

Phenindione solubility in mixed organic solvents: analysis of the role of specific hydrogen and non-hydrogen bonding interactions

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Summary

Phenindione, 2-phenyl-1,3-indanedione, exists predominantly in its diketo (I) rather than its enol (II) form in hydrocarbon solvents. Basic molecules interact with phenindione in cyclohexane resulting in formation of a tautomeric enol-complex (III). The solubility of hydrogen bond donor molecules in the presence of bases can often be defined by specific "chemical" or hydrogen bond interactions. In the present study the solubility of phenindione in cyclohexane in the presence of increasing concentrations of a number of dipolar bases, cosolvents, was studied. The purpose was to see if the increased solubility of phenindione in the presence of the bases was predictable from an earlier independently, spectrophotometrically determined hydrogen bonding interaction constants. In the presence of strong bases the solubility was predicted well by the increased presence of the enol-complex; however, in the presence of weak bases it was obvious that the non-specific "chemical" and/or "physical" effects were also operative.

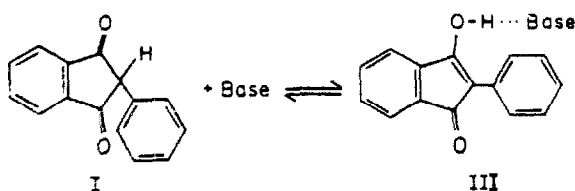
Introduction

Phenindione exists predominantly in its diketo form (I) rather than its enol form (II) in hydrocarbon solvents (Pipkin and Stella, 1982). Recently it was shown that aprotic basic molecules interact with phenindione in the hydrocarbon solvent, cyclohexane, resulting in formation of a tautomeric enol-complex (III, Scheme 1). In dilute solutions of the base, the hydrogen bonding interaction which stabilizes enol

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formation could be described by a 1:1 interaction constant which was found to correlate well with other measures of molecular basicity in condensed phases (Pipkin and Stella, 1982).



Scheme 1

Anderson et al. (1980) and others (Anderson, 1977; Fung and Higuchi, 1971) have proposed that alterations in the solubility of phenolic molecules in mixed organic solvents could be largely described by specific hydrogen bonding interactions after corrections for solute/solute and solvent/solvent interaction were made.

It would be interesting to study the solubility of phenindione in cyclohexane in the presence of increasing concentrations of a number of dipolar aprotic bases, cosolvents, to see if the interactions that result in the increased solubility of phenindione were predictable from the earlier independent, spectrophotometrically, determined interaction constants described by Scheme 1.

Experimental

Materials

Phenindione (K and K/ICN Pharmaceuticals, Plainview, NY, lot no. 16665), cyclohexanone (Aldrich Chemicals, Milwaukee, WI, 99.8%, Gold label, 99.5% purity by gas chromatography), triphenylphosphate (Aldrich Chemicals, Milwaukee, WI, 98%), pyridine (Eastman Organic Chemicals, Rochester, NY, Spectrograde, distilled numerous times and 184–185°C fraction collected and stored over molecular sieves, purity by gas chromatography of 99.75%), dimethylformamide (Fisher Scientific, Pittsburgh, PA, Certified ACS Spectranalyzed), tetramethyl urea (Aldrich Chemicals, Milwaukee, WI, 99%), dimethyl acetamide (Aldrich Chemicals, Milwaukee, WI, 99 + %, Gold Label), dimethyl sulfoxide (Aldrich Chemicals, Milwaukee, WI, 99 + %, Spectrophotometric grade, Gold Label) and cyclohexane (Baker, Phillipsburg, NJ, Baker Instra-Analyzed, GC-Spectrophotometric quality, lot nos. 2-1993, 910349, 910354 used after storage for 2 days over molecular sieves) were of the highest purity commercially available and were used without further purification in most instances except where indicated. The manufacturer's purity claims were verified by refractive index¹ and gas chromatography².

¹ Abbe-3C Refractometer calibrated with Clay-Adams Microscope Immersion Oil. The refractive index was measured at 20°C and 25°C for most solvents by thermostating the refractometer using a Haake Model FE Circulator, Haake Instruments, Karlsruhe, F.R.G. All solvents showed > 99.9% purity by refractive index measurements.

² Varian Associates, Model 3700 gas chromatograph equipped with flame ionization detector. Columns were 6 ft. long 4 mm i.d. glass column packed with 10% Carbowax 20M on 80/100 mesh Gas Chrom Q from Applied Sciences Laboratories.

Solubility determination

The phase solubility technique reviewed by Higuchi and Connors (1965) and by Connors and Mollica (1966) was used to determine solubilities as well as possible complex formation. A series of cyclohexane-aprotic basic cosolvent mixtures were prepared as described in an earlier study (Pipkin and Stella, 1982). Solid phenindione well in excess of its estimated saturation solubility (~ 200 mg) was added to lined (Teflon "M", American Can, Greenwich, CT) screw cap vials and vigorously mechanically agitated (Vortex Genie Mixer, Scientific Industries, Bohemia, NY). All vials were then wrapped in aluminum foil to prevent photodegradation of phenindione. Because air oxidation was a problem for phenindione (DeVries et al., 1975) all the head space of the vials were purged with dry N_2 prior to closure.

The vials were then placed upright in a shaking water bath (Evapomix, Buchler Instruments, Fort Lee, NJ) so as to submerge $\sim 75\%$ of the vial in the constant temperature water bath ($25 \pm 0.1^\circ\text{C}$) and allowed to equilibrate for 1–2 days. The limited submersion of the vials prevented problems associated with leakage of cyclohexane out of and seepage of water into the vials.

The vials were removed from the water after an appropriate time, immediately centrifuged (Dynac II, Clay Adams Div. of Becton, Dickinson, Parsippany, NJ) and the supernatant filtered through glass wool. The molar concentration of hydrogen-bonded enol complex was determined by measuring the absorbance of the filtrate on a spectrophotometer (Cary Model 219) at the wavelength of maximum absorbance due to the complex (III) for the two bases, cyclohexanone and triphenyl phosphate. For all the bases, the total molar concentration of all phenindione species in solution was determined spectrophotometrically by filtering a portion of the supernatant and diluting an aliquot with cyclohexane sufficiently for complex formation to be negligible. The absorbance of the diluted solutions was measured at the UV

TABLE 1

MOLAR ABSORPTIVITY VALUES DETERMINED FROM BEER-LAMBERT PLOTS FOR APROTIC BASIC COSOLVENTS AND PHENINDIONE USED IN SOLUBILITY COMPLEXATION STUDY

Compound	Wavelength (nm)	
	225	428
Phenindione	$56,400 \pm 300^a$	2.7 ± 0.2
Cyclohexanone	1.418 ± 0.009	$5.43 \pm 0.08 \times 10^{-3}^b$
Triphenyl phosphate	7.42 ± 0.012	0
Pyridine	307.8 ± 0.3	0
Dimethyl formamide	592 ± 8	0
Tetramethyl urea	917 ± 6	0.016 ± 0.001
Dimethyl acetamide	468 ± 3	0
Dimethyl sulfoxide	910 ± 7	0

^a Molar absorptivity ($\text{mol}^{-1} \cdot \text{cm}^{-1}$) \pm S.E. of least-squares line. $n = 4-6$.

^b $\lambda = 424$ nm.

wavelength of maximum absorbance for phenindione, 225 nm. Appropriate corrections were made for the small contribution to absorbances due to the presence of basic cosolvents. Using the molar absorptivity values for phenindione and the various bases (Table 1, reported molar absorptivities and S.E. determined from the least-squares lines) as determined from the appropriate Beer-Lambert plots, the concentration of phenindione in cyclohexane in the presence of basic cosolvents was determined. The solubility of phenindione without basic cosolvents present was determined spectrophotometrically, in triplicate, as described above and gave a value of 4.39×10^{-3} M (S.E.M. = $\pm 0.03 \times 10^{-3}$ M).

Results

The interaction between phenindione (D) and aprotic basic cosolvent (B) in cyclohexane was investigated using the solubility method (Kostenbauder and Higuchi, 1956; Higuchi and Connors, 1965; Connors and Mollica, 1966). Figs. 1–3 (darkened circles) are 3 representative examples of typical phase solubility diagrams observed experimentally for cyclohexanone, tetramethyl urea and dimethylsulfoxide, respectively. The abscissa is specified $[B]_T$, the total molar concentration of cosolvent. The ordinate gives $[D]_T$, the spectrophotometrically determined total molar concentration of all phenindione species found in solution after equilibration.

With the exception of the interaction of phenindione with dimethyl sulfoxide, all other aprotic base plots showed positive curvature and appear to conform to the 'Type A_p' diagrams as described by Higuchi and Connors (1965). This type of curve is expected if complexes were present to a higher order than unity in complexing agent. These phase solubility diagrams suggest that at least two complexes of different stoichiometry were present. In the simplest instance, the phase diagrams in Figs. 1 and 2 were attributed to the formation of 1 : 1 and 1 : 2 (phenindione : aprotic base cosolvent) complexes. Other stoichiometric ratios may in reality have existed in the system; however, this simplifying assumption appeared sufficient to describe the diagrams (Kostenbauder and Higuchi, 1956; Anderson, 1977).

To proceed with estimating the equilibrium constants for the formation of complexes with the presumed stoichiometry, the interactions proposed were assumed to follow the law of mass action. The pertinent complex formation equilibria and the equilibrium constants describing the extent of complex formation may be represented as:



$$K_{1:1} = \frac{[DB]}{[D].[B]} \quad (2)$$

and

$$K_{1:2} = \frac{[DB]_2}{[DB][B]} \quad (3)$$

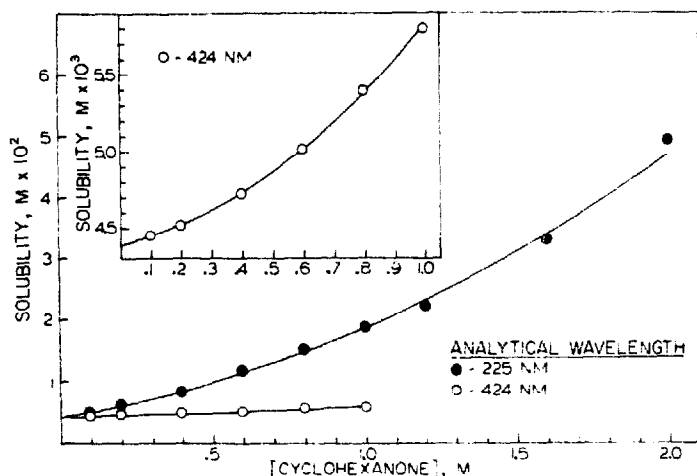


Fig. 1. Solubility of phenindione versus the molar concentration of cyclohexanone in cyclohexane as determined at 225 (all phenindione species) and 424 (phenindione uncomplexed, plus III) nm (insert) at 25°C. The smooth curves were calculated from Eqns. 4 and 5 and the computer derived constants from Tables 3 and 4.

where $[DB]$ and $[DB_2]$ are the molar concentrations of the complexes, $[D]_s$ is the saturation solubility of phenindione in cyclohexane and represents the uncomplexed D in solution, and $[B]$ is the molar concentration of uncomplexed basic cosolvent in cyclohexane. Since the solutions were saturated with respect to D , the activity of D in solution was constant. It will be initially assumed that the activity coefficients of all species were unity, hence, the activity of each species was equal to its respective concentration³. Thus, the constants $K_{1:1}$ and $K_{1:2}$ were concentration constants.

The mass balances on phenindione (D) and cosolvent (B) species in the equilibria are

$$\begin{aligned}
 [D]_T &= [D]_s + [DB] + [DB_2] \\
 &= [D]_s + k_{1:1} \cdot [D]_s \cdot [B] + K_{1:1} \cdot K_{1:2} \cdot [D]_s \cdot [B]^2
 \end{aligned} \tag{4}$$

and

$$\begin{aligned}
 [B]_T &= [B] + [DB] + 2[DB_2] \\
 &= [B] + K_{1:1} \cdot [D]_s \cdot [B] + 2K_{1:1} \cdot K_{1:2} \cdot [D]_s \cdot [B]^2
 \end{aligned} \tag{5}$$

³ $K_{1:1}^{\text{solubility}}$ could be defined as being equal to $K_{1:1} = \frac{[DB]}{[D]_s[B]} \frac{\gamma_{DB}}{\gamma_D \gamma_B}$ where the γ s refer to activity coefficients. Deviation from the proposed complexation model could then be attributed to activity coefficient differences rather than definable interactions between solute and solvent as well as solute/solute and solvent/solvent interactions.

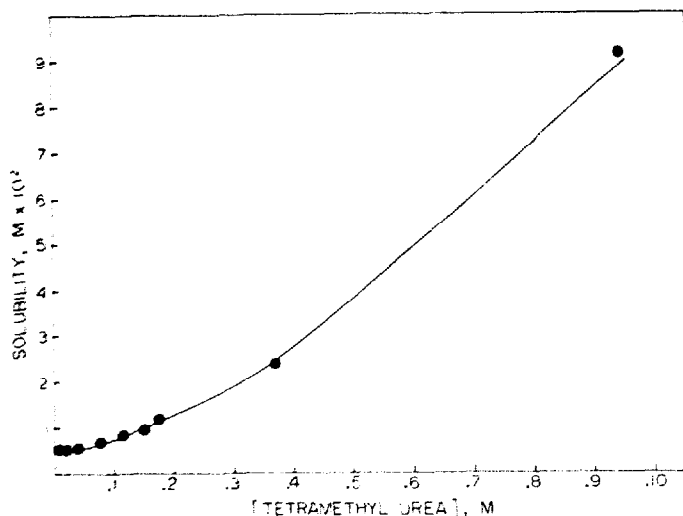


Fig. 2. Solubility of phenindione (all species) versus the molar concentration of tetramethyl urea in cyclohexane at 25°C. The curve drawn represents the calculated solubilities based on the computer derived constants from Table 3.

where $[D]_T$ represents the total concentration (solubility) of D in solution and $[B]_T$ is the total concentration of B in solution, i.e., the total cosolvent agent added.

As previously described by Anderson (1977) two techniques can be used to derive best estimates for the equilibrium constants.

(1) Graphical method for estimating equilibrium constants

The phase diagram for the interaction between phenindione and dimethyl sulfoxide did not show positive curvature but was linear (Type A_L) (Higuchi and Connors, 1966). The magnitude of the slope of such diagrams may indicate the stoichiometry of the complex(es) present. The slope in this instance is less than unity and in such an instance no definite conclusion can be drawn about the stoichiometry (Higuchi and Connors, 1966). However, in the absence of additional information the assumption of a 1:1 complex was made.

To determine the 1:1 equilibrium constant for phenindione interacting with dimethyl sulfoxide in cyclohexane, the 1:2 complex was ignored in Eqns. 4 and 5, giving after rearrangement

$$[DB] = [D]_T - [D]_s \tag{6}$$

and

$$[B] = [B]_T - [DB] = [B]_T - ([D]_T - [D]_s) \tag{7}$$

Substitution of Eqns. 6 and 7 in the equilibrium expression (Eqn. 1) gives

$$K_{1:1} = \frac{[D]_T - [D]_s}{[D]_s ([B]_T - ([D]_T - [D]_s))} \tag{8}$$

and since $([D]_T - [D]_s)/[B]_T$ represents the slope in Fig. 3,

$$K_{1:1} = \frac{\text{slope}}{[D]_s(1 - \text{slope})} \quad (9)$$

The complex formation constant for dimethyl sulfoxide interacting with phenindione was calculated using Eqn. 9 and the slope for the line in Fig. 3. The value of $K_{1:1}$ is recorded in Table 2 along with an estimate of its error (Mood et al., 1974), which has contributions from the standard error in the slope of the phase diagram and standard error in an independent determination of $[D]_s$.

In all the other phase diagrams positive curvature was noted, and at least two complexes were assumed responsible for the observed results. Under the assumption that DB and DB_2 complexes were formed according to Eqn. 1, the equilibrium constants were defined by Eqns. 2 and 3.

If the extent of complexation was fairly small then the amount of B in the complexes is small and $[B]_T \cong [B]$. Accordingly, this can be substituted into Eqn. 4 giving

$$\frac{[D]_T - [D]_s}{[B]_T} = K_{1:1} \cdot [D]_s + K_{1:1} \cdot K_{1:2} \cdot [D]_s \cdot [B]_T \quad (10)$$

$K_{1:1}$ and $K_{1:2}$ can be calculated from the slope and intercept of a plot of $([D]_T - [D]_s)/[B]_T$ versus $[B]_T$ as shown in Figs. 4 and 5 for the cosolvents: cyclohexanone, triphenylphosphate, pyridine, dimethyl formamide, tetramethyl urea and dimethyl acetamide. The values of $K_{1:1}$ and $K_{1:2}$ determined for these complexing agents are recorded in Table 2 along with an estimate of their errors which

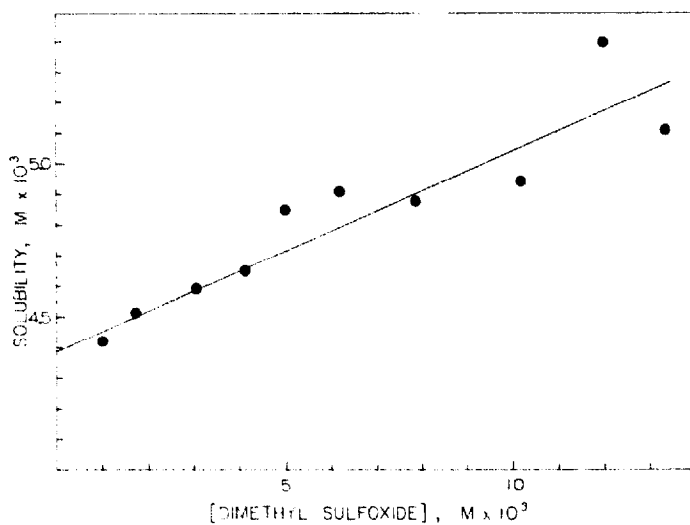


Fig. 3. Solubility of phenindione (all species) versus the molar concentration of dimethyl sulfoxide in cyclohexane at 25°C. The curve drawn represents the calculated solubilities based on the computer derived $K_{1:1}$ in Table 3.

TABLE 2

GRAPHICALLY EVALUATED EQUILIBRIUM CONSTANTS FOR THE FORMATION OF COMPLEXES OF PHENINDIONE WITH POLAR COMPLEXING AGENTS, BASES, IN CYCLOHEXANE FROM THE ENHANCED SOLUBILITY OF PHENINDIONE AT 25°C

Complexing agent	$K_{1:1}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)	$K_{1:2}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)
Cyclohexanone	1.77 ± 0.09^a	0.87 ± 0.06^a
Triphenyl phosphate	4.62 ± 0.22	3.66 ± 0.44
Pyridine	1.08 ± 0.15	3.86 ± 0.56
Dimethyl formamide	5.01 ± 0.13	2.67 ± 0.07
Tetramethyl urea	6.42 ± 0.14	2.43 ± 0.07
Dimethyl acetamide	5.83 ± 0.20	5.80 ± 0.28
Dimethyl sulfoxide	15 ± 3^b	-

^a S.E. calculated from the variances (V) and covariances (Cov) of the slope and intercept of the least-squares line (Mood et al., 1974), where $V_{K_{1:1}} = V_{\text{intercept}}$ and $V_{K_{1:2}} = (\text{slope}/K_{1:1})^2 [V_{\text{slope}}/(\text{slope})^2 + V_{K_{1:1}}/K_{1:1}^2 - 2\text{Cov}_{K_{1:1},\text{slope}}/(\text{slope})K_{1:1}]$. Number of points in each least-squares line (see Figs. 4 and 5) is 6-9.

^b S.E. calculated from the variances of the slope of the least-squares line (Mood et al., 1974) where $V_{K_{1:1}} = K_{1:1}^2 V_{\text{slope}}/(\text{slope})^2(1 - \text{slope})^2$. Number of points in least-squares line (Fig. 3) is 10.

have contributions from the standard error in the slope and intercept of the least-squares lines and from the standard error in an independent determination of $[D]$, (Mood et al., 1974).

(2) Computer fit determination of equilibrium constants

At high concentrations of basic cosolvent or solute, a considerable amount of the

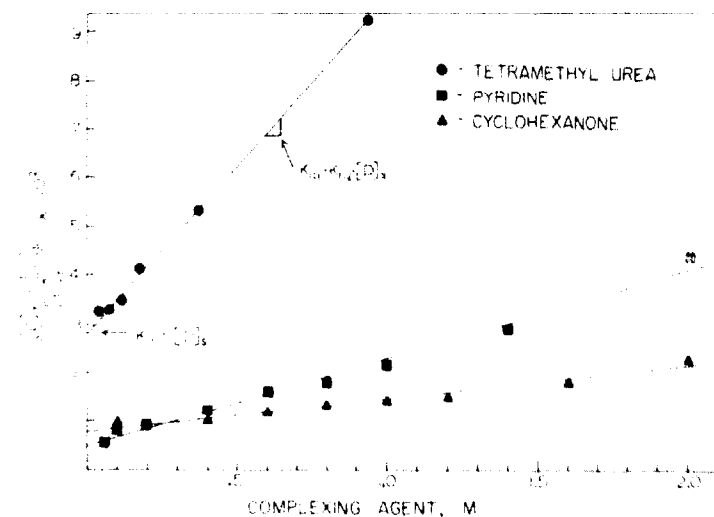


Fig. 4. Plot of fraction of basic cosolvent that is complexed versus the concentration of basic cosolvent for the determination of $K_{1:1}$ and $K_{1:2}$ for the interaction of phenindione with tetramethyl urea, pyridine and cyclohexanone in cyclohexane at 25°C.

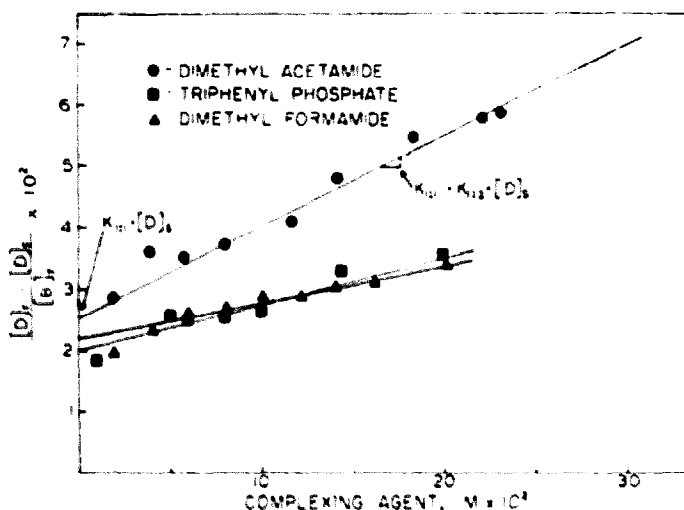


Fig. 5. Plot of fraction of basic cosolvent that is complexed versus the concentration of basic cosolvent for the determination of $K_{1:1}$ and $K_{1:2}$ for the interaction of phenindione with dimethyl acetamide, triphenyl phosphate, and dimethyl formamide in cyclohexane at 25°C.

cosolvent exists in complexed form. This leads to increasing disparity between $[B]_T$ and $[B]$ and the computation of $[B]$ becomes unwieldy. A computer program similar to that used by Anderson (1977) using the Simplex method of least-squares (Deming and Morgan, 1973a and b) was used to solve Eqns. 4 and 5 simultaneously, optimizing the values of the equilibrium constants. The sum of squares of percent deviation of the experimental solubilities from the calculated solubilities was minimized thereby giving a weight inversely proportional to the solubility measured at each basic cosolvent or solute concentration. As pointed out by Anderson (1977) the advantage of using squares of percent deviation rather than absolute deviations was the observed better agreement with solubility data at low cosolvent or solute concentrations where the data would be expected to better adhere to the complexation model. The computer calculated constants are listed in Table 3 and show good agreement with previously graphically determined values. The graphically determined 1:1 equilibrium constants were within 10% of the computer determined values whereas the 1:2 constants showed up to 20% deviation. The lines drawn in the phase diagrams, Figs. 1-3, are those generated by the computer determined constants in Table 3.

The data represented by open circles in the insert to Fig. 1 and the phase diagram for triphenyl phosphate (not shown) was also analyzed by computer and the resulting association constants are recorded in Table 4. The solubility shown in the insert represents the sum of the intrinsic solubility of phenindione in cyclohexane ($[D]_S = 4.39 (\pm 0.03) \times 10^{-3}$ M) plus the concentration of hydrogen-bonded enol-complex (III) determined from the absorbance of the filtered but undiluted supernatant at the long wavelength used in the earlier spectral study (Pipkin and Stella, 1982). The calculation of the concentration of enol-complex in cyclohexanone-phenindione and triphenyl phosphate-phenindione systems assumed that

TABLE 3

COMPUTER EVALUATED EQUILIBRIUM CONSTANTS FOR THE FORMATION OF COMPLEXES OF PHENINDIONE WITH BASIC COSOLVENTS AND SOLUTES IN CYCLOHEXANE FROM THE ENHANCED SOLUBILITY OF PHENINDIONE AT 25°C

Base	$K_{1:1}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)	$K_{1:2}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)	$\sigma\%$ ^a
Cyclohexanone	1.71	1.00	3.1
Triphenyl phosphate	4.98	3.57	2.0
Pyridine	0.93	5.06	4.9
Dimethyl formamide	4.95	3.32	1.8
Tetramethyl urea	5.82	3.97	7.5
Dimethyl acetamide	6.00	7.23	2.4
Dimethyl sulfoxide	15.8	—	2.5

^a $\sigma\%$ is the square-root of the sum of the squares of percent deviation between calculated and observed solubilities divided by the degrees of freedom.

whether the complex was related by 1:1 or 1:2 stoichiometry, the net extinction coefficient was the same, i.e. $\epsilon'_{1:1} = \epsilon'_{1:2} = 1114 \text{ mol}^{-1} \cdot \text{cm}^{-1}$ (Pipkin and Stella, 1982). The assumption of equal molar absorptivities for 1:1 and 1:2 complexes was a good one for weaker electron donors and hydrogen-bonded acceptors since the same chromophore was involved (Murray and Cromwell, 1976); however, with stronger bases, the molar absorptivity of the higher order complex may change significantly due to electronic changes accompanying the change in extent of hydrogen transfer induced by the strength and type of electron donor (Pipkin and Stella, 1982).

TABLE 4

COMPUTER EVALUATED EQUILIBRIUM CONSTANTS FOR THE FORMATION OF COMPLEXES OF PHENINDIONE WITH CYCLOHEXANONE AND TRIPHENYL PHOSPHATE IN CYCLOHEXANE FROM THE AMOUNT OF ENOL-COMPLEX FORMED IN SATURATED SOLUTIONS OF PHENINDIONE AT 25°C

Base	$K_{1:1}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)	$K_{1:2}$ ($\text{dm}^3 \cdot \text{mol}^{-1}$)	$\sigma\%$ ^a
Cyclohexanone	0.112	1.88	0.2
Triphenyl phosphate	0.74 0.90 ^b	4.28	0.6 0.1 ^b

^a $\sigma\%$ is the square-root of the sum of squares of percent deviation between the calculated and observed solubilities divided by the degrees of freedom.

^b Calculated for initial base concentrations less than 1 M.

Discussion

Table 5 compares the $K_{1:1}$ association constants between phenindione and various aprotic basic cosolvents determined by the spectral method (Pipkin and Stella, 1982) and solubility technique described in this study. Also included in Table 5 are $K_{1:1}$ constants determined by following the kinetics of complex formation determined spectrophotometrically (Pipkin, 1981). It can be seen that reasonable correlations exist between the kinetic and spectral techniques and that spectral and solubility determined constants correlate well for the stronger bases but very poorly for the weaker bases. The increases in solubility, as indicated by the solubility determined $K_{1:1}$ constants were greater than expected if just enol-base complexation was involved. This was indeed the situation as proven by determining the enol-complex content, III, in the supernatant (see Fig. 1, insert and Table 4) which was approximately that predicted by the spectroscopically determined association constants. As with cyclohexanone and triphenyl phosphate, the enhanced solubility of phenindione determined for the other bases was also greater than expected although the differences were less dramatic. Consequently, the equilibrium constants determined for pyridine, dimethyl formamide, tetramethyl urea and dimethylacetamide were reasonably consistent with those determined by the spectral study while dimethylsulfoxide showed a two-fold enhancement. An explanation for these observations is that the enhanced solubility of phenindione in cyclohexane-*aprotic* base cosolvent mixtures had contributions from other than just the 1:1 enol-complex. The possibilities may be formation of hydrogen-bonded diketo complexes or dipole-dipole and π - π interactions between the various phenindione species and the bases (Higuchi and Connors, 1966; Beak et al., 1980). Such interactions could be called "chemical" effects (van Laar, 1910). Deviation also may be due to "physical" solvent effects (Dolezalek, 1908; Acree and Rytting, 1982a and b).

TABLE 5
COMPARISON OF 1:1 EQUILIBRIUM CONSTANTS

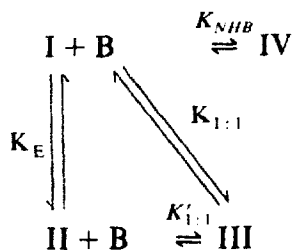
Base	$K_{1:1}$		
	Spectral ^a	Kinetic ^b	Solubility ^c
Cyclohexanone	0.11	0.263	1.71
Triphenyl phosphate	0.87		4.98
Pyridine	1.06		0.93
Dimethyl formamide	2.32		4.95
Tetramethyl urea	4.05		5.82
Dimethyl acetamide	5.10	5.11	6.00
Dimethyl sulfoxide	7.77		15.8

^a From Pipkin and Stella, 1982.

^b From Pipkin, 1981.

^c From Table 3.

Scheme 2 may be helpful in rationalizing this behavior. In Scheme 2, II represents the uncomplexed enol and IV⁴



Scheme 2

represents all non-enol hydrogen-bonded species formed between phenindione and the cosolvent, B. It has already been shown that $K_E \sim 1 \times 10^{-3}$ M, therefore, $K'_{1:1}$ values are related to $K_{1:1}$ by Eqn. 11 (Pipkin and Stella, 1982). Since the total solubility

$$K'_{1:1} = K_{1:1}/K_E \quad (11)$$

technique cannot discriminate between I, II, III and IV, the $K_{1:1}$ constants determined from the solubility study should actually be described by Eqn. 12 if the contribution of II is neglected⁵

$$K_{1:1}^{\text{solubility}} = \frac{[\text{IV}] + [\text{III}] + [\text{II}]}{[\text{I}][\text{B}]} \approx \frac{[\text{IV}] + [\text{III}]}{[\text{I}][\text{B}]} \approx K_{\text{NHB}} + K_{1:1}^{\text{spectral}} \quad (12)$$

where $K_{1:1}^{\text{solubility}}$ is the apparent 1:1 interaction constant determined from the solubility study, $K_{1:1}^{\text{spectral}}$ is the 1:1 interaction constant determined from spectral data and K_{NHB} is the equilibrium constant necessary to describe "chemical"/"physical" interactions not described by the enol-complex⁴. By subtracting $K_{1:1}^{\text{spectral}}$ from $K_{1:1}^{\text{solubility}}$, K_{NHB} can be determined and its values are given in Table 6 along with the dipole moments of the bases, polarizability, $K'_{1:1}$ and the [III]/[IV] ratio calculated assuming only 1:1 interaction of a specific hydrogen bonding and non-specific non-hydrogen bonding nature are occurring.

It can be seen from the data presented in Table 6 that K_{NHB} does not correlate well with $K'_{1:1}$, dipole moments or polarizability. This suggested that the non-specific improvement from these cosolvents may have come from various other interactions which may be related to the structure of the cosolvent molecule. For example, all the bases may interact with I (or II) via dipole-dipole or induced dipole interactions.

⁴ Note: IV may not actually represent "chemical" species per se but may represent the contribution to the increased solubility of phenindione caused by "physical" effects (Acree and Rytting, 1982a and b). Alternatively, the term K_{NHB} could be thought of as an excess term of unknown etiology attributable to activity coefficient effects—see footnote 3.

⁵ For a discussion of this point, see Pipkin and Stella (1982).

TABLE 6

RELATIVE CONTRIBUTIONS TO PHENINDIONE SOLUBILITY: ENOL-BASE VERSUS DI-KETO-BASE ASSOCIATION

Base ^a	Dipole ^b moment (debyes)	Polarizability ^c (cm ³ × 10 ⁻²⁴)	K' _{1:1} dm ³ ·mol ⁻¹	[III]/ [IV] ^d	K _{NHB}
Cyclohexanone	3.01	11.10	110	0.07	1.6
Triphenyl phosphate	—	—	870	0.21	4.1
Dimethyl formamide	3.86	7.90	2320	0.89	2.6
Tetramethyl urea	3.47	12.76	4050	2.25	1.8
Dimethyl acetamide	3.72	9.67	5100	5.67	0.9
Dimethyl sulfoxide	3.90	7.99	7770	0.97	8.03

^a Pyridine not included because earlier studies suggested possible ion pair formation (Pipkin and Stella, 1982).

^b At 25°C in benzene.

^c Calculated from the refractive index n according to

$$\text{Polarizability} = \frac{n^2 - 1}{n^2 + 2} \frac{M}{d} \frac{3}{4\pi N_0}$$

where M = molecular weight, d = density, and N_0 = Avogadro's number.

^d Calculated for $[III]/[IV] = K_{\text{spectral}}^{1:1}/K_{\text{NHB}} = K'_{1:1}/K_E K_{\text{NHB}}$ and would be applicable to concentration ranges in B where only apparent 1:1 interactions were operative, < 0.1 M in B.

but since the bases studied do not show consistent or large changes in dipole moments or polarizability, the contribution of these factors was probably relatively constant across all bases. On the other hand, π - π interaction may be more likely to occur with a base like triphenylphosphate.

By observing the [III]/[IV] ratio in Table 6 it can be seen that for the weak bases the relative contribution from the non-specific interactions to the total solubility was greater than the contribution from enol-base interaction ($[III]/[IV] \leq 1$) whereas for the stronger bases a greater contribution from the specific hydrogen bonding interaction was observed ($[III]/[IV] \geq 1$).

In our earlier study (Pipkin and Stella, 1982) it was shown that π^* , an experimentally determined solvent polarity scale which combined polarity and polarizability (Kamlet et al., 1977) and β , a scale of hydrogen bond acceptor ability (Kamlet and Taft, 1976) did correlate well with spectral shifts in the visible spectrum of phenindione in the same mixed solvents studied here. In order to see if any similar relationships existed within the present data, correlations were attempted between the logarithms of $K_{1:1}^{\text{spectral}}$, $K_{1:1}^{\text{solubility}}$ and K_{NHB} and π^* and β individually, as well as a combination of both parameters. Table 7 summarizes all the possible correlations.

As expected $K_{1:1}^{\text{spectral}}$, even with the limited number of bases used in the present study, correlated best with β ($r = 0.987$) compared with π^* ($r = 0.902$) and was not

TABLE 7

SUMMARY OF CORRELATIONS BETWEEN $\log K_{1:1}^{\text{spectral}}$, $\log K_{1:1}^{\text{solubility}}$ AND $\log K_{\text{NHB}}$ TO π^* ^a AND β ^a ACCORDING TO LINEAR OR MULTIPLE REGRESSION FITS^b TO EITHER: (i) $\log K = A + B\pi^*$; (ii) $\log K = A + C\beta$; OR (iii) $\log K = A + B\pi^* + C\beta$ FOR THE BASES CYCLOHEXANONE, TRIPHENYL PHOSPHATE^c, DIMETHYLFORMAMIDE, TETRAMETHYL UREA, DIMETHYL ACETAMIDE AND DIMETHYL SULFOXIDE

Constants	Equation	Coefficients			
		A	B	C	r^d
$K_{1:1}^{\text{spectral}}$	(i)	-6.29	7.39	-	0.902
	(ii)	-4.81	-	7.33	0.987
	(ii)' ^c	-4.57	-	7.03	0.981
	(iii)	-5.21	1.21	6.36	0.978
$K_{1:1}^{\text{solubility}}$	(i)	-2.49	3.61	-	0.951
	(ii)	-1.34	-	2.69	0.861
	(ii)' ^c	-1.10	-	2.67	0.825
	(iii)	-2.44	3.27	0.35	0.906
K_{NHB}	(i)	-1.76	2.36	-	0.603
	(ii)	-0.14	-	0.69	0.195
	(ii)' ^c	0.24	-	0.21	0.063
	(iii)	-2.67	7.55	-5.34	0.870

^a π^* and β values were the same as those used by Pipkin and Stella (1982). π^* (0.95) for tetramethyl urea estimated from Eqn. 1 in the Pipkin and Stella (1982) paper.

^b Hewlett/Packard model 85 microcomputer and the linear regression program in the Standard Pac (Eqns. (i), (ii) and (ii)') and the Multiple Linear Regression program in the General Statistics Pac.

^c Since a value for the π^* was not available for triphenyl phosphate it was excluded from all correlations Eqn. (i)–Eqn. (iii) except for Eqn. (ii)' which includes data for triphenyl phosphate as a β value was available from the literature.

^d Correlation coefficient.

improved with a combination of π^* and β ($r = 0.987$). On the other hand $K_{1:1}^{\text{solubility}}$ correlated better with π^* ($r = 0.951$) than with β ($r = 0.861$). The term K_{NHB} did not correlate at all with β ($r = 0.195$) and only poorly with π^* ($r = 0.603$). The multiple correlation to π^* and β gave a correlation coefficient of 0.870 suggesting that this excess term (K_{NHB}) probably was a complex term involving many interactions that could be of a "chemical" as well as a "physical" nature (Acree and Rytting, 1982a and b).

The results from the spectral and solubility studies disagree more with respect to the magnitude of the 1:2 interaction than the 1:1 interaction. The experimental 1:2 constants from the solubility data may only represent an empirical term for mathematically describing the curves rather than indicative of a particular interaction, or, because the 1:2 interaction occurs at higher base concentrations, they may include significant contributions from the self-association of the bases.

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