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Refractometric Studies of Molecular Complexes of *DDT* with Some Compounds of Biological Interest

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Formation of molecular complexes between *DDT* as acceptor and indole, 2-methylindole, 3-methylindole, benzene and naphtalene as donors have been studied in carbon tetrachloride using refractometric and differential refractometric measurements. Titration techniques through these measurements have indicated 1:1 stoichiometry of these complexes. Equilibrium constants (K_1) and extent of electronic polarization were calculated. Two types of complexes were observed, one association involving primarily the benzhydryltrichloromethyl grouping of *DDT* with a polar complexing agents, and the other interaction of the *DDT* aromatic π-electron system with π-electrons of donors in the complexing molecule. These data support the charge-transfer complex formation hypothesis for the mode of action of *DDT* on molecular level.

(Keywords: Charge-transfer complexes; DDT; Electronic polarization; Equilibrium constants; Indoles; Refractometry)

Refraktometrische Untersuchungen an Molekülkomplexen von DDT mit einigen biologisch relevanten Verbindungen

Es wurde die Bildung von Molekülkomplexen zwischen *DDT* als Acceptor und Indol, 2-Methyl-indol, 3-Methyl-indol, Benzol und Naphthalin als Donor in CCl_4 mittels Refraktometrie und differenzieller Refraktometrie untersucht. Es wurde 1:1-Stöchiometrie der Komplexe festgestellt, Gleichgewichtskonstanten und das Ausmaß der Elektronenpolarisation wurden berechnet. Zwei Typen von Komplexen wurden beobachtet; in einem Fall erfolgt die Assoziation primär über die Benzhydryltrichlormethyl-Gruppierung des *DDT*, im anderen Fall über π-Elektronenwechselwirkungen. Die Daten unterstützen ein charge-transfer-Modell der Komplexbildung von *DDT* mit geeigneten Donormolekülen.

Introduction

The stability of molecular complexes which mainly occurs through the interaction between electron donors and acceptors may play an essential role in understanding the mechanism of toxicity of some

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pesticides[1]. In our previous studies some evidences have been presented through NMR[2], spectrophotometric[3] and conductometric[4] measurements on the interaction of *DDT* with some compounds of biological interest. These studies have shown that *DDT* can undergo two types of complexation, one involving the benzhydryltrichloromethyl grouping of *DDT* with polar complexing agents, and the other interaction of the *DDT* aromatic π-electron system with π-electrons in the complexing molecule. In order to investigate on molecular level, the charge-transfer complexation involved for the mode of action of *DDT*, the interaction between some molecules of biological interest (e.g. indole, 2-methylindole, 3-methylindole, benzene and naphthalene) with *DDT* have been studied in non-aqueous solvents using refractometric and differential refractometric techniques.

Experimental and Data Analysis

DDT (Aldrich chemical, USA) was of 98.9% purity and used as such. Indole was recrystallized twice from cyclohexane, m.p. 52–53°. 2-Methylindole was recrystallized several times from cyclohexane, m.p. 59–60°. 3-Methylindole was recrystallized thrice from cyclohexane, m.p. 95–95.5°. Benzene and napthalene were purified as reported earlier[5]. Analytical grade carbon tetrachloride was kept over anhydrous calcium chloride for several days and it was distilled before use.

Stock solutions of donors and acceptor were prepared by weighing on an analytical balance and then diluted to the required volume in volumetric flasks in carbon tetrachloride. The solution employed for refractometric measurements was prepared from the stock solution by pipetting the calculated volumes in 10 ml volumetric flasks and then diluted subsequently with carbon tetrachloride. All the stock solutions were made on the day of measurements.

Refractive indices have been measured with a Bausch and Lomb refractometer with an accuracy of ± 0.0002 and at 30 °C.

The equilibrium constant (K_1) and extent of electronic polarization (α), have been calculated by using following Eqs. (1)–(4), recently developed by *Sahai* et al.[6–8].

$$\delta\Phi/C^\circ_D = \{K_1 C^\circ_A/\alpha(1+K_1 C^\circ_A)\} - \{K_1\delta\Phi/(1+K_1 C^\circ_A)^2\} \tag{1}$$

$$\Delta\Phi_a/C^\circ_D = \{K_1 C^\circ_A/\alpha(1+K_1 C^\circ_A)\} - \{K_1\Delta\Phi_a/(1+K_1 C^\circ_A)^2\} \tag{2}$$

$$\Delta\Phi_d/C^\circ_D = \{K_1 C^\circ_A/\alpha(1+K_1 C^\circ_A)\} - \{K_1\Delta\Phi_d/(1+K_1 C^\circ_A)^2\} \tag{3}$$

$$\Delta\Omega C_{DA}/C^\circ_D = \{K_1 C^\circ_A/\alpha(1+K_1 C^\circ_A)\} - \{K_1\Delta\Omega C_{DA}/(1+K_1 C^\circ_A)^2\} \tag{4}$$

C°_A and C°_D are the initial concentrations of acceptor and donor respectively and α is the extent of electronic polarization. $\delta\Phi$, $\Delta\Phi_a$, $\Delta\Phi_d$ and $\Delta\Omega C_{DA}$ may be calculated by using Eqs. (5)–(8).

$$\delta\Phi = 10^3(\Phi - \Phi_0) = 6000(n - n_0)n_0/(n_0^2+2)^2 \tag{5}$$

$$\Delta\Phi_a = 10^3(\Phi - \Phi_a) = 6000(n - n\ \ )n_A/(n_A^2+2)^2 \tag{6}$$

$$\Delta\Phi_d = 10^3(\Phi - \Phi_D) = 6000(n - n_D)n_D/(n_D^2+2)^2 \tag{7}$$

$$\begin{aligned}\Delta\Omega C_{DA} &= 10^3(\Phi - \Phi_D) - 10^3(\Phi_A - \Phi_0)\\ &= [6000(n - n_D)n_D/(n^2{}_D+2)^2] - [6000(n_A + n_0)n_0/(n_0^2+2)^2]\end{aligned} \tag{8}$$

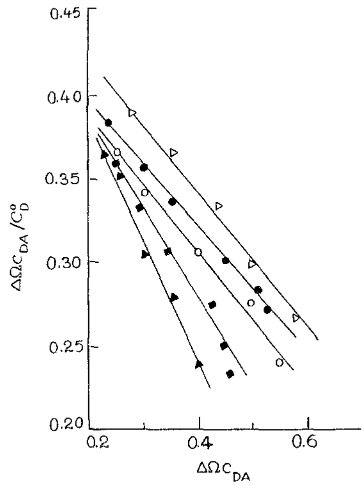

Fig. 1. Plot of $\Delta\Omega C_{DA}$ *vs.* $\Delta\Omega C_{DA}/C_D^\circ$ for indole—*DDT* (○—○—○), 2-methylindole—*DDT* (●—●—●), 3-methylindole—*DDT* (△—△—△), naphthalene—*DDT* (▲—▲—▲) and benzene—*DDT* (■—■—■) in CCl_4 at 30 °C

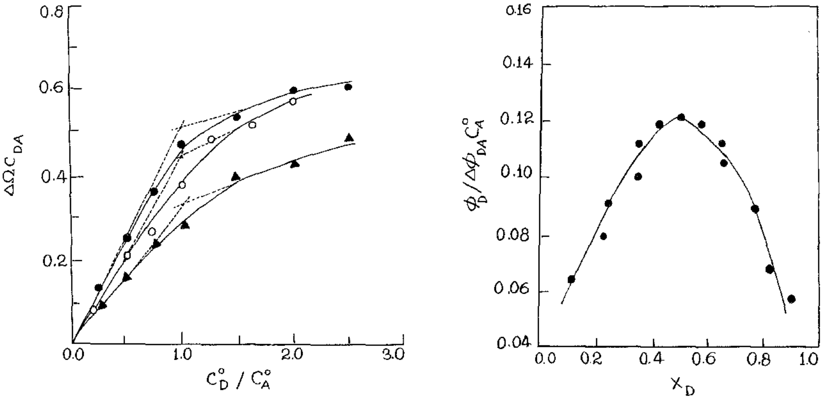

Fig. 2. Fig. 3

Fig. 2. Molar ratio plot for indole—*DDT* (○—○—○), 2-methylindole—*DDT* (▲—▲—▲) and 3-methylindole—*DDT* (●—●—●) in CCl_4 at 30 °C determined by the differential refractometric method

Fig. 3. Plot of X_D *vs.* $\Phi_D/\Delta\Phi_{AD}C_A^\circ$ indicating 1:1 stoichiometry of the 3-methylindole—*DDT* complex at 30 °C

where n, n_D, n_A and n_0 are the refractive indices of solution (donor + acceptor), donor, acceptor and solvent respectively. Φ, Φ_D, Φ_A and Φ_0 are the refraction per cm^3 of solution, donor, acceptor and solvent respectively and have been calculated as reported earlier[6,8,9]. As expected from Eqs. (1)-(4), the plots of $\delta\Phi$ *vs.* $\delta\Phi/C_D^\circ$, $\Delta\Phi_a$, Φ_a/C_D°, $\Delta\Phi_d$ *vs.* $\Delta\Phi_d/C_D^\circ$ and $\Delta\Omega C_{DA}$ *vs.* $\Delta\Omega C_{DA}/C_D^\circ$ were linear with a slope — $[K_1 C_A^\circ/(1+K_1 C_A^\circ)^2]$ and intercept $K_1 C_A^\circ/\alpha(1+K_1 C_A^\circ)$. A representative plot of $\Delta\Omega C_{DA}$ *vs.* $\Delta\Omega C_{DA}/C_D^\circ$ is shown in Fig. 1. Refractometric and differential refractometric titration techniques have indicated 1 : 1 stoichiometry of these complexes (Fig. 2). The K_1 has also been calculated using Eq. (9) recently developed by *Sahai* and *Singh*[10].

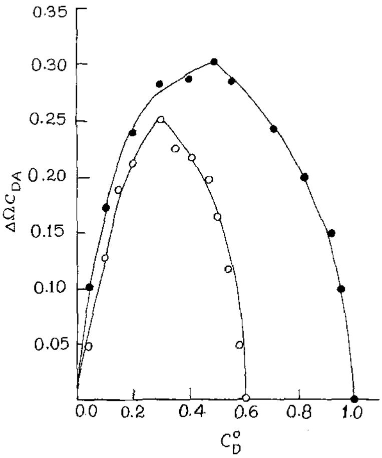

Fig. 4. Plot of molar ratio of solutes *vs.* $\Delta\Omega C_{DA}$ indicating 1 : 1 stoichiometry of the indole—*DDT* complex in CCl$_4$ at 30 °C

$$K_n = (\Phi_D/\Delta\Phi_{AD})/(C_D^\circ)^n (1-\Phi_D/\Delta\Phi_{AD})^{n+1} \tag{9}$$

The stoichiometry of the complexes have been observed by plotting $\Phi_D C_A^\circ$ (or $\Phi_D/\Delta\Phi_{AD} C_A^\circ$) against X_D [mole fraction of donor (Fig. 3)], the maximum was observed at $X_D = n/(1+n)$. Since in these case n was observed to be 1 obviously in Eq. (9) $n = 1$ and then K_1 has been evaluated. Thus, the K_1 data obtained are recorded in Table 2.

The K_1 have also been calculated by using *Yoshida* and *Ōsawa*'s[11] Eq. (10).

$$K_1 = 2\sqrt{k}\,[\sqrt{k}\,(C+C')-(C+kC')]/(C-kC')^2 \tag{10}$$

C and C' are the maximum concentrations of both the systems and k is the maximum deviation from the additive line when the molar ratio is plotted against the square of refractive index (n^2). K_1 have also been calculated by a modified *Yoshida-Ōsawa* method as suggested by *Sahai* and *Singh*[12] in which instead a plot of n^2 versus molar ratio of solutes, $\Delta\Omega C_{DA}$ is plotted against the molar ratio of solutes. A representative plot of $\Delta\Omega C_{DA}$ *vs.* molar ratio of solutes indicating 1 : 1 stoichiometry of the complex is shown in Fig. 4. $\Delta\Phi_a$ and $\Delta\Phi_d$

have also been used according to the *Yoshida-Ōsawa* method to determine the stoichiometry and K_1 of these complexes[7]. From these plots the percentage of contribution of donor or acceptor in total 30% solute aggregation, have been calculated* by using Eqs. (11) and (12) given recently by *Sahai* et al.[7].

$$SA_a = 30 \times \Delta K_d / \Delta K_{da} \tag{11}$$

$$SA_d = 30 \times \Delta K_a / \Delta K_{da} \tag{12}$$

SA_α and SA_d are the contribution in total 30% solute aggregation due to acceptor and donor respectively. The values of ΔK_{da}, ΔK_a and ΔK_d have been calculated as follows:

$\Delta K_{da} = K_{n^2} — K_{\Delta\Omega C_{DA}}$ = Total 30% solute aggregation.
$\Delta K_a = K_{n^2} — K_{\Delta\Phi_d}$ = Solute aggregation due to acceptor.
$\Delta K_d = \Delta K_{da} — \Delta K_a$ = Solute aggregation due to donor.

$K_{n^2} = K_1$, calculated from the plot of n^2 versus molar ratio of solutes or from Eq. (1).

$K_{\Delta\Phi_a} = K_1$, calculated from the plot of $\Delta\Phi_a$ *vs.* molar ratio of solutes or from Eq. (6).

$K_{\Delta\Phi_d} = K_1$, calculated from the plot of $\Delta\Phi_d$ *vs.* molar ratio of solutes or from Eq. (7).

$K_{\Delta\Omega C_{DA}} = K_1$, calculated from the plot of $\Delta\Omega C_{DA}$ *vs.* molar ratio of solutes or from Eq. (8).

Results

The K_1 and extent of electronic polarization (α) calculated for these complexes from Eqs. (1)-(4) are listed in Table 1. The K_1 show great differences; their percentage deviation from spectroscopic values is also high. In order to get appropriate variation in scale, due to limited accuracy of the instrument and low K_1 values, the solute concentration was raised (1.0-$0.10\,\mathrm{mol^{-1}\,dm^3}$). At such a high concentration solute aggregation occurs which prevents to get a reliable value for K_1[11]. K_1 thus calculated from Eq. (1) show maximum deviation from the spectroscopic data. This error becomes less when Eqs. (2) or (3) have been used but the best values are obtained by using Eq. (4) in which a differential refractometric method has been used to evaluate $\Delta\Omega C_{DA}$, the refraction per $\mathrm{cm^3}$ due to charge-transfer complexes. This is in parallel agreement with our recent observations[7].

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* Due to limited accuracy of the instrument and weak interactions, the solute concentration is kept high (1.0-$0.10\,\mathrm{mol^{-1}\,dm^3}$). At such a high concentration 30% solute aggregation occurs which can create a hinderance to get the reliable value of K_1.

Table 1. *Equilibrium constants (K_1), extent of electronic polarization (α) and solute aggregation data for* 1:1 *molecular complexes of some donors with DDT in carbon tetrachloride at 30 °C*

Donor	K_1 (dm^3 mol^{-1})						Extent of Polarization $\alpha \times 10^2$				Solute Aggregation	
	Refractometric Methods				NMR (Ref.[2])							
	Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	K_1	T °C	Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	SA_d	SA_a
Indole	0.98 ±0.04	0.88 ±0.03	0.83 ±0.03	0.62 ±0.02	0.308 ±0.010	31	2.82 ±0.05	2.30 ±0.20	2.20 ±0.10	1.60 ±0.02	8.33	21.66
2-Methylindole	1.06 ±0.05	0.98 ±0.03	0.98 ±0.03	0.68 ±0.03	0.330 ±0.013		3.24 ±0.08	2.71 ±0.25	2.40 ±0.20	1.71 ±0.05	6.31	23.68
3-Methylindole	1.12 ±0.08	1.04 ±0.08	0.96 ±0.08	0.75 ±0.04	0.468 ±0.024		3.80 ±0.10	3.10 ±0.21	2.80 ±0.20	1.77 ±0.15	6.48	23.51
Naphthalene	0.53 ±0.02	0.48 ±0.02	0.46 ±0.02	0.32 ±0.02			1.29 ±0.05	1.28 ±0.02	0.46 ±0.02	0.39 ±0.02	7.14	22.85
Benzene	0.63 ±0.03	0.59 ±0.03	0.56 ±0.02	0.48 ±0.02			1.68 ±0.06	1.35 ±0.02	1.31 ±0.10	1.25 ±0.04	8.00	22.00

The K_1 calculated from the plots of n^2 or $\Delta\,\Phi_a$ or $\Delta\,\Phi_d$ or $\Delta\,\Omega\,C_{DA}$ *vs.* molar ratio of solutes are listed in Table 2. For these complexes we could get different k values for the same system when plotted $\Delta\,\Phi_a$ or $\Delta\,\Phi_d$ *vs.* molar ratio of solutes. Thus for the same system, different K_1 values calculated from the plots are noted in Table 2. For these complexes, the best values have been observed when the differential refractometric method was used. Therefore it is evident that the contribution of refraction per cm³ of donor, acceptor and solvent is more important in these complexes. From Tables 1 and 2, it is clear that the contribution in solute aggregation of acceptor is more than that of donor. This is in good agreement with our previous observations[7].

Table 2. *Equilibrium constants (K_1) and solute aggregation data for* 1 : 1 *molecular complexes of some donors with DDT, obtained on the basis of the Yoshida-Ōsawa equation in carbon tetrachloride at 30 °C*

Donar	K_1 (dm³ mol⁻¹)					SA_d	SA_a
	Refractometric Methods*						
	1.	2.	3.	4.	5.		
Indole	1.02 ±0.05	0.92 ±0.04	0.88 ±0.04	0.68 ±0.02	0.71 ±0.03	8.82	21.18
2-Methylindole	1.10 ±0.05	0.96 ±0.04	0.83 ±0.06	0.71 ±0.03	0.82 ±0.04	10.76	19.24
3-Methylindole	1.18 ±0.08	1.02 ±0.08	0.94 ±0.06	0.82 ±0.04	0.86 ±0.04	13.33	16.66
Naphthalene	0.66 ±0.03	0.58 ±0.02	0.51 ±0.02	0.42 ±0.02	0.45 ±0.02	10.00	20.00
Benzene	0.60 ±0.02	0.55 ±0.04	0.50 ±0.02	0.46 ±0.02	0.42 ±0.02	10.71	19.29

* Calculated from the plots of: n^2 (1.), resp. $\Delta\,\Phi_a$ (2.), resp. $\Delta\,\Phi_d$ (3.), resp. $\Delta\,\Omega\,C_{DA}$ (4.) vs. molar ratio of solutes; 5. was calculated from Eq. (9).

Discussion

On mixing a solution of donors with a solution of acceptor (*DDT*) in the same solvent, an appreciable increase in refractive index was observed, with an increase in donor concentration and keeping the acceptor concentration constant. This appreciable increase in refractive index is due to the charge-transfer from donors to acceptor and not due to the relative increase of donor concentration. This has been confirmed through separate experiment. It is found that on mixing 1 ml of donor and 1 ml of acceptor solution, the refractive index increases appreciably more than that of the separate components. The refractive index of donors as well as that of *DDT* in carbon tetrachloride increases with concentration. The plot of Δn, the difference in refractive indices of calculated and observed values, against complex is linear indicating that there is no interaction between the complex and individual species. In the present cases, a small but positive deviation at 1:1 molar ratio of solutes was noted (Fig. 4). This indicates that these complexes are weak which is in parallel aggrement with earlier studies[12].

DDT has three probable sites of interaction. Apart from the electron deficient chlorophenyl rings and trichloromethyl group, the benzhydryl system can also act as the site of interaction through hydrogen bonding. Electron withdrawal by the trichloromethyl group results in increased polarity of the C—H bond involving the benzhydryl protons. The partial positive charges on the proton might make it possible to participate in hydrogen bond type association with the compounds having lone pair electrons on an oxygen or nitrogen. In the present cases (indoles—*DDT*) this type of possibility may be but it has been noted that hydrogen bonding between two components leads to a greater change in refractive index[13] or $\delta\,\Phi$, or $\Delta\,\Phi_a$ or $\Delta\,\Phi_d$ or $\Delta\,\Omega\,C_{DA}$. We are unable to get a greater change in these values but a small change was noted (Fig. 4). Consequently it can be interpreted that the donation is taking place from the π-electron pool of indoles and not from the lone pair of the nitrogen atom. This is in good agreement with results obtained through NMR measurements[2]. We are unable to locate the actual site of π-electron donation of indoles through this technique. MO calculations[14] on indoles and substituted indoles using the frontier-electron density principle[15,16] support the suggestion of *Szent-Gyorgyi* et al.[17–19], regarding somewhat localized π-charge-transfer interaction involving C-2—C-3 atoms of indoles. The low equilibrium constant values in the present systems are in good agreement with this hypothesis. An increase in K_1 values have been observed in 2- or 3-methyl indoles (Tables 1 and 2). Highest value of K_1 obtained in case of 3-methylindole is indicative of the most effective increase in electron density, and hence a formal negative charge by methylation at the 3-position. This methylation makes the 3-position more basic which increases the donor capability of the 3-methylindole more than others.

It has been reported[20] that with non polar aromatics, the π-pool of *DDT* acts as acceptor instead a benzhydryl trichloromethyl group. Through refractometric measurements it is difficult to specify the site of interaction in case of benzene—*DDT* or naphthalene—*DDT*. The K_1 calculated by means of this method are in agreement with that of spectroscopic methods through which it has already been proved that the π-electron pool of *DDT* acts as electron acceptor. Therefore on the basis of these K_1 data it can be visualized that π-σ^* type of interaction occurs in case of benzene—*DDT* and naphthalene—*DDT* systems.

The formation of above complexes is thus related with the mode of action of *DDT* and, further, it provides substantial support to *Holan*'s theory[21] of toxicity proposed recently in modification of *Mullins*' theory[22] and is in good agreement with our NMR investigation on these systems[2].

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