16d, 105665-68-7; **16g**, 105665-72-3; **16h**, 105665-74-5; **16j**, 105665-77-8; **16k**, 105665-79-0; **17**, 105665-89-2; **18**, 105665-90-5; **18** (demethylene), 105666-08-8; **19**, 105665-91-6; **20**, 105665-84-7; **21**, 105761-20-4; 3-acetyl-3-(3-iodopropyl)tetrahydro-2-furanone, 105666-07-7; (1*R**,2*R**)-1-isopropyl-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one, 105666-00-0; ethyl 2-isopropyl-6-oxoheptanoate, 105666-01-1; 7-bromo-4-methyl-3-oxooctane, 105666-02-2; 2-ethyl-1,3-dimethyl-2-cyclopentanol, 105666-03-3; ethyl 2-acetyl-6-iodo-2-methylhexanoate, 105666-04-4; (*R**,*R**)-ethyl 6-iodo-2-(1-hydroxyethyl)-2-methylhexanoate, 105666-05-5; (*R**,*S**)-ethyl 6-iodo-2-(1-hydroxyethyl)-2-methylhexanoate, 105666-06-6; ethyl 2-methyl-2-(*trans*-4-bromo-2-butenyl)-3-oxobutanoate, 105665-94-9; ethyl 2-methyl-3-oxobutanoate, 609-14-3; (1*R**,2*S**)-1,2-dimethyl-2-hydroxycyclopentanecarboxylic acid, 105665-97-2; 2-methyl-6-oxoheptanoic acid, 2570-68-5; (1*R**,4*S**)-*cis*-1,5-dimethyl-6-oxabicyclo[3.2.0]heptan-7-one, 105665-98-3; (*E*)-*N*,*N*-diethyl-2-acetyl-7-iodo-5-heptenamide, 105665-46-1; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide, 105665-45-0; (1*R**,2*S**,3*R**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide, 105761-18-0; (*E*)-*N*,*N*-diethyl-2-acetyl-8-bromo-6-octenamide, 105665-47-2; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide, 105665-48-3; (1*R**,2*S**,3*R**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide, 105761-19-1; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide (*m*-dinitrobenzoate ester), 105665-49-4; (1*R**,2*S**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxyliic acid, 105665-80-3; (1*R**,2*R**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylic acid, 105665-82-5; (1*R**,2*S**)-1,5-dimethyl-3-methylene-6-oxabicyclo[3.2.0]heptan-7-one, 105665-81-4; (1*R**,2*S**,3*S**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylic acid, 105665-87-0; (1*R**,4*S**,5*S**)-1,5-dimethyl-4-ethenyl-6-oxabicyclo[3.2.0]heptan-7-one, 105665-88-1; (*E*)-8-bromo-4-methyl-6-octen-3-one, 105665-95-0; (1*R**,2*S**)-1-ethyl-2-methyl-4-cyclohexen-1-ol, 105665-96-1; (1*R**,2*R**)-1-ethyl-2-methyl-4-cyclohexen-1-ol, 105665-99-4; ethyl (*E*)-2-methyl-2-acetyl-7-iodo-5-heptenoate, 105665-83-6; ethyl (*E*)-2-methyl-2-acetyl-7-bromo-5-heptenoate, 105665-85-8; (1*R**,2*R**,3*R**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate, 105761-21-5; (1*R**,2*S**,3*R**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate, 105761-22-6; ethyl (*Z*)-2-methyl-2-acetyl-7-iodo-5-heptenoate, 105665-86-9; ethyl (*E*)-2-methyl-2-acetyl-8-bromo-6-octenoate, 105665-92-7; (1*R**,2*S**,3*S**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105665-93-8; (1*R**,2*S**,3*R**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcylohexanecarboxylate, 105761-23-7; (1*R**,2*R**,3*S**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105761-24-8; (1*R**,2*R**,3*R**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105761-25-9; samarium diiodide, 32248-43-4.

Cooperativity and Anticooperativity in Solvation by Water: Imidazoles, Quinones, Nitrophenols, Nitrophenolate, and Nitrothiophenolate Ions†

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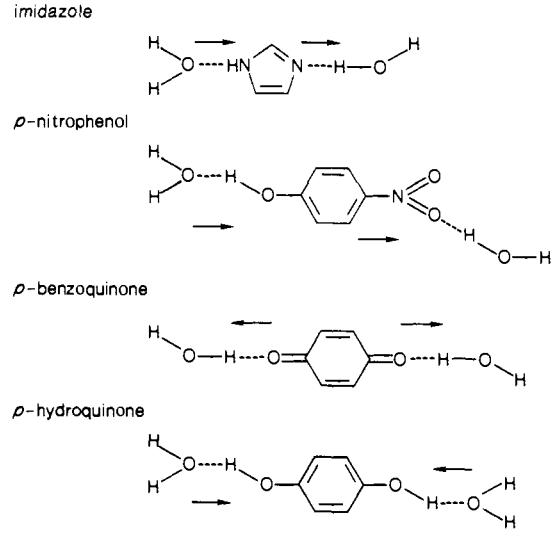
Abstract: Equilibrium constants for transfer from water to vapor, determined by dynamic vapor pressure measurements, show that the hydrophilic character of imidazole (log K(v/w) = −7.2) is no greater than might be expected on the basis of its constituent groups, whereas *p*-nitrophenol (log K(v/w) = −8.6) is about 30-fold more hydrophilic than would be the case if the effects of its constituent groups were additive. In contrast, the *p*-nitrophenolate ion (estimated log K(v/w) = −46) is less hydrophilic, by approximately 15 orders of magnitude, than might be expected if there were no interactions between its substituent groups. Thiopicric acid yields the most hydrophobic benzenoid anion that appears to have been reported thus far, its dissociated tetraethylammonium salt entering methylene chloride from water with an equilibrium constant approaching unity. The hydrophilic character of *p*-benzoquinone (log K(v/w) = −4.3) is much exceeded by that of *p*-hydroquinone (log K(v/w) = −7.5), so that solvent water exerts a major effect on the redox potential of this system. Comparison with model compounds indicates that in both *p*-benzoquinone and *p*-hydroquinone, solvation requirements of the symmetrical polar substituents are in conflict.

When two or more polar groups are present within the same molecule, their combined influence on its equilibrium of transfer from water to vapor, expressed in terms of free energy, if often found to be approximately additive. The regularity of these effects, first noticed by Butler,[1] has been amply confirmed by later investigators.[2-4]

Departures from additivity, observed occasionally, may indicate the presence of special interactions involving different parts of the solute molecule and the solvent that surrounds it. *p*-Nitrophenol[2] and imidazole,[5] for example, might be expected to be exceptionally hydrophilic if hydrogen bonds to solvent water from different parts of these solutes tended to reinforce each other by electronic effects transmitted through the solute molecules themselves (see arrows in Scheme I). For similar reasons, *p*-benzoquinone and hydroquinone might be less hydrophilic than would be anticipated if the effects of their polar substituents were additive.

Each of these potential effects is of biological interest. Side-chain imidazole groups are frequently involved in catalytic processes at the active sites of enzymes; if hydrogen bonding to solvent water were cooperative, then the chemical reactivity of histidine residues in proteins would be sensitive to the detailed environment of their nonreacting portions. The toxic effects of 2,4-dinitrophenol

Scheme I. Potential Electronic Interactions between Solvation Sites



†Supported by Grant No. PCM 7823016 from the National Science Foundation.

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Table I: Equilibrium Constants for Transfer of Imidazole and Related Compounds from Water to Vapor at 20 °C

compound	K_{eq}(vap/aq)	concn (aq)	λ_{max} (ϵ_M)
imidazole	6.6×10^{-8}	0.5–5 M	206 (4644)
1-methylimidazole	5.3×10^{-7}	0.5–5 M	211 (4365)
4-methylimidazole	7.0×10^{-8}	1–5 M	213 (4460)
pyrrole	2.7×10^{-4}	0.1–0.5 M	206 (6680)
1-methylpyrrole	6.9×10^{-3}	0.01–0.05M	212 (6300)
cyclopentadiene	8×10^{-2}	0.0013 M	238 (5300)

Table II. Equilibrium Constants for Transfer of Nitrophenols, Quinones, and Related Compounds from Water to Vapor at 20 °C

compound	K_{eq} (vap/aq)	concn (aq)	λ_{max} (ϵ_M)
o-nitrophenol	2.3×10^{-4}	0.5–10 mM	346 (3160)
m-nitrophenol	4.5×10^{-8}	2–10 mM	332 (2090)
p-nitrophenol	2.35×10^{-9}	10–80 mM	312 (10716)
p-benzoquinone	4.8×10^{-5}	20–150 mM	246 (19950)
p-hydroquinone	3.0×10^{-8}	70–500 mM	288 (2475)
p-methoxyphenol	5.85×10^{-7}	20–200 mM	288 (2445)
benzene	0.22 (ref 13)		
phenol	1.6×10^{-5} (ref 14)		
anisole	0.17 (ref 15)		
nitrobenzene	9.5×10^{-4c} (ref 16)		

are understood to arise from its ability to uncouple oxidative phosphorylation in mitochondria, and the differing solubility properties of its neutral and anionic forms are considered to permit 2,4-dinitrophenol to discharge a transmembrane proton gradient[6] that is essential for ATP biosynthesis. Benzoquinone and hydroquinone are represented in the mitochondrial respiratory chain by derivatives of ubiquinone, and any difference between their strengths of solvation would result in an effect of the local medium on its reduction potential.

To test these possibilities, it seemed desirable to obtain quantitative information about the affinities of imidazole, nitrophenol, benzoquinone, hydroquinone, and related compounds for solvent water. An earlier determination of the free energy of solvation of *p*-nitrophenol[7] appeared to be subject to uncertainty because of difficulties associated with the use of a Knudsen effusion cell for analysis[8] and because the result required a long extrapolation from values observed at high temperatures. This paper describes direct determinations of water-to-vapor distributions of imidazole, nitrophenol, and quinone derivatives. We have also measured the solvent–solvent distribution behavior of polynitrophenolate ions by the procedure of Gustavii,[9] comparing some properties of their fully dissociated tetraalkylammonium salts. Thiopicric acid yields the most hydrophobic benzenoid anion that appears to have been reported thus far.

Materials and Methods

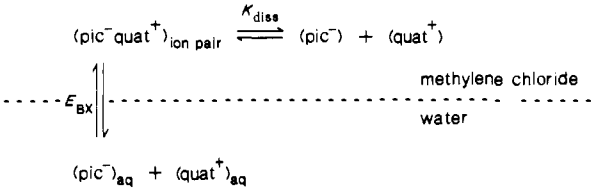
Materials. Nitrophenols, *p*-benzoquinone, *p*-hydroquinone *p*-methoxyphenol, imidazole, 4-methylimidazoles, pyrrole, 1-methylpyrrole, and dicyclopentadiene were purchased from Aldrich Chemical Co, and 1-methylimidazole was purchased from Fluka AG. Nitrophenols, benzoquinone, and hydroquinone were recrystallized from water and imidazole was recrystallized from ethanol. Methylimidazoles, pyrrole, and methylpyrrole were redistilled, and *p*-methoxyphenol was purified by sublimation. Thiopicric acid was synthesized by the method of Sharnin et al.,[10] and cyclopentadiene was generated by pyrolysis of the dimer, followed by distillation as described by Moffett.[11] Comparison of distribution coefficients obtained by repeated extractions from the same sample, and of ultraviolet absorption spectra of material recovered from the nonpolar phase in distribution experiments (see Results), indicated that these preparations did not contain impurities that might have affected the observations described below.

Table III. Equilibrium Constants for Transfer of Tetraalkylammonium Salts from Water to Methylene Chloride at 20 °C

anion	log E_{BX}[a]	log K_{diss}[b]	products
picrate/Me_4N^+	0.18	−4.68	3.2×10^{-5}
picrate/Et_4N^+	2.30	−4.33	9.2×10^{-3}
	(2.34)[d]	(−4.26)[d]	(1.2×10^{-2})[d]
thiopicrate/Me_4N^+	1.36	−4.57	6.1×10^{-4}
thiopicrate/Et_4N^+	4.08	−4.28	0.63
5-nitrosalicylate/Et_4N^+	0.08	−6.16	8.35×10^{-7}
3,5-dinitrosalicylate/Et_4N^+	2.00	−3.91	1.2×10^{-2}

[a] E_{BX} (expressed in L mol^{-1}) is an equilibrium constant describing the concentration of ion pairs in the organic phase divided by the concentrations of the individual ions in the aqueous phase in which dissociation of salts is complete (ref 9). [b] K_{diss} (expressed in mol L^{-1}) is the dissociation constant of the salt in the organic phase (ref 9). [c] Product (unitless) is obtained by multiplying (a) and (b) and is the equilibrium constant for transfer of the dissociated salt from water to the organic phase. [d] Values reported in ref 9.

Scheme II



Methods. Water-to-vapor distribution coefficients were determined at 20 °C by dynamic vapor pressure methods described previously.[12] Experiments carried out at various concentrations of solute in the pot (as indicated in Tables I–III) gave distribution coefficients that did not vary significantly, indicating the absence of self-association in solution at the concentrations studied. Water-to-vapor distributions were also measured for cyclopentadiene, 1-methylpyrrole, and 2-nitrophenol by direct observation, using a gas-tight cuvette of 1 light path (volume 800 mL), manufactured by Zeiss Inc. for use with the model PMQ II spectrophotometer, thermostated at 20 °C. A sample of solute (10 mL) was introduced, by injection through a septum, into a boat contained within this cuvette, whereupon the ultraviolet absorption in the vapor phase was observed to approach an equilibrium value by a process that followed first-order kinetics, with a half-time in the neighborhood of 6 min. Vapor phase extinction coefficients, used to calculate vapor pressures from these measurements, were estimated in separate experiments by injecting cyclohexane containing known concentrations of solute in a volume (0.2 mL) small enough to evaporate completely at room temperature in the cuvette.

Equilibria of transfer of picrate, thiopicrate, 5-nitrosalicylate, and 3,5-dinitrosalicylate from water to methylene chloride were determined by the extraction procedure of Gustavii.[9] Solute concentrations were caused to vary over a wide enough range to permit estimation of equilibrium constants for transfer of the fully dissociated salts from water to methylene chloride and of salt dissociation constants in the organic phase.

Results

Equilibrium constants observed for transfer of imidazole and related compounds from dilute aqueous solution to the vapor phase are assembled in Table I, and the corresponding constants for benzene derivatives are in Table II. These values refer to uncharged solutes and showed no significant variation with changing solute concentrations. Table III presents distribution constants for transfer from water to methylene chloride of tetramethylammonium and tetraethylammonium salts of picrate and related ions at 20 °C. Determination of apparent distribution coefficients as a function of changing concentration showed that the disso-

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Table IV. Equilibrium Constants for Phenol Ionization in Water and Vapor Phase, and for Phenolate Transfer from Water to Vapor at 20 °C

compound	pK_a(vap)[a]	pK_a(aq)[b]	log K_{PheO^-}(vap/aq)[c]
phenol	349.6	9.95	−58.7
o-nitrophenol	333.0	7.23	−50.05
m-nitrophenol	331.2	8.35	−51.3
p-nitrophenol	321.1	7.14	−46.4

[a] Calculated from the data of ref 14. [b] Reference 15. [c] Calculated from the data of Table II, according to Scheme III.

ciation constant of tetraethylammonium picrate in methylene chloride was approximately 5×10^{-5} M under these conditions,[9] and similar values were observed for the other picrate and thiopicrate salts (Table III, column 3, "K_{diss}"). The equilibrium constant for transfer of fully dissociated salts from water to methylene chloride, shown in the final column of Table III, is the arithmetical product of K_{diss} and E_{BX}. The relationship between these terms, adapted from Gustavii et al.,[9] is shown in Scheme II.

Discussion

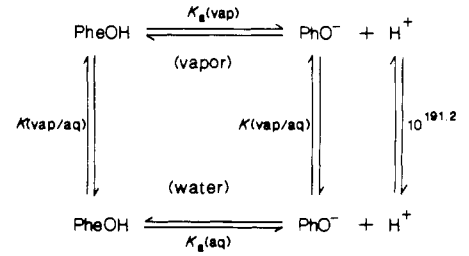
Imidazole and Related Compounds. The present results do not support the notion, suggested in Scheme I, that there is a large degree of cooperativity in hydrogen bonding to solvent water by the two polar groups of imidazole. It will be noted that the increase in hydrophilic character that is observed in passing from pyrrole to imidazole (4000-fold) exceeds the increase in hydrophilic character that is observed in passing from cyclopentadiene to pyrrole (300-fold). However, N-methylation of imidazole reduces its hydrophilic character by a factor of 8, somewhat less than the 25-fold reduction that results from N-methylation of pyrrole in which cooperativity of this kind is not possible. These factors may be compared with reductions of 13-fold in amides and 55-fold in aliphatic amines, when the last nitrogen-bound hydrogen atom is replaced by a methyl group.[12] Accordingly, the hydrophilic character of imidazole does not appear exceptional and may be of the approximate magnitude expected on the basis of its constituent groups.

Nitrophenols, Nitrophenolate, Picrate, and Thiopicrate Ions. *o*-Nitrophenol is about 5 orders of magnitude less hydrophilic than *p*-nitrophenol, in agreement with its ability to form an intramolecular hydrogen bond in the vapor phase that compensates for the loss of hydrogen bonds to solvent water. The negative free energy of formation of the intramolecular hydrogen bond in *o*-nitrophenol must evidently be very large in the vapor phase (in excess of −7 kcal) to explain the observed difference in water affinities between the ortho- and para-substituted phenols. Yet it appears to be broken almost entirely in water, since the pK_a values of *o*- and *p*-nitrophenol in water are almost identical (Table IV), and Kamlet and Taft have shown that the intramolecular H bond in *o*-nitrophenol is broken even in so weak a solvent as anisole.[13] As a result of these effects, the hydrophilic character of *o*-nitrophenol is only a little greater than that of nitrobenzene and less than that of phenol.

The present findings support the proposal by Hine and Mookerjee[2] that the nitro and hydroxyl groups of *p*-nitrophenol interact more strongly with water than do the nitro and hydroxyl groups of nitrobenzene and phenol, respectively. The water-to-vapor distributions of these latter compounds, compared with that of benzene, would lead one to expect a value of approximately 7×10^{-8} for nitrophenols, if the effects of the substituents were additive. This is similar to the value we observe for *m*-nitrophenol, but 30-fold higher than the new value for *p*-nitrophenol.

The present water-to-vapor distribution coefficients, in conjunction with aqueous[14] and vapor-phase[15] pK_a values, make it possible to estimate the relative water-to-vapor distributions of

Scheme III



the various phenolate anions as shown in Scheme III. If the water-to-vapor distribution coefficient of the proton is taken as $10^{-91.2}$,[16] then the water-to-vapor distribution coefficients of these anions can be calculated, with the results shown in Table IV. Evidently the three nitrophenolate ions are less hydrophilic than the phenolate ion, this effect being most pronounced for *p*-nitrophenolate. If the expected effect of a nitro substituent (2.4 orders of magnitude, based on the benzene–nitrobenzene comparison in Table II) is applied to the equilibrium constant for phenolate transfer from water to vapor (Table IV), log *K*(vap/aq) for nitrophenolate would be −61.1. Accordingly, *p*-nitrophenolate is about 14.7 orders of magnitude less hydrophilic than expected on the basis of additivity. This effect can be ascribed to delocalization of charge in the solute and is of a magnitude comparable with the observed difference in hydrophilic character between the ammonium ion and the trimethylammonium ion.[17]

If nitro substitution decreases the hydrophilic character of phenolate ions, then this tendency might be expected to appear in extreme form in 2,4,6-trinitrophenolate. It would be very difficult to test that hypothesis directly in terms of water-to-vapor transfer, with equipment presently available. However, the nonpolarity of the picrate and 2,4-dinitrophenolate ions[18] is familiar to physiologists, and it is often exploited in studies of ion permeability through biological membranes. Earlier work by Gustavii et al.[9] had established that distribution coefficients from water to methylene chloride could be determined for fully dissociated quaternary ammonium salts of picrate, and we extended that work in the present studies to include thiopicrate, 5-nitrosalicylate, and 3,5-dinitrosalicylate. Thiopicrate was chosen for examination because its negative charge was expected to be even more delocalized than in the case of picrate, in accord with earlier comparisons of the gas-phase acidities of phenol and thiophenol.[19,20]

In Table III, "product" is an equilibrium constant for transfer of each fully dissociated salt from water to methylene chloride, expressed in terms of the product of the concentrations of the ions in each phase. By choosing the same cation (e.g., tetraethylammonium), it is possible to compare absolute values for transfer of individual anions. Thiopicrate is evidently less hydrophilic than picrate by a factor of about 50. According to this criterion, thiopicrate may be the least polar simple benzenoid anion that has yet been described.

Benzoquinone, Hydroquinone, and Related Compounds. Water-to-vapor distribution coefficients of quinone-related compounds are shown in Table II. Hydroxylation of benzene increases its water affinity by 4.1 orders of magnitude, but the second hydroxyl group in *p*-hydroquinone produces a further increase of only 2.7 orders of magnitude. Evidently the solvation requirements of the para-oriented hydroxyl groups are in conflict, as might be expected from inductive and resonance effects if each substituent tended to act as a donor in hydrogen bonding to solvent water. When one of the substituent hydroxyl groups is methyl blocked

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in *p*-methoxyphenol, so that it cannot serve as a donor in hydrogen bonding to solvent water, these effects are not observed. Thus, conversion of anisole to *p*-methoxyphenol enhances its water affinity by 5.5 orders of magnitude, even more than expected from the benzene–phenol comparison.

The possibility that solvation of benzoquinone may also be "anticooperative" is clouded by the absence of closely related model compounds for comparison. However, *p*-benzoquinone, with two carbonyl groups, is only 3.7 orders of magnitude more hydrophilic than benzene, whereas acetone, with only a single carbonyl group, is 4.4 orders of magnitude more hydrophilic than propane. This apparent lack of hydrophilic character in *p*-benzoquinone, compared with benzene, may also be related, at least in part, to the absence of aromatic character that might render the π electrons of benzene accessible to hydrogen bonding interactions with solvent water.

p-Benzoquinone is about 3.2 orders of magnitude less strongly solvated by water than is *p*-hydroquinone. Because hydroquinone is so much more strongly solvated than benzoquinone, its reducing power in water is less by approximately 4.3 kcal (0.2 V) than it would be in surroundings of unit dielectric constant. Unless other biological redox pairs are affected to the same extent by removal from solvent water, this is a factor that is likely to affect the relative energies of components of the electron transport chain embedded in the mitochondiral inner membrane, as compared with the values that would be observed in dilute aqueous solution.

Registry No. Imidazole, 288-32-4; 1-methylimidazole, 616-47-7; 4-methylimidazole, 822-36-6; pyrrole, 109-97-7; 1-methylpyrrole, 96-54-8; cyclopentadiene, 542-92-7; *o*-nitrophenol, 88-75-5; *m*-nitrophenol, 554-84-7; *p*-nitrophenol, 100-02-7; *p*-benzoquinone, 106-51-4; *p*-hydroquinone, 123-31-9; *p*-methoxyphenol, 150-76-5; benzene, 71-43-2; phenol, 108-95-2; anisole, 100-66-3; nitrobenzene, 98-95-3; picrate/Me_4N^+, 733-60-8; picrate/Et_4N^+, 741-03-7; thiopicrate/Me_4N^+, 105598-14-9; thiopicrate/Et_4N^+, 105598-15-0; 5-nitrosalicylate/Et_4N^+, 105598-16-1; 3,5-dinitrosalicylate/Et_4N^+, 105598-17-2.

Barbituric Acids as Carbon Acids. Acidity Relationships and ^1H and ^2H Transfer in 1,3-Dimethyl-5-*tert*-butyl- and 5-*tert*-Butylbarbituric Acids[1]

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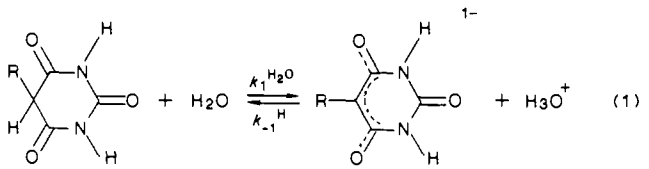
Abstract: Slow ionization and reprotonation at the C_5 carbon atom has been observed for 1,3-dimethyl-5-*tert*-butyl- (1,3-Me_2-5-*t*-Bu), 5-*tert*-butyl- (5-*t*-Bu), 1,3-diisopropyl- (1,3-*i*-Pr_2), and 1,5-diisopropyl- (1,5-*i*-Pr_2) barbituric acids (BA) in aqueous solution at 25.0 °C and I = 0.1 mol dm^{-3} (NaCl). For 1,3-Me_2-5-*t*-Bu(BA) (pK = 9.41) deprotonation follows the rate law $k_f = k_1^{H_2O} + k_1^{OH}[OH^-]$ with $k_1^{H_2O}$ = 4.0 × 10^{-4} s^{-1}, k_1^{OH} = 192 dm^3 mol^{-1} s^{-1} and reprotonation the rate law $k_r = k_{-1}^{H_2O} + k_{-1}^{H}[H^+]$ with $k_{-1}^{H_2O}$ = 8.9 × 10^{-3} s^{-1}, k_{-1}^{H} = 1.12 × 10^6 mol^{-1} dm^3 s^{-1} (pH range 6.91–12.89). For the $^2H(C_5)$ derivative the corresponding dedeuteriation rates are $k_1^{H_2O}$ = 7.7 × 10^{-5} s^{-1} (k_H/k_D = 5.2) and k_1^{OH} = 54 mol^{-1} dm^3 s^{-1} (k_H/k_D = 3.5). Deprotonation is catalyzed by general bases (k^B mol^{-1} dm^3 s^{-1}, k_H/k_D), 2,6-lutidine (0.0108, 10.0), dabco (29.6, 5.5), NH_3 (1.06, 7.1), $EtNH_2$ (14.7, 5.8), Et_2NH (18.0, 7.2), Et_3N (1.30, 7.2), but a linear correlation with pK_{BH} is not observed, and structural effects appear to play an important role. The measurement of precise primary kinetic isotope ratios (k_H/k_D) in water is discussed. In 5-*t*-Bu(BA) (KH_3) ionization at C_5 (pK = 8.09 ± 0.12) to produce the enolate anion (EH_2^-) comes into competition with ionization at imide nitrogen (pK = 7.88 ± 0.04) to produce the keto monoanion (KH_2^-). In strongly alkaline solution the species deprotonated at both imide nitrogen centers (KH^{2-}) is preferred by about 20:1 over the enolate dianion (EH^{2-}) (C_5, and imide nitrogen deprotonated). Such ionizations complicate a study of proton exchange at C_5 but this has been clarified by use of the $^2H(C_5)$ substituted acid (KDH_2). Deprotonation at C_5 occurs via pH independent ($k_1^{H_2O}$ = 2.59 × 10^{-3} s^{-1}, k_H/k_D = 7.1) and OH^- dependent (k_1^{OH} = 800 mol^{-1} dm^3 s^{-1}, k_H/k_D = 3.4) reactions of KH_3 and via the OH^- dependent reaction of KH_2^- (k_2^{OH} = 0.54 mol^{-1} dm^3 s^{-1}). Correspondingly, pathways for reprotonation of the enolate anions are available through the H^+ dependent (k_{-1}^{H} = 3.2 × 10^5 mol^{-1} dm^3 s^{-1}) and pH independent ($k_{-1}^{H_2O}$ = 1.62 × 10^{-3} s^{-1}) reactions of EH_2^- and through the pH independent reaction of EH^{2-} ($k_{-2}^{H_2O} \approx 0.4$ s^{-1}). The known rates of C_5 deprotonation ($k_1^{H_2O}$) and reprotonation (k_{-1}^{H}) for barbituric acids have been correlated with carbon acidity (K_c) via linear Brønsted relationships of slope 0.80 and 0.20, respectively (pK_c range 2.2–9.6). Barbituric acid carbon acidity is thus demonstrated to be controlled largely by substituent effects on the deprotonation reaction.

Two proton transfer studies on barbituric acids have been reported previously. The original classic experiments of Eigen, Ilgenfritz, and Kruse[2] used T-jump to investigate barbituric acid (BA) itself, and Koffer[3] extended this via P-jump and conductimetric detection to the C_5-substituted H, Me, Et, *i*-Pr, and Ph derivatives. These investigations showed that the rate of proton abstraction ($k_1^{H_2O}$), eq 1, varied from 1.33 s^{-1} for R = *i*-Pr to 184



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s^{-1} for R = Ph.[3] Reprotonation rates (k_{-1}^{H}) were, however, more constant at ~10^6 dm^3 mol^{-1} s^{-1} for all substrates irrespective of

(1) Abstracted in part from the Ph.D. Dissertation of Wong, O., University of Otago, 1984 (present address IPRX, University of Kansas Research Program; Lawrence, KS). A preliminary account has been given in *J. Chem. Soc., Chem. Commun.* **1984**, 1440.
(2) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.
(3) Koffer, H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 819.

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