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Effect of $\pi-\pi$ charge-transfer complexation on distribution of some aromatics between water and 2,2,4-trimethylpentane

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Summary

$\pi-\pi$ charge-transfer complexation between an electron acceptor (tetracyanoethylene) and some aromatic electron donors has been found to significantly increase the distribution of tetracyanoethylene between pH 7 phosphate buffer and 2,2,4-trimethylpentane. Agreement between values derived using a theoretical model and experimental values, indicates that for the systems studied the apparent liquid–liquid distribution coefficient of a species is related directly to its charge-transfer complexation constant (with a second complexing species) and the concentration of this second species.

Introduction

Liquid–liquid distribution coefficients have much current use in drug design (QSAR), preformulation and biopharmaceutical studies. These coefficients are regarded as: (a) measures of solute hydrophobicity; and (with some solvent pairs) as (b) measures of the combined effect of (a) and also solvation (or lipophilicity) in the oil (sic) phase. This has led to the general acceptance that these coefficients indicate a priori transport of solute through a lipid area (e.g. a membrane), or indicate the step of a drug from the aqueous biophase onto a (lipoprotein) receptor area. Although such extrapolations are both naive and, at once challenging, it does seem (Seydel and Schaper, 1982) that the oil/water distribution coefficient can be related

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to various individual pharmacokinetic processes in the body.

However, a number of physicochemical events can affect the apparent distribution coefficient — including ionization, ion pairing as well as various secondary equilibria such as aggregation. Since there is considerable indirect evidence that charge-transfer complexation is a frequent occurrence during the pharmacokinetic and (especially) pharmacodynamic events undergone by a drug (e.g. Pullman and Pullman, 1960; Snyder and Merril, 1965; Slifkin, 1971; Hetnarski and O'Brien, 1975; and Borazan and Ajeena, 1980), it would appear appropriate to examine the effect of such complexation on the distribution of a molecule between water and an oil.

Charge-transfer interactions have been described in quantum mechanical terms by Mulliken (1952). If an electron donor (a compound with a low ionization potential) approaches an electron acceptor (a compound with a high electron affinity) close enough and in a favoured conformation, an electron can be transferred from the donor molecule to the acceptor molecule. The two resulting charged molecules are attracted, and as their electronic configurations have changed, have different spectroscopic properties, often leading to an absorbance at visual wavelength. These reactions are reversible. Charge-transfer interactions can be described involving either only π-electrons, or lone-pair (n) donors or vacant-orbital (v) acceptors. Also acceptor σ-orbitals can be occupied with donated electrons.

For the present study we have chosen to examine the effect of only π–π interactions on solute transfer between water and an inert hydrocarbon (2,2,4-trimethylpentane), using tetracyanoethylene as the π-electron acceptor (Foster, 1969) and three methyl substituted benzene molecules as π-electron donors.

Materials and Methods

Chemicals

Tetracyanoethylene (TCE) was obtained from Merck (Amsterdam, The Netherlands), and was sublimated 3 times before use. 1,2,4,5-Tetramethylbenzene, pentamethylbenzene and hexamethylbenzene were obtained from Aldrich (Bease, Belgium). 2,2,4-Trimethylpentane (analytical grade) and buffer components were from Merck and were of high purity and were used as supplied. Water was freshly distilled from an all-glass still after deionization over a mixed-bed ion exchanger.

Determination of charge-transfer complex stability constants

Charge-transfer complex stability constants (K_{CT}) in 2,2,4-trimethylpentane have been determined using the approach according to Benesi and Hildebrand (1949). Thus, assuming 1 : 1 complexation, at a fixed concentration of TCE and at varying concentrations of substituted benzene (SB), the stability constant may be obtained from:

$$\frac{[TCE]}{A} = \frac{1}{K_{CT} \cdot \epsilon_{CT} \cdot [SB]} + \frac{1}{\epsilon_{CT}} \qquad (1)$$

where squared parentheses indicate concentrations ($mol \cdot dm^{-3}$), ϵ_{CT} is the molar extinction coefficient of the formed complex as its wavelength maximum and A is the measured absorbance at λ_{CT}. Measurements were carried out using a Pye-Unicam SP 8-100 spectrophotometer.

Distribution studies

Distribution of TCE between phosphate buffer (pH 7; USP XX) and 2,2,4-trimethylpentane was examined at 25.5°C using mutually saturated solvents in the absence and presence of substituted benzenes. Studies were carried out using an on-line rapid mix/filter-probe assembly as described previously (Kinkel et al., 1981; Tomlinson, 1982). All tubing and connections were constructed from stainless steel and Millipore type LC (10 μm) was used as the filter. TCE was added to the system in 2,2,4-trimethylpentane and the aromatic compounds subsequently dissolved in this solution. Upon addition of the buffer phase the alteration in absorbance of the organic phase with time was recorded. When the distribution of TCE alone was studied, its wavelength of maximum absorbance was used; and in the presence of substituted benzenes the wavelength of maximum absorbance of complex was used.

To examine whether the formed complex leaves the oil phase for the aqueous phase, gas chromatography was used to determine the concentration of substituted benzene in the 2,2,4-trimethylpentane solution in the presence and absence of TCE and the presence and absence of an aqueous phase. (Gas chromatographic conditions: stationary phase 3% OV-1 coated onto Chromosorb WHP 80–100; carrier gas nitrogen; FID-detector).

Results and Discussion

Table 1 gives the stability constants (K_{CT}), free-energies of formation, wavelengths of maximum absorbance (λ_{CT}), and extinction coefficients (at that wavelength) for the complexes formed between TCE and the substituted benzenes (in 2,2,4-trimethylpentane). It is seen that K_{CT} and λ_{CT} increase with an increasing number of methyl groups in the donor. This is to be expected since the ionization

TABLE 1

SPECTRAL, ELECTRONIC AND THERMODYNAMIC CHARACTERISTICS OF π-COMPLEXES OF TCE WITH SOME AROMATICS

Donor compound	Concentration range [a] ($mol \cdot dm^{-3}$)	K_{CT} ($mol^{-1} \cdot dm^3$)	ΔG_{CT} ($kJ \cdot mol^{-1}$)	λ_{CT} (nm)	ϵ_{CT}	I [b] (e.V)
1,2,4,5-tetramethylbenzene	3×10^{-3}–6×10^{-2}	58	−10.08	426	1997	8.05
pentamethylbenzene	6×10^{-4}–6×10^{-3}	161	−12.62	500	3132	7.92
hexamethylbenzene	4×10^{-4}–5×10^{-3}	220	−13.39	528	6043	7.85

[a] Concentration of TCE was 2.95×10^{-5} $mol \cdot dm^{-3}$.

[b] Ionization potential (Foster, 1969).

potential (i.e. that electrical potential required to release an electron from the donor molecule) decreases in the same direction. Similar results have been given by Merrifield and Phillips (1952) who found that the free energies of formation of π-complexes between TCE and various aromatic molecules are related linearly to the base (sic) ionization potentials. Similar observations have been made by Foster (1969).

Assuming that there is 1 : 1 complexation, and that neither the complex nor the uncomplexed aromatics are present in the aqueous phase, the apparent distribution coefficient of TCE (K_d^{app}) is given by:

$$K_d^{app} = \frac{[CTC]_o + [TCE]_o}{[TCE]_a} \tag{2}$$

where CTC refers to the charge-transfer complex and subscripts o and a refer to the organic and aqueous phases, respectively. Since

$$K_{CT} = [CTC]_o/[TCE]_o \cdot [SB]_o \tag{3}$$

and

$$TCE_a = TCE - TCE_{CT} - TCE_o \tag{4}$$

where TCE and TCE_{CT} are the total and complexed amounts of tetracyanoethylene, respectively, then it can be shown by introducing Eqns. 3 and 4 into 2 that:

$$K_d^{app} = \frac{V_a + (V_a/K_{CT} \cdot [SB])}{(\epsilon_{CT} \cdot TCE/A) - V_o - (V_o/K_{CT}[SB])} \tag{5}$$

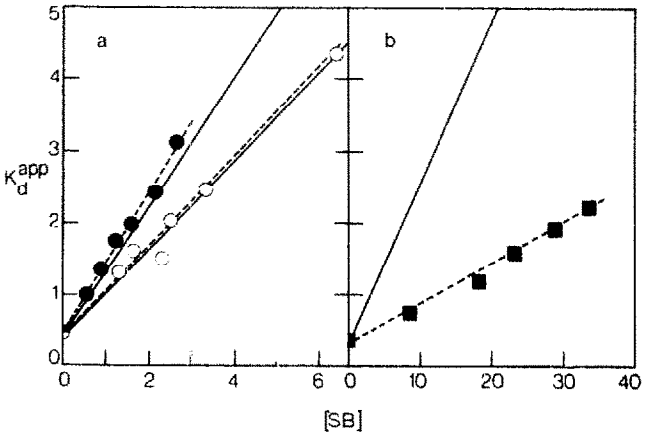

Fig. 1. Effect of substituted benzene concentration [SB] (mol·dm^{-3} × 10^2), in oil phase on the apparent distribution coefficient, K_d^{app} (× 10^4), of tetracyanoethylene between phosphate buffer (pH 7) and 2,2,4-trimethylpentane at 25.5°C. (a) For pentamethylbenzene (open datum points) and hexamethylbenzene (closed data points); and (b) with 1,2,4,5-tetramethylbenzene. Broken lines are linear regression lines for [SB] on experimental K_d^{app} values according to Eqn. 5. Solid lines are theoretical slopes according to Eqn. 8 using the appropriate K_d and K_{CT} values given in Table 1.

TABLE 2

APPARENT TCE DISTRIBUTION CONSTANTS (K_d^{app}) BETWEEN PHOSPHATE BUFFER (pH 7) AND 2,2,4-TRIMETHYLPENTANE AT 25.5°C IN THE PRESENCE OF A POLYMETHYL-SUBSTITUTED BENZENE

Substituted benzene	TCE (mmole)	[SB] (mol·dm^{-3})	$A_{\lambda_{CT}}$	K_d^{app}	m	x	r
Tetramethylbenzene	2.34	8.01×10^{-2}	0.006	7.13×10^{-5}			
	2.34	1.82×10^{-1}	0.010	1.15×10^{-4}			
	2.36	2.28×10^{-1}	0.013	1.63×10^{-4}			
	2.34	2.94×10^{-1}	0.017	1.92×10^{-4}			
	2.34	3.36×10^{-1}	0.018	2.20×10^{-4}			
		0		0.38×10^{-4}	3.06×10^{-5}	5.50×10^{-4}	0.992
Pentamethylbenzene	2.36	1.33×10^{-2}	0.013	1.24×10^{-4}			
	2.37	1.65×10^{-2}	0.018	1.64×10^{-4}			
	2.37	2.51×10^{-2}	0.018	1.48×10^{-4}			
	2.37	2.63×10^{-2}	0.025	2.00×10^{-4}			
	2.35	3.36×10^{-2}	0.025	2.37×10^{-4}			
		6.41×10^{-2}	0.044	4.37×10^{-4}			
		0		0.38×10^{-4}	3.27×10^{-5}	6.35×10^{-5}	0.984
Hexamethylbenzene	2.34	5.51×10^{-3}	0.021	1.04×10^{-4}			
	2.27	8.88×10^{-3}	0.025	1.24×10^{-4}			
	2.34	1.22×10^{-2}	0.036	1.70×10^{-4}			
	2.35	1.61×10^{-2}	0.041	1.95×10^{-4}			
	2.28	2.23×10^{-2}	0.053	2.38×10^{-4}			
	2.28	2.63×10^{-2}	0.057	3.10×10^{-4}			
		0		0.38×10^{-4}	4.29×10^{-5}	9.64×10^{-3}	0.992

m, x and r are the intercept, slope and correlation coefficients for least-squares regression of K_d^{app} on [SB]. V_a and V_o were between 0.032 and 0.042 ml, and 77 and 80 ml, respectively.

where V refers to volume of phase, and A is the absorbance in the oil phase at λ_{CT} (uncomplexed TCE has no absorbance at λ_{CT}). Using Eqn. 5, apparent distribution constants for the distribution of tetracyanoethylene between water and 2,2,4-trimethylpentane have been calculated for the three π-electron donors studied, using experimental A-values and the necessary constants from Table 1, and these are given in Table 2. Fig. 1 gives the relationships found between K_d^{app} and π-electron donor concentration, and shows that for all the substituted donors there is an increase in the distribution of TCE between water and 2,2,4-trimethylpentane, and that the enhancement in distribution is related to the number of methyl groups substituted into the benzene nucleus.

The liquid–liquid distribution coefficient (K_d) for TCE has been determined at 25.5°C as 3.8×10^{-5} with a standard deviation of 0.9×10^{-5} (molarity concentration scale). This value may be used to calculate the theoretical effect of π-electron donor concentration on distribution of TCE, for, since using gas chromatography no

free or complexed substituted benzene could be detected in the aqueous phase, and

$$[TCE]_a = [TCE]_o/K_d \tag{6}$$

and

$$[TCE]_o = [CTC]/K_{CT} \cdot [SB] \tag{7}$$

then, under the assumptions used in deriving Eqn. 5, it follows that

$$K_d^{app} = K_d \cdot K_{CT}[SB] + K_d \tag{8}$$

Using experimentally determined K_d and K_{CT} constants (Table 1), the theoretical K_d^{app} values at different concentrations of SB may be calculated. Thus the solid lines given in Fig. 1 have been constructed using these theoretical K_d^{app} values. Although for penta- and hexamethylbenzene the theoretical line approximates to the experimentally found apparent distribution coefficients, that for the tetramethyl derivative has a slope higher than expected relative to the experimentally found K_d^{app} values. According to Foster (1969), π–π donor–acceptor complexes frequently have a 2 : 1 stoichiometry, and this may be a reason why TCE–tetramethylbenzene does not follow the theoretical relationship. Further, an examination of the Benesi-Hildebrand relationship (Eqn. 1) shows that small errors in ϵ lead to large errors in K_{CT}, and it is likely that the low K_{CT} value for this complex (Table 1) is prone to large error. (A consequence of this low K_{CT} value is that large tetramethylbenzene concentrations — 8×10^{-2} to 3×10^{-1} mol · dm^{-3} — were needed to enhance TCE distribution, and it is possible that for these higher concentrations solute activities cannot be equated to concentrations.)

Conclusions

Although early methods for calculating charge-transfer complexation constants in organic solvents used an approach based on the use of an immiscible phase in which only one of the non-complexed species was soluble (Hayman, 1962), little attention has been given to the a priori determination of the effect of π–π charge-transfer on solute distribution.

Clearly π–π charge-transfer complexation in the non-aqueous phase can greatly affect the liquid–liquid distribution of organic solutes with, in this study, increases of greater than an order of magnitude being possible. Eqn. 8 indicates that for a 1 : 1 complex K_d^{app} should be related linearly to the charge-transfer complexation constant K_{CT}. From Fig. 1 and Tables 1 and 2 it can be seen that for the compounds studied here there is a reasonable linear relationship between K_{CT} and the enhancement in the apparent distribution coefficient of TCE (as indicated by the slope coefficients for the regressions of [SB] on K_d^{app}). Determinants of charge-transfer complexation are physicochemically different from those determining hydrophobic-

ity, and since this study shows that the nature and concentration of complexing agent can have a large influence on interphase transport, it is suggested that greater attention to this phenomena should be afforded in, for example, biopharmaceutics and drug design (QSAR) studies.

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