then concentrated to afford 0.085 g of a crude oil, which was purified on silica gel (1:1 (v:v) hexane-acetone) to give 0.069 g (80%) of **19** as a colorless oil. Calcd for $C_{19}H_{33}N_2O_4P$: 384.2177. Found: 384.2178.

To a blue solution of lithium (0.013 g, 1.85 mmol) in 5 mL of dry ethylamine under argon at 0 °C was added dropwise a solution of 0.068 g (1.77 mmol) of **19** in 1 mL of dry THF and 0.02 mL of *tert*-butyl alcohol. The resulting mixture was stirred at 0 °C for 20 min, and then enough solid NH_4Cl was added to destory the excess lithium. Water was added, the mixture warmed to room temperature, and extracted four times with ether. The ethereal layers were dried over potassium carbonate and concentrated to afford 0.038 g (92%) of **20** as an oil: IR 3040, 2990, 2930, 2880, 1630, 1380, 1080, 1030 cm^{-1}; ^1H NMR δ 5.79 (dt, J = 5.88, 2.2 Hz, 1 H), 5.30 (dt, J = 5.88, 2.2 Hz, 2 H), 4.10 (m, 2 H), 3.50 (m, 2 H), 2.72 (d, J = 16.9 Hz, 1 H), 2.07 (dt, J = 16.9, 2.2 Hz, 1 H), 1.88 (s, 2 H), 1.8-1.7 (m, 3 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 1.4-1.3 (m, 2 H), 1.09 (d, J = 9.9 Hz, 1 H). Calcd for $C_{15}H_{22}O_2$: 234.1619. Found 234.1619.

Preparation of *endo*-2,6-Bis(hydroxymethyl)tricyclo[5.2.1.0^{2,6}]dec-3-ene (23). A mixture of 0.071 g (0.3 mmol) of **20**, 0.01 g of *p*-toluenesulfonic acid, and 1.5 mL of dry methanol was stirred under nitrogen for 1 h at room temperature. The methanol was then evaporated, and the residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium bicarbonate and the resulting aqueous layer extracted four times with ethyl acetate. The organic layers were dried over magnesium sulfate and concentrated to give 0.053 g (91%) of **23** as a colorless solid: mp 193-194 °C dec; IR 3600, 3400, 3040, 2960, 2940, 2880, 1630, 1060, 1040 cm^{-1}; ^1H NMR δ 5.95 (dt, J = 5.9, 2.2 Hz, 1 H), 5.34 (dt, J = 5.9, 2.2 Hz, 1 H), 4.03 (d, J = 11.4 Hz, 1 H), 3.98 (d, J = 11.4 Hz, 1 H), 3.5 (br s, 1 H), 2.97 (d, J = 11.4 Hz, 1 H), 2.97 (dt, J = 17.28, 2.2 Hz, 1 H), 2.8 (br s, 1 H), 2.03 (dt, J = 17.28, 2.2 Hz, 1 H), 1.94 (s, 2 H), 1.74 (d, J = 9.9 Hz, 1 H), 1.6-1.3 (m, 4 H), 1.04 (dt, J = 9.9, 1.47 Hz, 1 H). Calcd for $C_{12}H_{18}O_2$: 194.1306. Found: 194.1307.

Acknowledgment. We thank the National Institutes of Health-General Medical Sciences for their generous support of our programs. We express our thanks to Laboratories Fournier SA for making it possible for P.R. to spend this time in our laboratories.

Registry No. (±)-**4**, 67180-07-8; **6** (X = OAc), 72047-94-0; **6** (X = Me_3SiO), 83378-96-5; **6** (X = OH), 81302-80-9; **8**, 17931-56-5; **9**, 83378-86-3; **11**, 83378-87-4; **11** acetonide, 83378-88-5; **12**, 83378-89-6; (±)-**13**, 83378-90-9; **18**, 83378-91-0; (±)-**19**, 83378-92-1; (±)-**20**, 83378-93-2; (±)-**23**, 83378-94-3; (±)-**24**, 83435-70-5; $[(i\text{-PrO})_3P]_4Pd$, 82838-61-7; $[(CH_3)_2N]_2P(O)Cl$, 1605-65-8; $(Ph_3P)_4Pd$, 14221-01-3; 2-methyl-2-propen-1-ol, 513-42-8.

Tautomerism of Phenindione, 2-Phenyl-1,3-indandione, in Dipolar Aprotic/Hydrocarbon Solvent Mixtures[1]

J. D. Pipkin[2b] **and V. J. Stella***[2a]

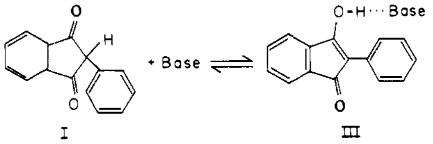
Contribution from the Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas 66045.

Received October 13, 1981

Abstract: Phenindione, 2-phenyl-1,3-indandione, exists in its diketo form in hydrocarbon solvents but enolizes in the presence of dipolar aprotic molecules. The enolization could be easily quantitated since it results in a large spectral shift to longer wavelength. In dilute solutions of phenindione, 5 × 10^{-4} M, and various bases, 0-2 M in cyclohexane, a 1:1 interaction constant could be determined that correlated well with other measures of basicity. The interaction was attributed to a hydrogen bond between the enolic hydrogen and the base. Phenindione is, therefore, proposed as a possible indicator molecule as its tautomerism is very sensitive to changes in solvent basicity and quantitation of the interactions can be determined rapidly by use of simple spectrophotometric measurements.

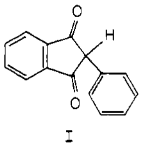
In the course of various investigations into the simultaneous solid to liquid mass transport and ionization of various carbon acids[3-6] including phenindione[5,6] (I), some interesting nonaqueous aprotic chemistry of a phenindione analogue was uncovered.[7] Phenyl-1,3-indandiones appeared to enolize in the presence of dipolar aprotic bases to an extent that qualitatively followed the expected basicity of the interacting bases. Such observations have also been qualitatively observed with other cyclic and acyclic 1,3-diketones.[8-16]

Scheme I

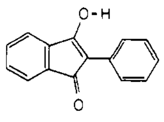


I III

On the basis of these observations, a quantitative study was undertaken to investigate the prototropic equilibrium between the diketo (I) and enol (II) isomers of the cyclic 1,3-dicarbonyl carbon acid, phenindione (2-phenyl-1,3-indandione), in a saturated hydrocarbon solvent, cyclohexane, in the presence of increasing



I



II

---

(1) This work was supported by NIH Grant GM22357 and the University of Kansas General Research Funds.

(2) (a) Address inquires to this author. (b) Current address: Squibb Institute for Medical Research, New Brunswick, NJ 08903.

(3) V. Stella, *J. Pharm. Sci.*, **64**, 706 (1975).

(4) V. Stella and J. D. Pipkin, *J. Pharm. Sci.*, **65**, 1161 (1976).

(5) V. J. Stella and R. Gish, *J. Pharm. Sci.*, **68**, 1042 (1979).

(6) V. J. Stella and R. Gish, *J. Pharm. Sci.*, **68**, 1047 (1979).

(7) The NMR spectrum of chlorindione, 2-(4-chlorophenyl)-1,3-indandione, varied greatly when run in $CDCl_3$ compared to acetone-d_6 and dimethyl-d_6-sulfoxide. Solutions in chloroform were also achromatic while acetone and dimethyl sulfoxide solutions were an intense orange. These observations were consistent with formation of the tautomeric enol isomer in the presence of the basic aprotic solvents.

(8) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattin, *J. Am. Chem. Soc.*, **71**, 1068 (1949).

(9) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954).

(10) L. J. Bellamy and R. F. Branch, *J. Chem. Soc.*, 4491 (1954).

(11) J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2106 (1964).

(12) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **82**, 5426 (1960).

(13) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **84**, 1440 (1962).

(14) Ya. Lindaberg, O. Neiland, A. Veiss, and G. Vanag, *Dokl. Akad. Nauk SSSR*, **154**, 1385 (1964).

(15) H. Hart, *Chem. Rev.*, 79, 515 (1979).

(16) A. I. Kol'tsov and E. M. Kheifets, *Russ. Chem. Rev. (Engl. Transl.)*, **40**, 773 (1971).

0002-7863/82/1504-6672$01.25/0

Table I. Spectral Data for I and IV in Various Solvents and π^* and β Values for Various Solvents

solvent	π^*[a]	β[b]	$\nu(\mathrm{IV})_{\max} \times 10^{-3}$, cm^{-1}	$\nu(\mathrm{I})_{\max} \times 10^{-3}$, cm^{-1}
nonpolar				
cyclohexane	0	0	25.51	*c*
benzene	0.59	0.10	25.12	*c*
chloroform	*d*	*d*	24.88	*c*
polar aprotic				
p-dioxane	0.55	0.37	25.12	23.26
triacetin	NA[e]	NA[e]	24.81	23.04
acetonitrile	0.75	0.31	24.81	22.94
triolein	NA[e]	NA[e]	ND[f]	23.58
ethylacetate	0.55	0.45	25.38	23.81
butylacetate	0.46	ND[f]	25.25	23.47
diethylether	0.27	0.47	25.38	23.81
n-propylether	NA[e]	0.46	25.25	23.47
dioxolone	NA[e]	NA[e]	25.00	22.62
acetone	0.71	0.48	25.00	23.26
γ-butyrolactone	0.87	0.49	24.63	22.83
2-butanone	0.67	0.49	25.00	22.94
cyclohexanone	0.76	0.53	24.88	23.26
dimethylformamide	0.88	0.69	24.57	22.73
triethyl phosphate	0.72	0.77	ND[f]	22.94
dimethyl sulfoxide	1.00	0.76	24.33	22.62
dimethylacetamide	0.88	0.76	24.51	22.73
pyridine	0.87	0.64	24.63	22.47
tetramethylurea	NA[e]	0.78	24.57	22.42
triphenyl phosphate	NA[e]	0.62[g]	ND[f]	ND[f]
N-methyl-2-pyrrolidinone	0.92	0.77	ND[f]	ND[f]
N,*N*-triethylamine	0.14	0.71	ND[f]	ND[f]
2,6-dimethyl-γ-pyrone	NA[e]	0.79	ND[f]	ND[f]
triphenylphosphine oxide	NA[e]	0.94	ND[f]	ND[f]

[a] A solvent polarity scale; see ref 30. [b] A scale of hydrogen-bond-acceptor ability; see ref 29. [c] Could not be determined. [d] Excluded from any calculations because hydrogen-bonding acid. [e] NA means not available. [f] ND means not determined. [g] Unpublished information provided by M. Kamlet.

concentrations of dipolar aprotic molecules.

Formation of the enol isomer was promoted by formation of a hydrogen-bond interaction, as described by Scheme I. The overall objective of this study, therefore, was to explore the possible use of phenindione as an indicator molecule for determining the basicity of various aprotic basic molecules in a condensed hydrocarbon phase where both the substrate, phenindione, and ligand, aprotic basic molecules, were present in dilute concentrations to minimize substrate–substrate and ligand–ligand interactions.

Experimental Section

Materials. All reagents used were of the highest purity commercially available and were used without further purification in most instances.[17] The manufacturer's purity claim was verified by analysis by refractive index and/or gas chromatography. Some of the bases were stored over molecular sieves if residual moisture was a problem.

1-Methoxy-2-phenyl-3-indenone (IV) was prepared by the method of Lindaberg et al.[14] mp 74–75 °C, light yellow plates from multiple recrystallizations from hexane. Anal. Calcd: C, 81.36; H, 5.08. Found: C, 81.49; H, 5.20.

Tetrabutylammonium 2-Phenyl-1,3-indandione Enolate. Equimolar amounts of phenindione and tetrabutylammonium fluoride trihydrate were added to tetrahydrofuran. No precipitate was formed. The mixture was evaporated to dryness, leaving a red residue. The residue was taken up in tetrahydrofuran and cyrstallized out when ethyl ether was added. The red plates were washed with ethyl ether and dried over $CaCl_2$ in a vacuum desiccator, mp 141–142 °C (uncorrected). The NMR and IR spectra and elemental analysis corresponded to the enolate. No fluoride was detectable. Anal. Calcd for $C_{31}H_{45}NO_2$(M_r 463.71): C, 80.29; H, 9.78; N, 3.03. Found: C, 79.62; H, 9.62; N, 2.82.

Spectral Studies. The position of the long-wavelength absorption, 390–450 nm, of phenindione and its *O*-methyl ether (IV) in the nonpolar solvents cyclohexane, benzene, and chloroform was recorded and compared to the wavelength of maximum absorption measured in the polar aprotic solvents. The concentration of phenindione and IV was maintained constant at 5×10^{-4} M in all of the solvents. The spectral measurements were performed on a Cary Model 219 spectrophotometer in a cell compartment maintained (thermostated) at 25 ± 0.05 °C.

The interaction of phenindione with dilute aprotic bases in cyclohexane was also quantitated by spectral methods. The background for this procedure has been discussed previously,[18–25] but basically the procedure involved quantitating the degree of enolization of phenindione (5×10^{-4} M) in solutions of cyclohexane containing various molar concentrations of dipolar aprotic bases.[26] The absorbance change of the solutions in the visible spectra at the wavelength of maximum absorbance for the complex relative to the same solvent mixture containing no phenindione was measured spectrophotometrically on a Varian/Cary Model 219 spectrophotometer. The cell holder and compartment were jacketed and a Haake Model FE circulator was used to maintain temperature at 25 ± 0.05 °C.

The solutions of phenindione show very little absorbance ($\epsilon \leq 3$) in the wavelength range 420–440 nm. Since sample and reference solutions contained equal concentrations of the base, the increase in absorbance at 420–440 nm was attributed to the indenone chromophore formed as a result of the complex (III) and a small amount due to I. From this measured absorbance change an apparent association constant, $K_{1:1}$, was calculated.

The complexation of phenindione with dimethylacetamide was studied by the spectral method at 15, 25, 35, 45, and 55 °C. The temperatures were maintained within ±0.05 °C by use of the circulator–water baths (Haake Model FE and Lauda Brinkman Model RC20B) mentioned previously. The molarities of the dimethylacetamide and phenindione were converted to molarities at other temperatures by using the densities of cyclohexane at the appropriate temperature.[27] There were eight

---

(17) Source of chemicals, lot numbers, purity checks, and methods of purification, where necessary, are available from authors upon request.

(18) M. Nakano, N. I. Nakano, and T. Higuchi, *J. Phys. Chem.*, **71**, 3954 (1967).

(19) C. C. Pimentel and A. L. McClellan, "The Hydrogen Bond", W. H. Freeman, San Francisco and London, 1960, pp 157–212.

(20) M. D. Joesten and L. T. Schaad, "Hydrogen Bond", Marcell Dekker, New York, 1974, p 28.

(21) K. A. Connors and J. A. Mollica, Jr., *J. Pharm. Sci.*, **55**, 772 (1966).

(22) H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949).

(23) G. D. Johnson and R. E. Bowen, *J. Am. Chem. Soc.*, **87**, 1655 (1965).

(24) L. E. Orgel and R. S. Mulliken, *J. Am. Chem. Soc.*, **79**, 4839 (1957).

(25) R. A. LaBudde and M. Tamres, *J. Phys. Chem.*, **74**, 4009 (1970).

(26) I. D. Kuntz, Jr., F. P. Gasparro, M. D. Johnston, Jr., and R. P. Taylor, *J. Am. Chem. Soc.*, **90**, 4778 (1968).

(27) J. Timmermans, "Physico-Chemical Constants of Organic Compounds", Elsevier, Amsterdam, 1950.

Table II. Comparison of the Solvent Dependency of the Visible Spectra of IV and the Tetrabutylammonium Enolate of Phenindione at 25 °C

	solvent (dielectric constant)			
compd	cyclohexane (2.015^a)	benzene (2.274^a)	chloroform (4.806^a)	acetonitrile (37.5^b)
phenindione, methyl ether (IV)	392 (1117)^c	398 (1121)^c	402 (936)^c	404 (1010)^c
tetrabutylammonium enolate		448 (1490)^c	457 (1400)^c	450 (1900)^c

^{a} 20 °C, ref 37. ^{b} 25 °C, ref 38. ^{c} λ_{max}, nm (molar absorptivity).

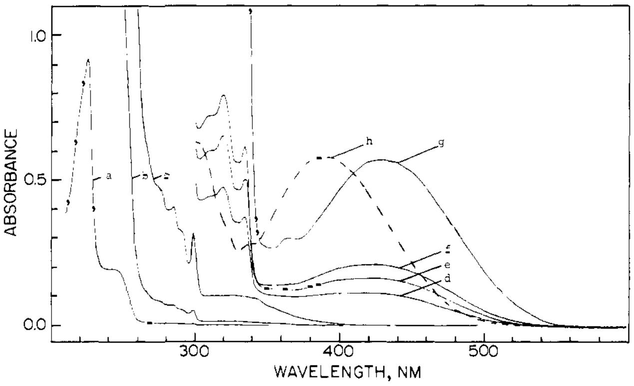


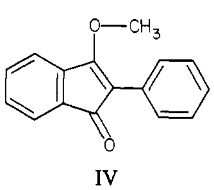
Figure 1. UV/visible spectra of phenindione: 1.5×10^{-5} M (a), 1.0×10^{-4} M (b), and 5.0×10^{-4} M (c) in cyclohexane and 5×10^{-4} M phenindione in dimethylacetamide–cyclohexane mixtures; 0.05 M (d), 0.075 M (e), 0.1 M (f), and 0.5 M (g) and 5.0×10^{-4} M phenindione-methyl ether (IV,h) in cyclohexane.

concentrations of base, between 0.01 and 2 M, while the concentration of phenindione was maintained constant at 5.0×10^{-4} M. The absorption spectra of the ternary mixtures were measured over the range 660–350 nm at temperatures from 15 to 55 °C. The molar absorptivity of the 1:1 and 1:2 (phenindione:dimethylacetamide) complexes were shown to be temperature independent. The association constants, $K_{1:1}$ and $K_{1:2}$, were calculated at each temperature from the absorbance recorded at the wavelength maximum for complex formation.

The complexation of phenindione with pyridine was also studied as a function of temperature. The procedure was as described above; however, absorbance measurements were made on a Perkin-Elmer Model 555 recording spectrophotometer equipped with thermoelectric Peltier module temperature-controlled cell holders.

Results

Spectral Changes of Phenindione in the Presence of Aprotic Bases. The ultraviolet/visible spectrum of phenindione was altered by the presence of dipolar aprotic basic molecules (Table I and Figure 1). The effects of the basic molecules on phenindione relative to its methyl ether, IV, which was incapable of being a proton donor in basic solvents, was to displace the absorption maximum in the visible region to longer wavelengths (bathochromic or red shift).



IV

The low-energy transition (Figure 1, 390–450 nm) in the visible spectrum of phenindione in the presence of dimethylacetamide can be attributed to the 1-indenone chromophore, which was formed upon tautomerization of phenindione. Murray and Cromwell[28] have studied the effects of solvent on the long-wavelength absorption band in 2-methylindenones. The bathochromic shift upon changing to a polar aprotic solvent indicated that the transition responsible for the absorption at ~390 nm probably involves a polar excited state.

Methyl ethers or methyl substituents on active hydrogen-bonding sites have been used as model compounds to assess the magnitude of non-hydrogen-bonding interactions and conversely to affirm a hydrogen-bonded interaction.[14,29] In the present investigation, IV has been used in both senses, to show significant hydrogen bonding and to estimate an approximate molar absorptivity for III.

Compound IV shows an absorption maximum at 392 nm ($\nu(\mathrm{IV})_{max} = 25.51 \times 10^3$ cm^{-1}) in cyclohexane which shifts to 411 nm ($\nu(\mathrm{IV})_{max} = 24.33 \times 10^3$ cm^{-1}) in dimethyl sulfoxide, the most polar solvent listed. The long-wavelength absorption maximum of phenindione in basic solvents showed shifts from 420 nm ($\nu(\mathrm{I})_{max} = 23.81 \times 10^3$ cm^{-1}) in diethyl ether to 446 nm ($\nu(\mathrm{I})_{max} = 22.42 \times 10^3$ cm^{-1}) in tetramethylurea. Kamlet and co-workers[29–31] have made extensive use of chromophore electronic shifts in studies of solvated species and proton affinity of solvents. For example, shifts of 4-nitrophenol have been compared to those of 4-nitroanisole in a series of basic solvents. The shift of 4-nitroanisole represents a correction for the shift caused by solvent polarity.

Unfortunately, since the spectrum of II could not be assessed by non-hydrogen-bonding solvents, a quantitative treatment of the frequency shifts ($\Delta\Delta\nu$) could not be assessed accurately for the phenindione series. However, the relationships of $\nu(\mathrm{I})_{max}$ and $\nu(\mathrm{IV})_{max}$ to π^* and β could be assessed, where π^* represents a solvent polarity scale that combines polarity and polarizability[30] and β represents a scale of hydrogen-bond acceptor ability.[29] With the available data in Table I, $\nu(\mathrm{IV})_{max}$ was found to be linearly correlated with π^* ($n = 16$, $r = 0.934$, $\sigma = 0.12$), as described by eq 1. The $\sigma \times 10^3$ value of 0.12×10^3 cm^{-1} compares with

$$\nu(\mathrm{IV})_{max} \times 10^{-3} = 25.74 - 1.23\pi^* \qquad (1)$$

the 0.10×10^3 cm^{-1} precision expected of "well-behaved" spectra.[30] The correlation was not substantially improved, as expected, on multiple parameter correlation with π^* and β ($n = 15$, $r = 0.934$) given by eq 2 since IV cannot act as an acid. Again with the

$$\nu(\mathrm{IV})_{max} \times 10^{-3} = 25.72 - 1.23\pi^* + 0.0002\beta \qquad (2)$$

available data in Table I, $\nu(\mathrm{I})_{max}$ also showed reasonably good linearity with π^* ($n = 13$ (excluding pyridine which may undergo proton transfer), $r = 0.925$, $\sigma = 0.13$) as described by eq 3, and

$$\nu(\mathrm{I})_{max} \times 10^{-3} = 24.22 - 1.61\pi^* \qquad (3)$$

as expected,[32–35] multiple parameter correlation with both π^* and β did show a modest dependency also on β ($n = 13$ (excluding pyridine), $r = 0.927$), eq 4. If the absorption maximum of II

$$\nu(\mathrm{I})_{max} \times 10^{-3} = 24.26 - 1.56\pi^* - 0.14\beta \qquad (4)$$

in cyclohexane was assumed to be that calculated from eq 3, when π^* was zero, the energies for the enhanced bathochromic shifts were in the range of 5–7 kcal/mol. These values were comparable

---

(28) R. J. Murray and N. H. Cromwell, *J. Org. Chem.*, **41**, 3540 (1976).

(29) M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377 (1976).

(30) M. J. Kamlet, J. L. Abboud, and R. W. Taft, *J. Am. Chem. Soc.*, 99, 6027 (1977).

(31) M. J. Kamlet, A. Solomonovici, and R. W. Taft, *J. Org. Chem.*, **44**, 2599 (1979).

(32) T. Gramstad and J. Sandstrom, *Spectrochim. Acta, Part A*, **25A**, 31 (1969).

(33) (a) T. Gramstad, *Spectrochim. Acta, Part A*, **19A**, 497 (1963); (b) *ibid.* 829 (1963).

(34) T. Gramstad and W. J. Fuglevik, *Spectrochim. Acta, Part A*, **21A**, 343 (1965).

(35) U. Blindheim and T. Gramstad, *Spectrochim. Acta, Part A*, **21A**, 1073 (1965).

to the expected range of hydrogen-bond energies.[19,20,36]

Determination of the Molar Absorptivity of the Phenindione Enol Complex. Neither the molar absorptivity of the enol (II) nor the enol complex (III) can be determined from measurements on solutions in cyclohexane. For placement of a value on the molar absorptivity of the enol, IV and the tetrabutylammonium salt of phenindione were isolated and the solvent effects on the visible spectra of these compounds were characterized.

Solvent effects on the wavelength of maximum absorption and intensity of absorption for IV and the tetrabutylammonium salt are reported in Table II. The principal features of Table II are as follows: (1) As compared to the salt, IV shows consistent bathochromic shifts with increasing solvent polarity; however, the intensity of absorption remains constant. (2) The quaternary salt shows an inconsistent shift in the wavelength of maximum absorption with changing solvent polarity and an increase in intensity in changing solvents from $CHCl_3$ to acetonitrile, an aprotic dipolar solvent with weak proton-accepting ability.

The primary motivation for synthesizing the tetrabutylammonium salt was to determine an apparent maximum absorptivity for the complex in as nonpolar a solvent as possible. The molar absorptivity of the ionized enol should give the hypothetical upper limit for the absorptivity of the complexed enol. The value so obtained for the maximum molar absorptivity should represent the complete transfer of the proton from phenindione enol to base.

As a result of the observations summarized in Table II, IV was chosen as the better model for the enol or enol complex of phenindione. The selection was based upon the following information:

(1) The maximum molar absorptivity expected would be for the enol bearing a negative charge (ionized), i.e., having completely transferred the hydrogen to the base. The maximum molar absorptivitiy reported in Table II for such a species, the tetrabutylammonium salt, in the most nonpolar solvent capable of dissolving the salt was 1490, but the trend was toward lower molar absorptivities as solvent dielectric constant decreased. Hence, the differences between a molar absorptivity of 1100 for the methyl ether and 1490 for the tetrabutylammonium salt in benzene would be predicted to be even smaller in cyclohexane.

(2) The extent of proton transfer within the complex for similar systems has been determined by Gurka and Taft as being less than 30%.[39] Hence, the molar absorptivity of an ionized model, like the tetrabutylammonium salt in solution, would indeed be a poorer model for the hydrogen-bonded enol complex.

Determination of the Association Constants. If it was assumed that the bases interact with phenindione in a 1:1 complex, the interaction could be described by eq 5 and 6:

$$D + B \underset{}{\overset{K_{1:1}}{\rightleftharpoons}} DB \qquad (5)$$

$$K_{1:1} = \frac{[DB]}{([D]_0 - [DB])([B]_0 - [DB])} \qquad (6)$$

where [D] represents phenindione concentration, [B] is the aprotic base concentration, $[D]_0$ and $[B]_0$ are the initial molar concentrations of phenindione and base, respectively, and [DB] is the equilibrium concentration of the complex. If D, B, and DB are the only UV-absorbing species in the region studied spectrophotometrically and only a 1:1 interaction occurs in the concentration range of B studied, then eq 7 follows:

$$OD = \epsilon_D([D]_0 - [DB]) + \epsilon_B([B]_0 - [DB]) + \epsilon_{DB}(DB) \qquad (7)$$

where OD is the total absorbance and ϵ_D, ϵ_B, and ϵ_{DB} are the extinction coefficients for the three species. Since B is always present in excess, the absorbance is measured against a reference containing B_0, and ϵ_D is known, then the absorbance due to the enol (complex) is

$$OD' = OD - \epsilon_D[D]_0 - \epsilon_B[B]_0 \qquad (8)$$

If we let

$$\epsilon' = \epsilon_{DB} - \epsilon_D - \epsilon_B \qquad (9)$$

then

$$OD' = \epsilon'[DB] \qquad (10)$$

The term ϵ' is the net molar absorptivity and can be calculated if it is assumed that $\epsilon_{DB} = \epsilon_{IV}$, where ϵ_{IV} is the molar absorptivity of IV under identical conditions. At 428 nm, $\epsilon_D{}^{428} \leq 3$, and $\epsilon_B{}^{428} \sim 0$, $\epsilon_{IV}{}^{392} = 1117$; therefore, $\epsilon' = 1114$.

Since $[B]_0 \gg [D]_0$ and thus $[B]_0 - [DB] \sim [B]_0$, it follows that

$$\frac{[DB]}{[D]} = \frac{OD'/\epsilon'}{[D]_0 - OD'/\epsilon'} = K_{1:1}[B]_0 \qquad (11)$$

A plot of the left-hand side of eq 11 vs. $[B]_0$ should give a straight line of slope $K_{1:1}$. Figures 2–4 show some representative examples where linear plots were observed. All plots were forced through zero, and considerable scatter can be seen with the poorer ester bases (Figure 2). Where deviation from linearity was observed, at higher concentration, a curve-stripping procedure was necessary to select the concentration range of the aprotic base that met the

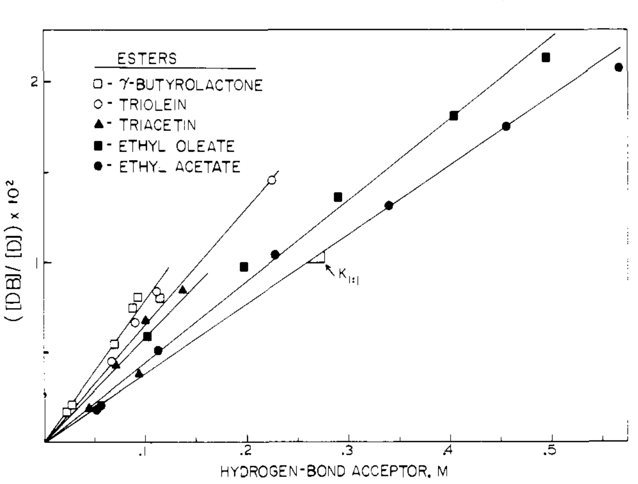


Figure 2. Ratio of the concentration of hydrogen-bonded complex (III) to the concentration of free phenindione vs. the initial molar concentration of ester-type hydrogen-bond acceptors at 25 °C. The calculated least-squares line forced through zero has been drawn through the data points.

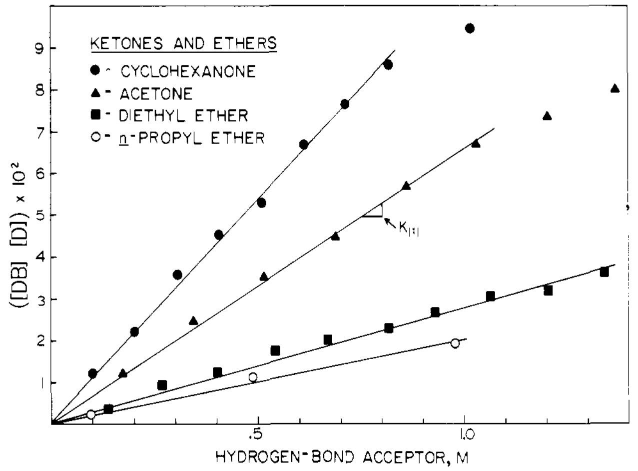


Figure 3. Ratio of the concentration of hydrogen-bonded complex to the concentration of free phenindione vs. the initial molar concentration of ketone- and ether-type hydrogen-bond acceptors at 25 °C. The calculated least-squares line forced through zero has been drawn through the data points.

---

(36) S. M. Vinogradox and R. H. Linnell, "Hydrogen Bonding", Van Nostrand Reinhold, New York, 1971, p 124.

(37) "Handbook of Chemistry and Physics", 59th ed., CRC Press, Cleveland, OH, 1978–1979, p ES6.

(38) J. A. Riddick and W. B. Bunger, "Techniques in Chemistry. Vol. II. Organic Solvents: Physical Properties and Methods of Purification", 3rd ed., Wiley-Interscience, New York, 1970.

(39) D. Gurka and R. W. Taft, *J. Am. Chem. Soc.*, 91, 4794 (1969).

Table III. Experimental Conditions and Equilibrium Constants for the Formation of Hydrogen-Bonded Complexes of Phenindione in Mixtures of Basic Solvents and Solutes in Cyclohexane at 25 °C

base	$[B]_0/[D]_0$[a]	λ, nm	$K_{1:1}$[b] ± SE, $dm^3 mol^{-1}$	extreme $[B]_0$ for linearity, M
n-propyl ether	200-2000	420	0.0204 ± 0.0010	1.0
diethyl ether	270-19 100	424	0.0279 ± 0.0004	1.3
ethyl acetate	230-1135	428	0.0382 ± 0.0008	0.57
ethyl oleate	200-1000	428	0.0447 ± 0.0003	0.50
triacetin	90-270	428	0.0584 ± 0.0060	0.14
triolein	100-450	428	0.0645 ± 0.0040	0.11
triphenyl phosphate	30-250	428	0.868 ± 0.014	0.10
pyridine	250-25 000	420	1.061 ± 0.010	0.38
acetone	350-27 000	428	0.0658 ± 0.0005	1.0
γ-butyrolactone	24-230	420	0.0774 ± 0.0036	0.12
cyclohexanone	200-19 200	430	0.1068 ± 0.0010	0.82
N,*N*-dimethylpivalamide	20-200	428	1.689 ± 0.027	0.10
N,*N*-dimethylformamide	30-1200	426	2.321 ± 0.037	0.07
N,*N*-dimethylbutyramide	20-200	428	3.192 ± 0.027	0.05
N,*N*-dibutylformamide	20-200	428	3.140 ± 0.093	0.04
N,*N*-dimethylpropionamide	20-100	428	3.174 ± 0.035	0.05
N,*N*-diisopropylformamide	20-200	428	3.520 ± 0.074	0.05
N,*N*-dimethylvaleramide	20-200	428	3.752 ± 0.035	0.06
N,*N*-diethylformamide	20-200	428	2.927 ± 0.043	0.05
1,1,3,3-tetramethylurea	10-16 700	428	4.047 ± 0.017	0.05
N,*N*-dimethyldodecamide	20-200	427	4.110 ± 0.039	0.05
N,*N*-dimethylacetamide	20-21 500	428	5.10 ± 0.10	0.04
N-methyl-2-pyrrolidinone	10-20 700	428	6.17 ± 0.10	0.02
1,3-dimethyl-2-imidazolidinone	12-1400	428	6.797 ± 0.089	0.05
triethylamine	1-6	430	6.811 ± 0.073	0.003
2,6-dimethyl-γ-pyrone	4-30	428	7.68 ± 0.13	0.009
dimethyl sulfoxide	3-50	424	7.772 ± 0.078	0.013
triethyl phosphate	1-11 800	428	8.322 ± 0.051	0.005
n-decylmethyl sulfoxide	4-44	428	12.84 ± 0.15	0.012
triphenyl phosphine oxide	1-6	430	68.83 ± 0.83	0.0015

[a] Entire experimental range, where $[D]_0 = 5 \times 10^{-4}$ mol dm^{-3}. [b] Only in dilute solutions of base (typically <0.1 M) and giving linear relationship according to eq 11.

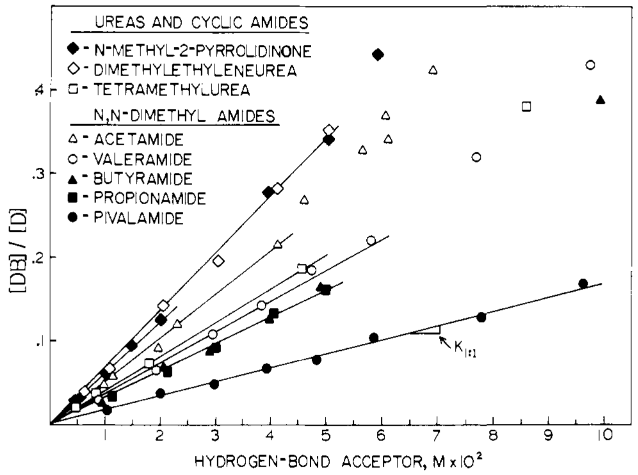


Figure 4. Ratio of the concentration of hydrogen-bonded complex to the concentration of free phenindione vs. the initial molar concentration of amide- and urea-type hydrogen-bond acceptors at 25 °C. The calculated least-squares line forced through zero has been drawn through the data points.

assumption of 1:1 stoichiometry and consequently gave a linear plot as indicated by eq 11.[40] Values obtained for $K_{1:1}$ in this manner in the solvent systems studied are included in Table III. The standard error in the association constant is the calculated standard error in the slope and reflects the errors in the experimental spectral measurements and any deviations from the assumption of linearity.

Calculation of 1:1 Association Constants Assuming the Molar Absorptivity of the Complex Is Unknown. The method employed by Kostenbauder and Higuchi[41] for determination of association constants from UV/visible spectrophotometric data and adapted for polarimetric data by Meier and Higuchi[42] was used. Assume that in dilute solutions of phenindione and base that 1:1 interactions predominate and that no self-association of phenindione or the base takes place. Hence for the interaction between phenindione, D, and base, **B**, the same equilibrium holds as stated previously by eq 5. Equation 6 can be rearranged to give eq 12.

$$[DB] = \frac{[D]_0[\mathbf{B}]_0 + [DB]^2}{1/K_{1:1} + [D]_0 + [B]_0} \tag{12}$$

If we assume initially that $[DB]^2 \ll [D]_0[B]_0$, then it can be shown that

$$\frac{[D]_0[B]_0}{OD'} = \frac{[D]_0 + [B]_0}{\epsilon'} + \frac{1}{K_{1:1}\epsilon'} \tag{13}$$

By plotting the left-hand side of eq 13 against the sum of the initial concentrations of phenindione and base, the molar absorptivity of the complex can be obtained from the reciprocal of the slope and the equilibrium constant can be obtained by dividing the slope by the intercept.

Because $[DB]^2$ may not be negligible, the equilibrium constant calculated above is only an approximate value. Equation 12 may be rearranged without neglecting the $[DB]^2$ term,

$$[DB]^2 - [DB]([B]_0 + [D]_0 + 1/K_{1:1}) + [D]_0[B]_0 = 0 \tag{14}$$

and

$$[DB] = ([D]_0 + [B]_0 + 1/K_{1:1} - [([D]_0 + [B]_0 + 1/K_{1:1})^2 - 4[D]_0[B]_0]^{1/2})/2 \tag{15}$$

---

(40) Points were selected for the linear portion upon the following criteria: the first three points (the lowest base concentrations) were used to construct the first linear estimate and additional points were added individually, if its ordinate value was within three standard deviations of value estimated for it by the previous line. The association constant, $K_{1:1}$ is given by the slope of this plot.

(41) H. B. Kostenbauder and T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 518 (1956).

(42) J. Meier and T. Higuchi, *J. Pharm. Sci.*, **54**, 1183 (1965).

Table IV. Equilibrium Constants for Formation of Hydrogen-Bonded Complexes of Phenindione with Bases in Cyclohexane at 25 °C according to the Iterative Method, Eq 13-16

base	$K_{1:1}{}^a$ ± SE, $\mathrm{dm^3\,mol^{-1}}$	$\epsilon'_{1:1}$ ± SE, $\mathrm{mol^{-1}\,cm^{-1}}$
triphenyl phosphate	0.83 ± 0.02	1133 ± 23
pyridine	0.84 ± 0.03	1343 ± 46
dimethylformamide	3.10 ± 0.30	1013 ± 34
tetramethylurea	4.34 ± 0.75	1050 ± 180

[a] Determined only in dilute solutions of bases where 1:1 stoichiometry predominates.

Thus, from the initial concentrations of D and B and the value for $K_{1:1}$ calculated from eq 13, the complex concentration, [DB], can be calculated from eq 15. If eq 12 is combined with eq 10 without neglecting the $[\mathrm{DB}]^2$ term, then the following exact equation is obtained:

$$\frac{([\mathrm{D}]_0[\mathrm{B}]_0 + [\mathrm{DB}]^2)}{\mathrm{OD}'} = \frac{[\mathrm{D}]_0 + [\mathrm{B}]_0}{\epsilon'} + \frac{1}{K_{1:1}\epsilon'} \tag{16}$$

The complex equilibrium constant obtained from a plot to the left-hand side of eq 16 against $([\mathrm{D}]_0 + [\mathrm{B}]_0)$ should be a better estimator of $K_{1:1}$ than that obtained from eq 13. With the new value of $K_{1:1}$, [DB] was recalculated from eq 15 and this value used again in eq 16. These computations were continued, and the criterion for acceptance of constant [DB] and $K_{1:1}$ values was no more than a 0.01% difference between successive values of $K_{1:1}$. Final values for the molar absorptivity, ϵ', and equilibrium constant, $K_{1:1}$, are contained in Table IV. The values of ϵ' compare very favorably to ϵ' calculated from the extinction coefficient for IV.

Determination of Association Constants Assuming Multiple Complex Equilibria and Known and Unknown Molar Absorptivities for the Complexes. The analysis of spectrophotometric data up until now has only considered the data from dilute solutions of the base. In dilute solution the predominant interactions were assumed and appeared to be only 1:1. The method of Connors and Rosanske[43] and also of Hudson et al.[44] for analyzing spectral data over a broader base concentration profile, where multiple equilibria may be involved, was attempted.

Figure 5 describes the change in absorbance (OD′) at a fixed wavelength produced by phenindione over a large concentration range of selected bases in cyclohexane. The curves have a shape characteristic of simple 1:1 complexing; however, extension of previous methods of analysis from dilute to more concentrated solutions of base shows curvature suggestive of higher order complexes in base species.

The complex formation equilibria between D and base, B, may be represented as

$$\mathrm{D} + \mathrm{B} \rightleftharpoons \mathrm{DB} \overset{+\mathrm{B}}{\rightleftharpoons} \mathrm{DB}_2 \overset{+\mathrm{B}}{\rightleftharpoons} \ldots\mathrm{DB}_n \tag{17}$$

and the equilibrium constants for the formation of each complex are

$$K_{1:1} = \frac{[\mathrm{DB}]}{[\mathrm{D}][\mathrm{B}]} \tag{18}$$

and

$$K_{1:n} = \frac{[\mathrm{DB}_n]}{[\mathrm{DB}_{n-1}][\mathrm{B}]} \tag{19}$$

where $K_{1:1}$ and $K_{1:n}$ are concentration constants. The mass balances on D and B are

$$\begin{aligned} D_0 &= [\mathrm{D}] + K_{1:1}[\mathrm{D}][\mathrm{B}] + K_{1:1}K_{1:2}[\mathrm{D}][\mathrm{B}]^2 + \ldots \\ &= [\mathrm{D}](1 + K_{1:1}[\mathrm{B}] + K_{1:1}K_{1:2}[\mathrm{B}]^2 + \ldots) \end{aligned} \tag{20}$$

The absorbance for unit path length phenindione solution containing base vs. a reference solution containing just the base at an equivalent concentration is given by application of the Beer–Lambert law:

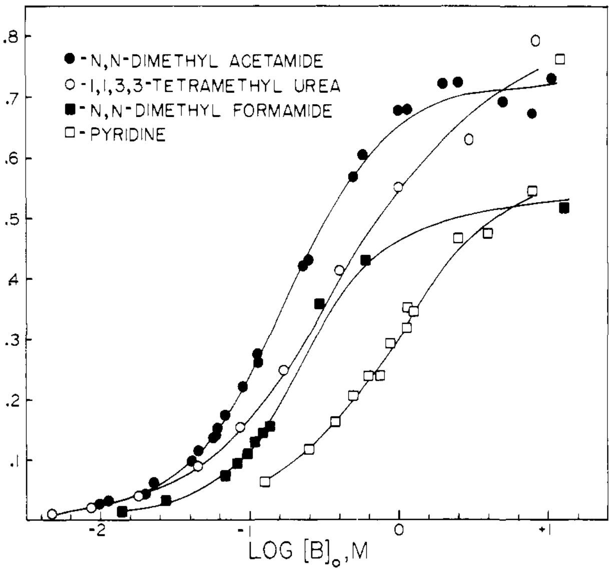


Figure 5. Change in absorbance produced by the initial concentration of dimethylacetamide (●) at 428 nm, tetramethylurea (○) at 428 nm, dimethylformamide (■) at 426 nm, and pyridine (□) at 420 nm in their respective systems. The initial phenindione concentration was 5 × 10^{-4} M. The smooth curve was calculated with eq 22 and 23 and the appropriate constants from Table V.

$$\mathrm{OD} = \epsilon_{\mathrm{D}}[\mathrm{D}] + \epsilon_{1:1}[\mathrm{DB}] + \epsilon_{1:2}[\mathrm{DB}_2] + \ldots \tag{21}$$

where OD is the optical density (absorbance) and $\epsilon_{\mathrm{D}}, \epsilon_{1:1}, \epsilon_{1:2}$, etc. are the molar absorptivities of phenindione and complexes, respectively.

We define $\mathrm{OD}' = \mathrm{OD} - \epsilon_{\mathrm{D}}[\mathrm{D}]_0$, $\epsilon'_{1:1} = \epsilon_{1:1} - \epsilon_{\mathrm{D}}$, $\epsilon'_{1:2} = \epsilon_{1:2} - \epsilon_{\mathrm{D}}$, etc., such that the net absorbance, OD′, is related to the free base concentration [B] by the mass balance on D. Since only two equilibrium constants (or four parameters: $K_{1:1}$, $\epsilon'_{1:1}$, $K_{1:2}$, $\epsilon'_{1:2}$) were necessary to describe the curves in Figure 5, the relationship between OD′ and free base concentration is

$$\mathrm{OD}' = \frac{[\mathrm{D}]_0 K_{1:1}[\mathrm{B}](\epsilon'_{1:1} + \epsilon'_{1:2}K_{1:2}[\mathrm{B}])}{1 + K_{1:1}[\mathrm{B}] + K_{1:1}K_{1:2}[\mathrm{B}]^2} \tag{22}$$

From the mass balance on B

$$[\mathrm{B}]_0 = [\mathrm{B}] + \frac{[\mathrm{D}]_0 K_{1:1}[\mathrm{B}](1 + 2K_{1:2}[\mathrm{B}])}{1 + K_{1:1}[\mathrm{B}] + K_{1:1}K_{1:2}[\mathrm{B}]^2} \tag{23}$$

Since it was too cumbersome to explicitly express OD′ as a function of the initial base concentration, $[\mathrm{B}]_0$, a computer program was used to fit the data in Figure 5. The program used the simplex method of least squares[45,46] to solve eq 22 and 23 simultaneously, thereby optimizing the variables $K_{1:1}$, $K_{1:2}$, $\epsilon'_{1:1}$, and $\epsilon'_{1:2}$. However, values of $\epsilon'_{1:1}$ were constrained by previously determined values or fixed to the molar absorptivity of IV. Values of $\epsilon'_{1:2}$ were limited to $\epsilon'_{1:1} \sim \epsilon'_{1:2} \leq 2000$. Since OD′ in Figure 5 tends to increase with increasing initial base concentration with slight plateauing at higher concentrations of base, $\epsilon'_{1:2}$ was generally of the same magnitude as $\epsilon'_{1:1}$ and $\epsilon'_{1:2}$ and was expected to be less than 2000. Figure 5 is a plot of OD′ vs. log $[\mathrm{B}]_0$ for phenindione plus several base mixtures in cyclohexane. The smooth curves in this figure were drawn by substituting into eq 22 and 23 the values of $K_{1:1}$, $K_{1:2}$, $\epsilon'_{1:1}$, and $\epsilon'_{1:2}$ listed in Table V. The sum of squares of percent deviation of the experimental from calculated net absorbances, OD′, was minimized, thereby giving a weight inversely proportional to the net absorbance. The square root of the sum of squares of percent deviation divided by the degrees of freedom (the number

---

(43) K. A. Connors and T. W. Rosanske, *J. Pharm. Sci.*, **69**, 173 (1980).

(44) R. A. Hudson, R. M. Scott, and S. N. Vinogradov, *Spectrochim. Acta, Part A*, **26A**, 337 (1970).

(45) S. N. Deming and S. L. Morgan, *Anal. Chem.*, **45**, 278A (1973).

(46) S. N. Deming and S. L. Morgan, *Anal. Chem.*, **46**, 1170 (1973).

Table V. Equilibrium Constants for the Formation of Hydrogen-Bonded Complexes of Phenindione with Aprotic Basic Molecules in Cyclohexane at 25 °C according to Computer Optimization Fitting to Eq 22 and 23

base	concn range, M	$K_{1:1}$, dm^3 mol^{-1}	$K_{1:2}$, dm^3 mol^{-1}	$\sigma\%^a$
cyclohexanone	0–1	0.109		4.6^b
triphenyl phosphate	0–0.1	0.86		8.5^b
pyridine	0–10	0.99	0.27	2.3^b
		0.98	0.31 (1091)	2.2^c
dimethylformamide	0–10	1.83	4.44	7.4^b
		1.80	5.32 (1020)	6.6^c
tetramethylurea	0–10	3.86	1.84	11.8^b
		3.98	0.57 (1563)	4.2^c
dimethylacetamide	0–10	4.39	7.08	12.5^b
		4.63	3.82 (1443)	1.9^c
dimethyl sulfoxide	0–0.025	6.97		9.4^b

[a] $\sigma\%$ is the square root of the sum of the squares of percent deviation between calculated and observed OD' divided by the degrees of freedom. [b] $\epsilon'_{1:1} = \epsilon'_{1:2} = 1114$. [c] $\epsilon'_{1:1} = 1114$ and $\epsilon'_{1:2}$ allowed to vary freely, convergent value in parentheses.

Table VI. Thermodynamic Parameters for the Formation of Hydrogen-Bonded Complexes of Phenindione in Cyclohexane

parameter	temp, °C 15	25	35	45	55
	N,*N*-Dimethylacetamide				
$K_{1:1}$,^{a} dm^3 mol^{-1}	5.60	4.33	3.46	2.77	2.25
$\Delta G°$, kcal mol^{-1}		-0.87 ± 0.01^c			
$\Delta H°$, kcal mol^{-1}		-4.27 ± 0.03			
$\Delta S°$, eu (cal deg^{-1} mol^{-1})		-11.4 ± 0.1			
$K_{1:2}$,^{a} dm^3 mol^{-1}	4.10	3.64	2.81	2.41	2.13
$\Delta G°$, kcal mol^{-1}		-0.73 ± 0.05			
$\Delta H°$, kcal mol^{-1}		-3.11 ± 0.12			
$\Delta S°$, eu		-8.0 ± 0.4			
$\sigma\%$	5.2	3.4	2.1	1.9	3.3
	Pyridine				
$K_{1:1}$,^{b} dm^3 mol^{-1}	1.48	1.04	0.75	0.56	0.43
$\Delta G°$, cal mol^{-1}		-25.5 ± 0.4			
$\Delta H°$, kcal mol^{-1}		-5.83 ± 0.07			
$\Delta S°$, eu		-19.5 ± 0.2			
$\sigma\%$	5.2	3.4	1.7	0.8	1.2

[a] Constants determined from computer curve fit with $\Delta\epsilon'_{1:1} = 1114$ and $\Delta\epsilon'_{1:2} = 1440$. [b] Constants determined from computer curve fit with $\Delta\epsilon'_{1:1} = 1114$ only in region where 1:1 predominates. [c] Standard error as determined from standard error in the slope and intercept of the van't Hoff plot.

of points minus two) is listed in Table V under the column labeled $\sigma\%$; smaller values of $\sigma\%$ indicate a better fit.

Thermodynamic Study. The temperature dependence of the 1:1 and 1:2 complex association constant between phenindione and dimethylacetamide and the 1:1 equilibrium constant for the interaction between phenindione and pyridine was studied spectrophotometrically at five temperatures between 15 and 55 °C. Although complexation between phenindione and pyridine had been described by both 1:1 and 1:2 (phenindione:pyridine) complexes, the concentration range (<1 M) was such that only the 1:1 complex was necessary to define the system.

The equilibrium association constants were determined at each temperature by simultaneous computer optimization of eq 22 and 23 such that the relation between change in absorbance due to complexation and the initial base concentration was defined. The values calculated for the association constants are presented in Table VI, along with $\sigma\%$, the square root of the percent deviation of the observed absorbances from those calculated with the optimized constants.

The van't Hoff equation was used to obtain enthalpy, $\Delta H°$, and entropy, $\Delta S°$, of complex formation from the estimates of $K_{1:n}$ at several temperatures. Assuming $\Delta H°$ was constant over the temperature range studied, a plot of log $K_{1:n}$ vs. $1/T$ K gave excellent straight lines. Free energy, enthalpy, and entropy of complex formation for $T = 298$ K, calculated from association constant and the slopes and intercepts, are presented in Table VI. These values are all negative in sign, where the favorable change in free energy has a large favorable enthaipic contribution compensated in part by an unfavorable decrease in entropy.

Discussion

Evidence for a Hydrogen-Bonding Interaction between Phenindione and Aprotic Basic Molecules. Basic molecules, as defined by Lewis,[47] appear to interact with phenindione, causing a shift in the protomeric equilibrium to the phenindione enol. In the absence of these basic molecules, the enol of phenindione was not observed in cyclohexane solutions. In the presence of the bases, the formation of a hydrogen-bonded enol complex stabilizing the enol tautomer relative to the diketo tautomer was believed to account for the noted shift in keto–enol equilibrium. The following evidence substantiated the formation of the hydrogen-bonding complex: (1) According to Pauling,[48] hydrogen bonding was most likely to occur when the hydrogen atom was between two electronegative atoms like the oxygen of the enol bearing the hydrogen and, for instance, an oxygen of a basic carbonyl function. Furthermore, the acidic nature of phenindione and basic nature (electron-donating ability) of the molecules studied suggested the possibility of an acid–base type interaction. The aqueous pK_a's of phenindione are pK_a(diketo) = 4.1 and pK_a(enol) = 2.4,[5,6] which show that the diketo phenindione is an unusually strong carbon acid and that the more acidic hydrogen is the one on the enol oxygen. In an aprotic solvent of low dielectric constant, such as cyclohexane, reaction between a proton donor and proton acceptor may lead either to the formation of a hydrogen-bonded complex or an ion pair, but not complete ionization or proton transfer, as would accompany a typical acid–base reaction in aqueous media.[49,50] A considerable amount of charge generation and separation occurs in ion-pair formation, so that only hydrogen-bonded complexes will form, unless energy can be supplied by some other process, like electron delocalization.[50] Gurka and Taft[39] concluded from fluorine NMR studies of hydrogen-bonded complex formation that in carbon tetrachloride (CCl_4), *p*-fluorophenol (*p*-FC_6H_4OH) formed only hydrogen-bonded complexes with all of the bases used in the present study with the possible exception of triethylamine. Also, their results were consistent with the hydrogen-bonded complex having a well-defined and relatively low extent (≤30%) of apparent proton transfer. In the present study, the low pK_a of phenindione might suggest that ion-pair formation was possible while the experimental evidence was against it. On the other hand, as suggested by Kreevoy and Chang,[51] a resonance hybrid might exist where partial proton transfer between the donor and acceptor was possible such that the absorption spectrum of the complex changed continuously from that predicted by complexation with no proton transfer toward that predicted for ion-pair formation.[51] (2) Qualitatively, the magnitudes of the enhanced bathochromic shifts corresponding to 5–7 kcal mol^{-1} observed for the enol relative to the methyl ether of phenindione increased with solvent basicity and were consistent with hydrogen-bond energies.[19,20,28,38] (3) The relative magnitudes of the 1:1 association constants determined in dilute solutions of phenindione and base are recorded in Table III. These constants followed the expected qualitative relationship to the relative basicity of the different functional groups represented in the table.[52,53] Furthermore, it will be established that a quantitative

---

(47) G. N. Lewis, "Valence and the Structure of Atoms and Molecules", The Chemical Catalogue Co., New York, 1923, p 142.

(48) L. Pauling, "The Nature of the Chemical Bond", 3rd ed., Cornell University Press, Ithaca, New York, 1960.

(49) M. M. Davis, "Acid-Base Behavior in Aprotic Organic Solvents", National Bureau of Standards Monograph 105, 1968, Chapter 4.

(50) J. E. Crooks and B. H. Robinson, *Symp. Faraday Soc.*, **10**, 29 (1975).

(51) M. M. Kreevoy and K.-C. Chang, *J. Phys. Chem.*, **80**, 25 (1976).

(52) D. Hadzi, "Hydrogen Bonding", Pergamon Press, New York, 1957.

(53) E. M. Arnett, E. J. Mitchell, and T. S. S. R. Murty, *J. Am. Chem. Soc.*, **96**, 3875 (1974).

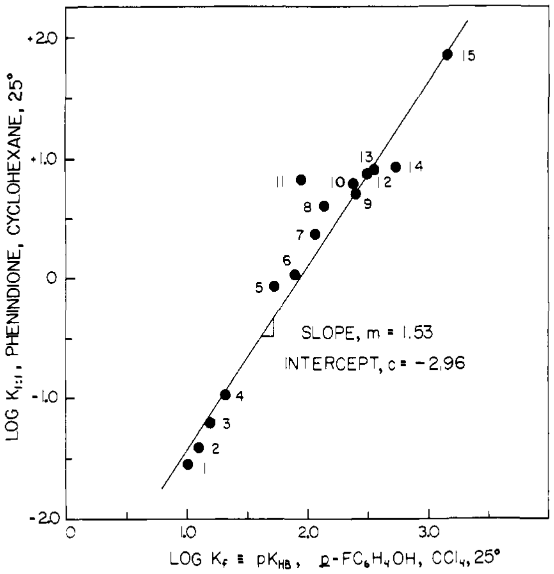


Figure 6. Linear free energy relationship for hydrogen-bonded complex formation with phenindione in cyclohexane (ordinate) and p-FC_6H_4OH in CCl_4 (abscissa), both at 25 °C: (1) diethyl ether; (2) ethyl acetate; (3) acetone; (4) cyclohexanone; (5) triphenyl phosphate; (6) pyridine; (7) dimethylformamide; (8) tetramethylurea; (9) dimethylacetamide; (10) *N*-methyl-2-pyrrolidinone; (11) triethylamine; (12) 2,6-dimethyl-8-pyrone; (13) dimethyl sulfoxide; (14) triethyl phosphate; (15) triphenylphosphine oxide.

relationship existed between these 1:1 association constants and constants for other hydrogen-bonding systems, e.g., the hydrogen-bond basicity scale established by Arnett[53] and Taft[54] that used the equilibrium constant for hydrogen-bonded complex formation between p-fluorophenol and basic species in CCl_4 as the standard reference system. (4) The observed enthalpy and entropy for the interaction between phenindione and dimethylacetamide and pyridine in cyclohexane was consistent with thermodynamic values for hydrogen-bond formation reported in the literature, where the bonding is homogeneous, O–H···O ($-\Delta H^\circ$ = 3–6 kcal mol^{-1}, $-\Delta S^\circ$ = 12–15 eu), and heterogenous, O–H···N ($-\Delta H^\circ$ = 2–8 kcal mol^{-1}, $-\Delta S^\circ$ = 15–18 eu).[19,20,36]

Correlation of 1:1 Formation Constants with Hydrogen-Bonding Effects. Arnett,[53] Taft,[54] and others[39,55] have chosen p-FC_6H_4OH as the standard reference acid in studies of hydrogen-bonded complexation. From the equilibrium constants for the interaction of p-FC_6H_4OH with basic species in CCl_4, Taft[54] constructed the pK_{HB} scale of basicity. Other measures of basicity were related to pK_{HB} through eq 24 and 25,[54] where K_f is the formation constant

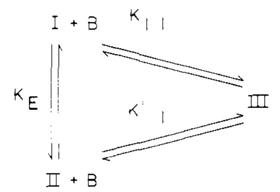
$$\log K_f = m \log (K_f)_0 + c \qquad (24)$$

$$pK_{HB} = \log (K_f)_0 \qquad (25)$$

for the hydrogen-bonded complex between a specific hydrogen-bond donor and various bases in a specific solvent and a particular temperature while $(K_f)_0$ is the reference formation constant for the complex between p-FC_6H_4OH and different bases in CCl_4 at 25 °C. The form of eq 24 is typical of the linear free energy relationships which can be constructed for interaction constants, K_f, for different reference acids, different temperatures, and different condensed phases, e.g., cyclohexane, methylene chloride, chloroform, etc. The parameters m and c of eq 24 are constants characteristic of the reference acid, solvent, and temperature.

Figure 6 is a plot of $\log K_{1:1}$ vs. pK_{HB} according to eq. 24 for those bases that have been studied under both systems. The parameters for eq 24 describing the line in Figure 6 are listed in Table VII along with parameters from other systems with different reference acids in CCl_4.[53]

Scheme II



The values for m and c from the present investigation have contributions not only from the difference in reference acid, phenindione, but also from the difference in solvent used, cyclohexane vs. CCl_4. Joris et al.[55] studied the effects of changing solvents on the linear free energy relationships in hydrogen-bonded complex formation using p-FC_6H_4OH as the reference acid. The m and c values for different solvents both decrease with increasing solvent polarity while m and c tend to increase with decreasing aqueous pK_a of the aliphatic acids. The m and c values for the aromatic acids were distinctly less than their aqueous pK_a would suggest, providing the trend in the aliphatic acids could be extended to the aromatic acids. The observations suggested that the larger m value obtained from the relationship between the complex formation constants derived from the present study and those for p-FC_6H_4OH was due in large part to the much smaller pK_a of the enol of phenindione and to a minor extent the change in solvent from CCl_4 to cyclohexane. The larger value of m, consistent with the greater acidity of phenindione relative to the other reference acids, points out the greater sensitivity of phenindione enolization to basicity changes relative to the interactions of the bases with other reference acids.

Since the β scale was found to be linear with pK_{HB}, the $\log K_{1:1}$ values were also expected to be linear with β. The correlations are described by eq 26 (n = 17, r = 0.980, σ = 0.22) and eq 27

$$\log K_{1:1} = -4.61 + 7.03\beta \qquad (26)$$

$$\log K_{1:1} = -4.61 + 6.99\beta \qquad (27)$$

(n = 16 (triethylamine excluded), r = 0.985, σ = 0.19). The coefficient for β of ~7 compared with 4.3 for p-FC_6H_4OH complexes in cyclohexane was consistent with the greater acidity of phenindione.

Phenindione has two aqueous pK_a's, pK_a(diketo) and pK_a(enol).[5,6] The proper choice for acidity comparisons was pK_a(enol) since this was the apparent site of the hydrogen bonding. In light of the generalization made above, the magnitude of c in the present correlation was large and negative. This discrepancy in c was affected by the definition of $K_{1:1}$. Also, the magnitudes of some of the 1:1 constants as defined by $K_{1:1}$ were less than 1 dm^3 mol^{-1}, which would not seem to be indicative of an interaction as strong as hydrogen bonding.[56] Although the constant $K_{1:1}$, defined earlier by Scheme I, described the measured interaction of phenindione with bases, the interaction may better be represented by Scheme II. The terms I, II, and III represent the diketo and enol forms of phenindione and the hydrogen-bonded enol complex, respectively. When complex formation constants with different reference acids are compared, the constant for comparison would better be represented by $K'_{1:1}$, since $K'_{1:1}$ represents complex formation with enol directly. $K'_{1:1}$ is related to $K_{1:1}$ by the enol–keto equilibrium constant K_E (eq 28). The value of K_E in cyclohexane was small

$$K'_{1:1} = K_{1:1}/K_E \qquad (28)$$

and could not be determined accurately by spectrophotometry since the spectrum of phenindione in cyclohexane showed little evidence of any enol being present (Figure 1). If the small amount of absorbance detected at 428 nm ($\epsilon \leq 3$) was attributed to the enol, a maximum value for K_E of 2.5×10^{-3} was estimated.

Another estimate for K_E can be made from the value of c, which was predicted to be at least positive in accordance with the trends established for m and c with respect to the aqueous pK_a of the

---

[54] R. W. Taft, D. Gurka, L. Joris, P. von R. Schleyer, and J. W. Rakshys, *J. Am. Chem. Soc.*, **91**, 4801 (1969).

[55] L. Joris, J. Mitsky, and R. W. Taft, *J. Am. Chem. Soc.*, **94**, 8438 (1972).

[56] B. D. Anderson, Ph.D. Dissertation, The University of Kansas, Lawrence, KS, 1977.

Table VII. Summary of Parameters for the Linear Free Energy Relationship between Reference Acids of Differing pK_a and $p\text{-}FC_6H_4OH$ as Defined by Eq 24 at 25 °C

acid	pK_a	m	c
$C_2H_5OH^a$	15.9	0.51	−0.53
CH_3OH^a	15.5	0.51	−0.39
$CF_3CH_2OH^a$	12.4	0.92	−0.17
$C_6H_5OH^a$	10.0	0.97	−0.13
naphthol[a]	9.8	0.92	+0.18
$(CF_3)_2CHOH^a$	9.3	1.16	+0.32
phenindione (as enol)	2.4	1.53	−2.96

[a] Data reproduced from Taft et al.[53]

reference acid (Table VII). The difference between the expected magnitude for c of greater than zero and the actual value reported in Table VII was at least 3 logarithmic units. This difference represents the proportionality constant, $1/K_E$, between $K'_{1:1}$ and $K_{1:1}$. Hence, $K_E \simeq 1.0 \times 10^{-3}$. If one chose for the sake of convenience this minimum value for K_E, the linear log $K_{1:1}$ vs. pK_{HB} relationship would be displaced vertically by ~3 logarithmic units if log $K'_{1:1}$ were plotted against pK_{HB}.

Some of the points in Figure 6 show some deviation from the line. Triethylamine (11) shows a positive deviation. Triethylamine was unusual in that it was the only base to produce an insoluble compound upon reaction with phenindione in cyclohexane. The isolated solid was characterized as the triethylammonium enolate and its visible absorption spectrum was consistent with considerable charge separation. The deviation triethylamine displayed was probably due to the increased extent of proton of ion-pair formation. If the extinction coefficient for the triethylamine complex was assumed to be that for the tetrabutylammonium enolate, the $K_{1:1}$ value tends to fall more in line with the other results.

The magnitudes of the 1:2 complexes were not analyzed in great depth. From the trends in the 1:2 constants it was not likely that these represented hydrogen-bonded interactions. More than likely, the extra mole of base interacted with the 1:1 complex via a dipole–dipole interaction.

Functional Group and Structure Effects on Relative Basicity. For single functional group bases the observed order of basicity, strongest to weakest, was phosphine oxide > aliphatic phosphate > sulfoxide > amide > aromatic amine > ketone > ester > ether. The observed order was consistent with previous studies. Within a functional group the cyclic bases, such as γ-butyrolactone, cyclohexanone, and *N*-methyl-2-pyrrolidinone, were stronger bases than their acyclic analogues. This had been previously described as due to the greater electron donating tendency of the cyclized alkyl chain and to a steric effect whereby the carbonyl group was more exposed than in simple esters, ketones, and amides.[57-59] As might be expected, this steric effect and the constrained conformation were also manifested in higher dipole moments for the cyclic bases compared to those of the corresponding acyclic bases.[31]

Multifunctional compounds such as the triglycerides triacetin and triolein showed approximately the same magnitude of $K_{1:1}$ as the monoesters ethyl acetate and ethyl oleate. Consequently, the triesters behave like the monoesters, forming only one hydrogen bond per molecule rather than per ester function. This was probably due to the greater entropic requirements for 2:1 and 3:1 complexes and greater steric crowding in the triesters.[57,60]

The effect of *N*-alkyl substituents on the $K_{1:1}$ constants for formamides (Table III) was analyzed. The substituents effects were correlated by the Taft extrathermodynamic relationship to σ^* values,[30,61,62] and a ρ^* of −1 was observed. The negative value for ρ^* indicated that as electron-donating ability of the substituents increased, the value of the 1:1 interaction constant and correspondingly the basicity of the formamides also increased.

The effect of side-chain alkyl substituents on the basicity of *N,N*-dimethyl amides as expressed by $K_{1:1}$ values (Table III) was also evaluated. The $K_{1:1}$ values for the dimethyl amides did not correlate with the σ^* substituent constant or linear combination of substituent constants (σ^* and E_s). The interaction constants for the ethyl (propinamide), propyl (butyramide), and butyl (valeramide) substituents appeared to follow the electron-donating tendency of the substituent, whereas steric effects appeared important for a hydrogen (formamide) or *tert*-butyl (pivalamide) substituent. Joesten and Drago,[63] who studied the interaction of *N,N*-dimethyl amides with phenol, provided another explanation for the lack of correlation with σ^*. They suggested that a correlation does exist for the hydrogen and methyl substituents. Consequently, the ethyl, propyl, butyl, and *tert*-butyl substituents show negative deviation from the line given by plotting log $K_{1:1}$ vs. σ^* for the hydrogen and methyl substituents. They proposed that the low interaction constants they obtained for the interaction of dimethylpropionamide arises from the differential interaction of the extra methyl group with the rehybridized oxygen causing a preferential interaction with one rotomer. Hyperconjugative effects have been proposed as an alternative explanation by Gramstad and Fuglevik.[64]

Conclusion

Basic aprotic molecules interact with phenindione in cyclohexane to promote and stabilize formation of the enol isomer of phenindione through hydrogen bonding to an extent characteristic of their hydrogen-bond-accepting ability, i.e., base strength. The formation of a hydrogen-bonded enol complex was established spectroscopically by formation of the indenone chromophore, by spectral band shift, and by comparison to other reference acid hydrogen-bonding systems. Phenindione enol as a hydroxy reference acid showed great sensitivity toward base strength. An added advantage was that the interactions can be determined in dilute solutions of the phenindione and base and can be determined easily and rapidly with simple spectrophotometric measurements.

Registry No. I, 83-12-5; II, 13031-53-3; IV, 2136-67-6; tetrabutylammonium 2-phenyl-1,3-indandione enolate, 64487-70-3.

---

(57) S. Chulkaratana, Ph.D. Dissertation, University of Wisconsin, Madison, WI, 1964.

(58) N. I. Nakano, Ph.D. Thesis, University of Wisconsin, Madison, WI, 1967.

(59) M. L. Bender, *Chem. Rev.*, **60**, 54 (1960).

(60) D. A. Zuck, Ph.D. Thesis, University of Wisconsin, Madison, WI, 1952.

(61) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York and London, 1963, pp 219–229.

(62) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).

(63) M. D. Joesten and R. C. Drago, *J. Am. Chem. Soc.*, **84**, 2696 (1962).

(64) T. Gramstad and W. J. Fuglevik, *Acta Chem. Scand.*, **16**, 1369 (1962).