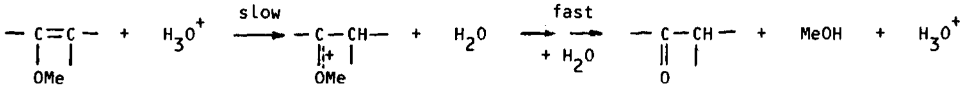
Table 1.- Comparison between CH-Acidity Constants $(pK_a)_{\overset{+}{C}H}$ of Oxocarbenium Ions Derived from Methyl Enol Ethers $[XC_6H_4\overset{+}{C}(OMe)CH_3]$ and from Enols $[XC_6H_4\overset{+}{C}(OH)CH_3]$, Calculated from Literature Data.

X	$10^2(K_{ac}^{eth})$[a]	$10^4(K_{ac}^{oxo})$[b]	$(pK_a)_{CH}^{Me}$ [c]	pK_E[d]	$(pK_a)_{OH}$[e]	$(pK_a)_{CH}^{H}$ [f]
4-OMe	7.7	720	-0.03	8.80[g]	-3.76	5.04
4-Me	6.1	41	-1.17	8.34[g]	-3.67	4.67
H	6.0	9.3	-1.81	7.97[h]	-4.16	3.81
4-Cl or 4-Br	6.1	1.8	-2.53	7.77[g]	-4.20	3.57
3-Cl or 3-Br	7.0	0.29	-3.39	7.46[i]	-4.86	2.60
4-NO$_2$	4.0	0.023	-4.23	7.15[i]	-5.00	2.15

[a] Acetal-to-enol ether equilibrium constants in water; data from ref. 12. [b] Acetal-to-oxonium ion equilibrium constants in water; data from ref. 11 or extrapolated. [c] Calculated as log $(K_{ac}^{oxo}/K_{ac}^{eth})$. [d] $-\log K_E$, with K_E, the keto-enol equilibrium constants. [e] From ref. 3. [f] $(pK_a)_{CH}^{H} = (pK_a)_{OH} + pK_E$. [g] From ref. 9d. [h] From ref. 9b. [i] Calculated by extrapolation or interpolation of HKSW's data (ref. 9d)(pK_E depends on σ^+ with $\rho^+ = -1.14$).

The situation should be similar to that for the conjugate acids of phenols and anisoles (σ-adducts)[14] (e.g. -10.14 and -11.67 for the conjugate acids of 1-hydroxy-3,5-dimethylbenzene and of 1-methoxy-3,5-dimethylbenzene, respectively), even though positive charge delocalisation by the ring double bonds can slightly lessen the pK_a difference.

It has been shown[10] that the H_3O^+-catalytic rate constants for proton transfer to ring-substituted α-methoxystyrenes [the rate-limiting step of hydrolysis (eq 3)] are accounted for by the Marcus

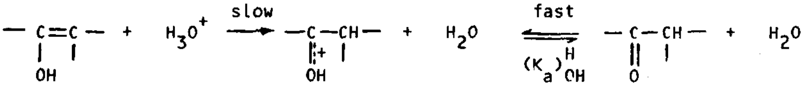


$$-\underset{\mathrm{OMe}}{\mathrm{C}}=\mathrm{C}- \;+\; H_3O^+ \xrightarrow{\text{slow}} -\underset{\mathrm{OMe}}{\overset{}{\mathrm{C}}}{}^{+}-\mathrm{CH}- \;+\; H_2O \xrightarrow{\text{fast}} \xrightarrow[+\,H_2O]{} -\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{CH}- \;+\; \mathrm{MeOH} \;+\; H_3O^+ \qquad (3)$$

equation (eq 4)[15] when log $k_{H_3O^+}$ (related to $\Delta G^{\ddagger}$) is plotted against pK_a, the acidity constant of the

$$\Delta G^{\ddagger} = W_r + \Delta G_o^{\ddagger}\left[1 + \frac{\Delta G° + W_p - W_r}{4\Delta G_o^{\ddagger}}\right]^2 \qquad (4)$$

corresponding oxocarbenium ion (related to ΔG°, the Gibbs energy increment of the first step), and that the Marcus parameters, $\Delta G_o^{\ddagger}$ (15.0 kJ mol^{-1}), W_r (44.5 kJ mol^{-1}), and W_p (52.0 kJ Mol^{-1})(corresponding to the intrinsic barrier and to the Gibbs free energies for encounter pair formation between reactants and products, respectively) are close or identical to those derived when the catalyst is changed instead of the substituent.[16] Corresponding behaviour is expected for acid-catalysed enol ketonisation for which, because of mechanistic analogies (eq 3 and 5)(rate-limiting proton transfer to the double bond), there



$$-\underset{\mathrm{OH}}{\mathrm{C}}=\mathrm{C}- \;+\; H_3O^+ \xrightarrow{\text{slow}} -\underset{\mathrm{OH}}{\mathrm{C}}{}^{+}-\mathrm{CH}- \;+\; H_2O \;\underset{(K_a)_{CH}^{H}}{\overset{\text{fast}}{\rightleftharpoons}}\; -\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{CH}- \;+\; H_2O \qquad (5)$$

are close similarities with enol hydrolysis:[17,18] (i) the rate constants for H_3O^+-catalysis are only one order of magnitude larger than those for the parent ethers; (ii) solvent isotope effects are almost identical, suggesting about the same degrees of proton transfer at the transition state; and (iii) the Brönsted exponents α, accounting for the dependence on pK_a of the catalytic constants associated with acids HA, are similar. It follows that the Marcus parameters for enol ketonisation[19] can be assumed to be close to those for enol ether hydrolysis, and that the CH-acidity constants of the oxonium ions, related to ΔG°, can be calculated from rate data for H_3O^+-catalysed enol ketonisation by the reverse form of eq 4 (including statistical corrections in the case of acetone).

It was first assumed that $\Delta G_o^{\ddagger}$, W_r and W_p are rigorously the same as for enol ether protonation, but data in Table 2 show: (i) that the calculated pK_a values for CH-acidity, although far more

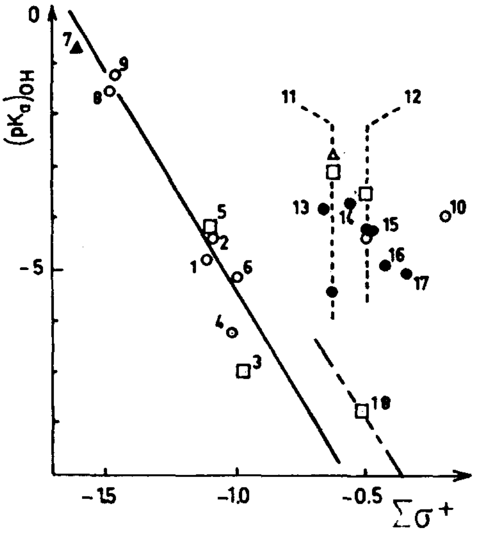


Fig. 1- Literature data on pK_a of the conjugate acids of carbonyl compounds (R^1-CO-R^2) vs. ($\sigma^+_{R^1} + \sigma^+_{R^2}$).
○ : From ref. 6; □ : from ref. 7; ● : from ref. 3; △ : from ref. 2; ▲ : from ref. 8. R^1 and R^2 as listed: OH, Ph (1); OH, CH=CHPh (2); OMe, Ph (3); OEt, Ph (4); OMe, Me (5); OMe, CH=CHPh (6); NH_2, CH_3 (7); NH_2, Ph (8); NH_2, CH=CHPh (9); Ph, H (10), Me, Me (11); Me, Ph (12); Me, 4-An (13); Me, 4-To (14); Me, 4-BrPh (15); Me, 3-BrPh (16); Me, 4-NO_2Ph (17); tBu, tBu (18). The dashed line corresponds to the main line of Fig. 1.

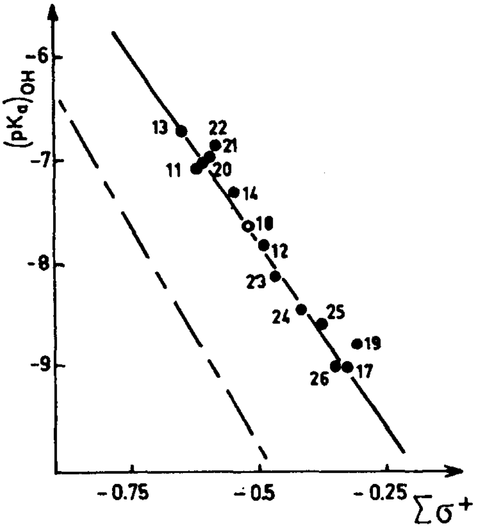


Fig. 2- Estimated pK_a for the conjugate acids of methyl ketones (CH_3-CO-R) vs. ($\sigma^+_{CH_3} + \sigma^+_R$)[data from Table 2, second estimates, except di-t-butylketone (18)(○)(data from ref. 7)]. The dashed line corresponds to the main line of Fig. 1. For the XC_6H_4 groups, σ^+_R was calculated as in ref. 5).

Table 2.-Calculated $(pK_a)_{OH}$ of Oxocarbenium Ions derived from Simple Carbonyl Compounds

Carbonyl Compound	$k^K_{H^+}$ [a]	pK_E [b]	First estimates		Second estimates	
			$(pK_a)^H_{CH}$ [c]	$(pK_a)_{OH}$ [d]	$(pK_a)^H_{CH}$ [e]	$(pK_a)_{OH}$ [d]
CH_3CHO (19)	33 [f]	6.23 [f]	-2.02	-8.25	-2.53	-8.76
CH_3COCH_3 (11)	5400 [f]	8.33 [f]	2.48	-5.85	1.27	-7.06
CH_3COEt (20)	6300 [f]	8.76 [f]	2.97	-5.79	1.73	-7.03
CH_3COiPr (21)	5900 [f]	8.61 [f]	2.98	-5.73	1.66	-6.94
CH_3COtBu (22)	7500 [f]	8.76 [f]	3.20	-5.56	1.90	-6.86
X in $XC_6H_4COCH_3$						
4-OMe (13)	9020 [g]	8.80 [g]	3.45	-5.35	2.09	-6.71
4-Me (14)	3080 [g]	8.34 [g]	2.11	-6.23	1.04	-7.30
H (12)	1140 [h]	7.97 [h]	1.04	-6.93	0.16	-7.81
4-Cl (23)	620 [g]	7.77 [g]	0.45	-7.32	-0.35	-8.12
3-Cl (24)	303 [i]	7.52 [i]	-0.21	-7.73	-0.92	-8.44
3-CF_3(25)	209 [g]	7.38 [g]	-0.53	-7.91	-1.20	-8.58
3-NO_2 (26)	86 [i]	7.15 [i]	-1.27	-8.42	-1.85	-9.00
4-NO_2 (17)	73 [i]	7.02 [i]	-1.40	-8.42	-1.98	-9.00

[a] H_3O^+-catalysed enol ketonisation rate constants ($dm^3\ mol^{-1}\ s^{-1}$). [b] $pK_E = -\log K_E$. [c] Calculated as $-(\Delta G°/RT + 1.74)$, $\Delta G°$ being derived from eq 4 with $\Delta G^{\ddagger}_o = 15.0$, $W_r = 44.5$ and $W_p = 52.0\ kJ\ mol^{-1}$. [d] Calculated as $(pK_a)^H_{CH} - pK_E$. [e] Calculated from eq 4 with $\Delta G^{\ddagger}_o = 15.0$, $W_r = 40.0$ and $W_p = 52.0\ kJ\ mol^{-1}$. [f] From ref. 9a. [g] From ref. 9d. See also note 20. [h] From ref. 9b. [i] See footnote i of Table 1.

consistent than those calculated in Table 1, are still 2.8-3.5 units above the CH-acidity constants for methyl derivatives, and (ii) that, contrary to what is expected, the difference between the two series of $(pK_a)_{CH}$ values increases slightly on going from the 3-NO_2 to the 4-OMe substituent. Table 2 shows that more satisfactory data are obtained by taking a slightly lower W_r value, 40 kJ mol^{-1}, but keeping the $\Delta G^{\ddagger}_o$ and W_p terms derived for α-methoxystyrene hydrolysis. The differences in pK_a values (ca. 2) are close to those expected by comparison with the phenol-anisole system (ca. 1.5) and are approximately independent of substituent. Table 2 also lists the OH-acidity constants derived by combining the latter values and the keto-enol equilibrium constants; the values obtained are in most cases 3-5 units more negative than those determined directly, but Figure 2 shows that the points fall remarkably close to a line parallel, but only 1.5 unit above, that for other carbonyl compounds.

It may be significant that the point corresponding to di-t-butylketone, for which the value of -7.66 has been reported,[7] falls on the same line. Since in this case it can be expected that errors due to side reactions and/or to the formation of hydrogen-bonded association complexes are reduced, this suggests that the large disagreement between literature data and those expected stems from difficulties in dealing with a protonation process more complicated in highly concentrated solutions than that usually assumed. It can also be argued that literature pK_a have been obtained by long-range extrapolation, but that the values of the H_o acidity function at half-protonation are relatively close to the pK_a values estimated here. Therefore, the large inconsistencies would not stem from errors in primary data, but from the way pK_a's have been derived.

References and Notes

1. For a recent review, see: A. Bagno, G. Scorrano and R.A. More O'Ferrall, Rev. Chem. Intermed., 1987, 7, 313.
2. R.A. McClelland and W.F. Reynolds, Can. J. Chem., 1976, 54, 718.
3. R.A. Cox, C.R. Smith and K. Yates, Can. J. Chem., 1979, 57, 2952.
4. V.A. Palm, U.L. Haldna and A.J. Talvik, in "The Chemistry of the Carbonyl Group", S. Patai, Ed., Wiley, New York, 1966, p. 439.
5. W.K. Chwang, P. Knittel, K.M. Koshy and T.T. Tidwell, J. Am. Chem. Soc., 1977, 99, 3395.
6. J.T. Edward and S.C. Wong, J. Am. Chem. Soc., 1977, 99, 4229.
7. From ref. 1. See also: A. Bagno, V. Lucchini and G. Scorrano, Bull. Soc. Chim. Fr., 1987, 563; A. Bagno, G. Scorrano and V. Lucchini, Gazz. Chem. Ital., 1987, 117, 475.
8. R.A. Cox, L.M. Druet, A.E. Klausner, T.A. Modro, P. Wan and K. Yates, Can. J. Chem., 1981, 59, 1568.
9. (a) J.R. Keeffe, A.J. Kresge, and N.P. Schepp, J. Am. Chem. Soc., 1988, 110, 1993, and ref. cited therein. (b) J.R. Keeffe, A.J. Kresge and J. Toullec, Can. J. Chem., 1986, 64, 1224. (c) J. Toullec, Tetrahedron Lett., 1984, 25, 4401. (d) R.A. Hochstrasser, A.J. Kresge, N.P. Schepp and J. Wirz, personal communication.
10. J. Toullec, J. Chem. Soc., Perkin Trans. 2, in press.
11. P.R. Young and W.P. Jencks, J. Am. Chem. Soc., 1977, 99, 8238.
12. J. Toullec and M. El-Alaoui, J. Org. Chem., 1986, 51, 4054.
13. σ^+ values (H.C. Brown and Y. Okamoto, J. Am. Chem. Soc., 1958, 80, 4979) are -0.92 and -0.78 for the OH and OMe groups, respectively.
14. A.J. Kresge, H.L. Chen, L.E. Hakka and J.E. Kouba, J. Am. Chem. Soc., 1971, 93, 6174. pK_a data are recalculated in ref. 1.
15. For leading references on the Marcus equation written in this form, see ref. 16.
16. A.J. Kresge, D.S. Sagatys and H.L. Chen, J. Am. Chem. Soc., 1977, 99, 7228.
17. J. Toullec, Adv. Phys. Org. Chem., 1982, 18, 1.
18. Y. Chiang, A.J. Kresge and P.A. Walsh, J. Am. Chem. Soc., 1986, 108, 6314. Y. Chiang, M. Hojatti, J.R. Keeffe, A.J. Kresge, N.P. Schepp and J. Wirz, J. Am. Chem. Soc., 1987, 109, 4000.
19. This should be valid only for enols derived from methyl ketones because the same populations of oxonium ion conformations [corresponding to rotation around the C(O)-C(Me) bond] could be assumed. For other enols, unknown statistical factors should be taken into account to deal with the differences in conformational populations and with the stereoelectronic conditions for proton removal (see ref. 17).
20. Keto-enol equilibrium constants were calculated by HKSW (ref. 9d) as the ratios between enolisation rate constants and directly measured enol ketonisation rate constants. By combining these data with the experimental $K_E k_{Br}$ (ref. 9d), where k_{Br} is the rate constant for enol bromination, HKSW observed that k_{Br} depends slightly on substituent, suggesting that k_{Br} is not rigorously diffusion-controlled and substituent-independent as assumed previously. This accounts for the slight differences in keto-enol equilibrium constants and in ketonisation rate constants from those reported in ref. 9c.

(Received in France 11 August 1988)