Measurement of Equilibrium Constants for Complex Formation between Phenol and Hydrogen-Bond Acceptors by Kinetic Laser Flash Photolysis[1]

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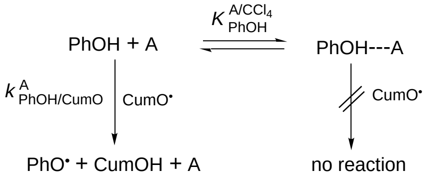
Received March 28, 1996

Although hydrogen bonding is obviously of major importance in determining the nature of our external and internal environment (e.g., *liquid* water under ambient conditions, double-stranded DNA, etc.), there are surprisingly few methods for measuring the equilibrium constant, $K^{\mathrm{A}}_{\mathrm{DOH}}$, for hydrogen-bond formation between a hydrogen-bond donor (HBD), DOH, and a hydrogen-bond acceptor (HBA), A.[3] Infrared spectroscopy is by far the most commonly employed method for measuring $K^{\mathrm{A}}_{\mathrm{DOH}}$. The experimental technique generally involves using a constant concentration of DOH[4] in $\mathrm{CCl_4}$ as solvent[5] and monitoring the decrease in the intensity (peak height) of the O−H fundamental stretching frequency, ν_{OH}, induced by the addition of known concentrations of the HBA. It is, of course, essential to avoid any "interference" in the critical O−H stretching region of the spectrum. Because this critical requirement cannot easily be met if A also contains OH groups, i.e., AOH, there would appear to be extremely few measurements of equilibrium constants for hydrogen-bond formation between a DOH HBD and an AOH HBA (i.e. DOH---O(H)A).[6]

$$\mathrm{DOH} + \mathrm{A} \xrightleftharpoons{K^{\mathrm{A/CCl_4}}_{\mathrm{DOH}}} \mathrm{DOH{-}{-}{-}A} \tag{1}$$

Our work on kinetic solvent effects (KSE) on free radical reactions[8−12] has serendipitously led to a completely new method for measuring equilibrium constants for hydrogen bonding from a variety of DOH to very many A in $\mathrm{CCl_4}$ solvent, $K^{\mathrm{A/CCl_4}}_{\mathrm{DOH}}$. Since this method does not use infrared spectroscopy it can also be used to measure $K^{\mathrm{AOH/CCl_4}}_{\mathrm{DOH}}$ provided only that the hydroxylic hydrogen atom in DOH can be abstracted by free radicals. Fortunately, there are a host of scientifically interesting and commercially important DOH HBD's which meet this criterion.[13] Herein we demonstrate the validity and simplicity of this new technique using phenol as DOH. Our kinetic measurements yield $K^{\mathrm{A/CCl_4}}_{\mathrm{PhOH}}$ with four HBA's which do not contain OH groups and which serve as a check for our method and $K^{\mathrm{AOH/CCl_4}}_{\mathrm{PhOH}}$ with three HBA's which do contain OH groups, acetic acid, methanol, and *tert*-butyl alcohol.

The kinetic model advanced in our original communication[9] to explain the progressive reduction in the rate of hydrogen atom abstraction from phenol (and *tert*-butyl hydroperoxide) by cumyloxyl radicals, $\mathrm{CumO^{\bullet}}$ (ca. 10 μM, generated by 308 nm laser flash photolysis of dicumyl peroxide), as the HBA abilities of the solvents increased invoked reactive non-hydrogen bonded DOH and non-reactive hydrogen-bonded DOH, e.g.,



Although we now recognize that this model is oversimplified[10] it does yield a very simple and useful kinetic equation, viz.:[9]

$$k^{\mathrm{CCl_4}}_{\mathrm{PhOH/CumO}} = k^{\mathrm{A}}_{\mathrm{PhOH/CumO}}(1 + K^{\mathrm{A/CCl_4}}_{\mathrm{PhOH}}[\mathrm{A}]) \tag{2}$$

which can be rearranged to

$$\frac{1}{k^{\mathrm{A}}_{\mathrm{PhOH/CumO}}} = \frac{1}{k^{\mathrm{CCl_4}}_{\mathrm{PhOH/CumO}}} + \frac{K^{\mathrm{A/CCl_4}}_{\mathrm{PhOH}}[\mathrm{A}]}{k^{\mathrm{CCl_4}}_{\mathrm{PhOH/CumO}}} \tag{3}$$

Thus, for *dilute* phenol and A in $\mathrm{CCl_4}$ (where their activity coefficients will be unity) a plot of the reciprocal of the rate constant (i.e., $1/k^{\mathrm{A/CCl_4}}_{\mathrm{PhOH/CumO}}$) measured at 25 °C against [A], the concentration of the HBA in $\mathrm{CCl_4}$, should yield a straight line with an intercept equal to the reciprocal of the measured rate constant in $\mathrm{CCl_4}$ and with a (slope)/(intercept) ratio equal to $K^{\mathrm{A/CCl_4}}_{\mathrm{PhOH}}$. Two representative plots according to eq 3 are shown in the figures.[14] The kinetically derived equilibrium constants for hydrogen bonding between phenol and A are summarized in Table 1 and are compared therein with the ranges of equilibrium constants which have been obtained by the infrared (IR) method at 25 °C. For those A for which kinetic measurements could be made in neat A[15] the measured values of $k^{\mathrm{A(neat)}}_{\mathrm{PhOH/CumO}}$ were roughly half as large as the values obtained by extrapolating the linear portion of the plots of $k^{\mathrm{A/CCl_4}}_{\mathrm{PhOH/CumO}}$ vs [A],[16] i.e. all these plots curve upward at high [A] because the

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(1) Issued as NRCC No. 39108.

(2) NRCC Research Associate 1994−96.

(3) (a) Pimental, G. C.; McClellan, A. L. *The Hydrogen Bond* ; W. H. Freeman and Co.: San Francisco, 1960. (b) Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcell Dekker: New York, 1974. (c) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer Verlag: Berlin, 1991.

(4) Except, of course, for studies of self-association where both the HBD and HBA are DOH.

(5) Values of $K^{\mathrm{A}}_{\mathrm{DOH}}$ are generally measured in a solvent which is as weak an HBA as practicable and which has no infrared absorption near $\nu_{\mathrm{DO-H}}$. The first requirement is best met using an alkane as solvent but the intense C−H stretching bands can interfere with reliable measurements of $\nu_{\mathrm{DO-H}}$ intensities. For this reason, most measurements of $K^{\mathrm{A}}_{\mathrm{DOH}}$ are made in $\mathrm{CCl_4}$, i.e., $K^{\mathrm{A/CCl_4}}_{\mathrm{DOH}}$, although $\mathrm{CCl_4}$ is, itself, a weak HBA.

(6) A modern data base[7] containing nearly 500 measured values of $K^{\mathrm{A}}_{\mathrm{PhOH}}$ (A ≠ PhOH, mostly at 20 or 25 °C) has not one A which contains an OH group. Reference 3a lists about 50 $K^{\mathrm{A}}_{\mathrm{PhOH}}$ (A ≠ PhOH) values measured prior to 1960 with no OH containing HBA's. Reference 3b (pp 309−335) lists about 700 $K^{\mathrm{A}}_{\mathrm{PhOH}}$ (A ≠ PhOH) values at 25 °C (and/or values of $\Delta H^{\mathrm{A}}_{\mathrm{PhOH}}$ and $\Delta S^{\mathrm{A}}_{\mathrm{PhOH}}$) measured between 1960 and 1973 with just two OH containing HBA's (*t*-BuOH and $\mathrm{Me_3SiOH}$), *vide infra*.

(7) Compiled by Dr. Merete F. Nielsen, Department of Chemistry, University of Copenhagen. We thank Dr. Nielsen for sharing the fruits of her labor with us.

(8) Avila, D. V.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 466−470.

(9) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929−2930.

(10) Valgimigli, L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 9966−9971.

(11) MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 1316−1321.

(12) Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* To be submitted for publication.

(13) For example, phenolic antioxidants of commercial (e.g., BHT) and biological (e.g., vitamin E) importance,[9,10,12] hydroperoxides,[9] and N-mono- and N,N-disubstituted hydroxylamines. The method would also be suitable for many NH-containing compounds such as diarylamine antioxidants.[11]

(14) It should be noted that each point on these figures corresponds to the actual measurement of k_{exptl} at one concentration of A but at six different concentrations of phenol: $k_{\mathrm{exptl}} = k_{\mathrm{o}} + k^{\mathrm{A/CCl_4}}_{\mathrm{PhOH/CumO}}[\mathrm{PhOH}]$, where k_{o} corresponds to all first-order and pseudo-first-order reactions of $\mathrm{CumO^{\bullet}}$ other than the reaction with PhOH. The end of the abscissa corresponds to the neat solvent.

(15) Measurements could not be made in *neat* MeOH, $\mathrm{Me_2NCHO}$, or pyridine; the first two solvents are too reactive toward $\mathrm{CumO^{\bullet}}$ and the last absorbed too strongly at 308 nm, the laser wavelength.

(16) Values of $10^{-6}\ k^{\mathrm{A(neat)}}_{\mathrm{PhOH/CumO}}/\mathrm{M^{-1}\ s^{-1}}$ by extrapolation and, when possible,[15] by direct measurement (in parentheses) were as follows: $\mathrm{CCl_4}$, (860); MeC(O)OH, 34 (18); MeCN, 13 (5.8); MeC(O)OEt, 12 (7.5); MeOH, 3.2; *t*-BuOH, 6.3 (3.8); pyridine, 2.3; $\mathrm{Me_2NCHO}$, 1.0.

S0002-7863(96)01032-3 CCC: $12.00

Table 1. Equilibrium Constants for Hydrogen Bond Formation at 25 °C between Phenol and Some Hydrogen Bond Acceptors Measured by the Kinetic Method (Comparison with 25 °C Equilibrium Constants Measured by Infrared Spectroscopy from the Literature)

HBA	[HBA] max (M)[a]	K_{PhOH}^{A/CCl_4} (M^{-1}) kinetic	infrared (lit)[b]
MeC(O)OH	1.2	1.4	no value[c]
MeCN	0.6	3.5	4.6−6.5
MeC(O)OEt	1.5	6.6	8.8−12.3
MeOH	1.2	11	no value
t-BuOH	0.5	14	44[d]
pyridine	0.3	30	41−53
Me_2NCHO	0.17	69	64−76

[a] Maximum HBA concentration used to determine the equilibrium constant by the kinetic method. Full data are available as supporting information. [b] The range of values reported in the literature is given. These values were either measured at 25 °C or interpolated by the present authors from the literature data if 25 °C fell within the reported temperature range. Individual equilibrium constants and the appropriate references are given as supporting information. [c] Our own IR measurements gave 1.9, see text. [d] Reference 17. This value is not reliable, see text.

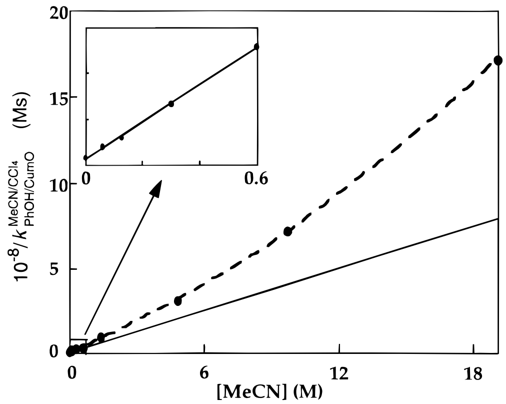

Figure 1. Dependence of $1/k_{PhOHCumO}^{MeCN/CCl_4}$ on [MeCN].

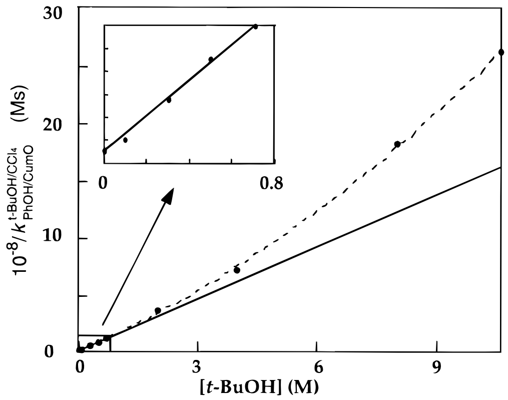

Figure 2. Dependence of $1/k_{PhOH/CumO}^{t\text{-}BuOH/CCl_4}$ on [*t*-BuOH].

activity coefficients are no longer equal to one, see Figures 1 and 2. Our full kinetic data are available as supporting information.

The agreement between the kinetic- and infrared-derived equilibrium constants is satisfactory for the four non-hydroxylic HBA's, particularly when one considers the range of K_{PhOH}^{A/CCl_4} values that have been reported in each of these A/CCl_4 solvent mixtures by workers using the IR method. For the three relatively weak HBA's which are non-hydroxylic (acetonitrile, ethyl acetate, and pyridine), the kinetic method gives consistently lower K_{PhOH}^{A/CCl_4} values than the IR method which implies that the two techniques sample slightly different ensembles of "non-hydrogen bonded" molecules of phenol. For example, at least some of those phenol molecules which are very weakly hydrogen bonded (bond energies $\leq kT$) might appear to be bonded by the IR method but unbonded in our kinetic measurements. However, there is no *a priori* reason to believe that one experimental method gives inherently "better" equilibrium constants than the other.

For the three HBA's which contain a hydroxyl group there would appear to be only a single IR measurement of an equilibrium constant, viz.,[17] $K_{PhOH}^{t\text{-}BuOH/CCl_4} = 460\ mf^{-1} \equiv 44\ M^{-1}$. This value was purportedly measured at [PhOH] = 4.3 mM and [*t*-BuOH] = 1.2 mM.[18] Since it differed so dramatically from the kinetic value of 14 M^{-1} measured with [PhOH] = 0.0−45 mM and [*t*-BuOH] in the range 0.0−0.7 M we attempted to repeat the infrared measurement. However, we found this to be impossible because the O−H bands for phenol ($\nu_{OH} = 3610\ cm^{-1}$) and *tert*-butyl alcohol ($\nu_{OH} = 3617\ cm^{-1}$) are not resolved from one another.[19] The same was true with methanol as the HBA ($\nu_{OH} = 3644\ cm^{-1}$).[19] Although it would appear that no one has ever tried to measure the equilibrium constant for hydrogen bonding from phenol to acetic acid by the IR method we discovered that such a measurement was completely straightforward.[22] The value found for K_{PhOH}^{AcOH/CCl_4} was 1.9 M^{-1} by IR, which is in satisfactory agreement with our kinetic value of 1.4 M^{-1}.

In conclusion, we have discovered a new method for measuring equilibrium constants for hydrogen bonding from phenol (and from any other DOH which has an abstractable hydrogen atom) to any HBA, including alcohols. We emphasize that this kinetic method does not require the experimenter to have access to a laser flash photolysis system. Our KSE work has clearly demonstrated that we could just as well have done our experiments on phenol using the relatively unreactive diphenylpicrylhydrazyl (DPPH) radical and a simple spectrophotometer.[10]

Supporting Information Available: A table of literature values of K_{PhOH}^{A/CCl_4} at 25 °C, with references, for the seven hydrogen-bond acceptors listed in Table 1 and tables of the kinetic data (k_{exptl} at 25 °C) used for the determination of $k_{PhOH/CumO}^{A/CCl_4}$ values (12 pages). See any current masthead page for ordering information and Internet access instructions.

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(17) Rouviére, J.; Salvinen, J. *J. Chim. Phys., Phys.-Chim. Biol.* **1969**, *66*, 149−153.

(18) At [*t*-BuOH] = 6.5 and 13.3 mM the equilibrium constants are given as 452 and 444 mf $^{-1}$, respectively.[17]

(19) In this connection, we note that Laurence et al.[20] have reported measurements of the equilibrium constants for hydrogen bond formation between 4-fluorophenol ($\nu_{OH} = 3613\ cm^{-1}$) and a few alcohols in CCl_4 at 25 °C using a rather ill-defined IR method. However, it is clear that these workers were uncomfortable with their method since they comment, "Fully aware, however, of some imprecision in the values so obtained...". Nevertheless, the equilibrium constants reported were 6.6 M^{-1} for methanol and 13 M^{-1} for *tert*-butyl alcohol and these can be converted to equilibrium constants for hydrogen bonding by phenol to these two alcohols using an equation due to Taft et al.,[21] viz, $\log K_{PhOH}^{A/CCl_4} = 0.97 \log K_{p\text{-}FC_6H_4OH}^{A/CCl_4} - 0.13$ (at 25 °C). This yields equilibrium constants for hydrogen bonding of phenol to methanol and *tert*-butyl alcohol equal to 4.6 and 9.4 M^{-1}, respectively, which can be compared with our kinetically determined values of 11 and 14 M^{-1}, respectively. For relatively weak HBA's the normal IR method gives larger equilibrium constants than the kinetic method (*vide supra* and Table 1) rather than smaller. It would appear that reliable equilibrium constants for hydrogen bonding between phenols and alcohols cannot be obtained by IR spectroscopy.

(20) Laurence, C.; Berthelot, M.; Helbert, M.; Sraidi, K. *J. Phys. Chem.* **1989**, *93*, 3799−3802.

(21) Taft, R. W.; Gurka, D.; Joris, L.; Schleyer, P. v. R.; Rakshys, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 4801−4807.

(22) The vast majority of the acetic acid molecules are "tied up" in hydrogen-bonded dimers and there is only a small OH band for "free" acetic acid ($\nu_{OH} = 3534\ cm^{-1}$). This band is well seperated from the O−H band for phenol.