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(spectroscopy/association constants/NMR)

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ABSTRACT Association constants for 1:1 molecular complexes formed between 1,3,5-trinitrobenzene and various methoxy-substituted indoles have been determined by chemical-shift measurements in their nuclear magnetic resonance spectra. The values of association constants for the molecular complexes are comparable to those obtained by optical spectroscopy. The effect on the association constants and relative chemical shifts of the acceptor protons of the pure complexes of various donors is considered. The association constants and relative chemical shifts of the complexes determined by different protons on the indoles in the presence of an excess of 1,3,5-trinitrobenzene are different. The possible structure of the complexes is discussed. The molecular complexes between tetracyanoethylene and various methoxyindoles have also been studied.

An electron donor (D) interacts with an electron acceptor (A), reversibly, usually weakly, to form a 1:1 molecular complex (DA).

$$D + A \overset{K}{\rightleftharpoons} DA \qquad [1]$$

The structure and chemistry of these electron donor-acceptor complexes (so-called charge-transfer complexes) between aromatic hydrocarbons and various electron acceptors have been extensively investigated in recent years (1–5). Molecular complex formation may be important in biological systems (6, 7). The activity of biologically active compounds may depend on their capacities to form such molecular complexes with biological receptors. Many biologically active compounds contain an indole ring. The molecular complexes of indole (8) and methylated indoles (9) with various electron-acceptor molecules have been studied by spectroscopic techniques. Szent-Györgyi and coworkers suggested that indole could form a complex with iodine in which the binding is localized over the C_2–C_3 positions (10). Nuclear magnetic resonance has been used to study molecular complexes between methylindoles and 1,3,5-trinitrobenzene $(NO_2)_3Bz$ (11). The NMR study supports the hypothesis that there is some localization over C_2–C_3 positions. Such observations do not directly demonstrate a preferred orientation of one molecule with respect to the other in the complex, although such an arrangement seems likely.

We have studied the molecular complexes between methoxyindoles and $(NO_2)_3Bz$. The methoxyindoles were chosen so as to have a different number of methoxy groups at various positions on the benzene ring of the indole compound. Several benzyloxy-substituted indoles were also studied. Some 1:1 solid complexes have been isolated. The association constants for the molecular complexes were determined by means of chemical-shift measurements and by spectrophotometric measurements. Structures of the complexes have been suggested. The binding between the two components may have some localization over the highest electrical charge position, namely the imino position of the indole. An optical study of molecular complexes between the methoxyindoles and tetracyanoethylene $(CN)_4C_2$ (12) is included.

Abbreviation: $(NO_2)_3Bz$, 1,3,5-trinitrobenzene.

EXPERIMENTAL

Materials. $(NO_2)_3Bz$ was recrystallized twice from ethanol: mp 123°. $(CN)_4C_2$ was sublimed twice at 100° (1 mm): mp 198°. Dimethoxyindoles and trimethoxyindoles were supplied by Dr. P. J. Mulligan, University of San Francisco. Monomethoxyindoles (Aldrich) and benzyloxyindoles (Regis) were sublimed or recrystallized from hexane–chloroform 1:1. All indoles had analytical data in accord with literature values. Dichloromethane and 1,2-dichloroethane, which were used as solvents, were spectro grade and were used without further treatment.

Solid Complexes of Methoxyindoles and $(NO_2)_3Bz$. Several stable complexes were isolated by mixing equimolar quantities of each component in dichloromethane and slowly evaporating the solvent. These solid complexes were recrystallized from chloroform–carbon tetrachloride 1:2 to give orange to deep-red crystals. The infrared spectra of the solid complexes, like other π-molecular complexes (1), are essentially composites of the spectra of the free components. NMR spectra and elemental analysis showed that they are 1:1 complexes. Melting point and elemental analyses for each of the complexes is shown in Table 1.

NMR Method. The association constants were measured by the method described by Foster (2), in the form:

$$\text{when } [D]_0 \gg [A] \quad \Delta^A_{obs}/[D]_0 = -\Delta^A_{obs}K + \Delta^A_{DA}K \qquad [2]$$

$$\text{when } [A]_0 \gg [D] \quad \Delta^D_{obs}/[A]_0 = -\Delta^D_{obs}K + \Delta^D_{DA}K \qquad [2a]$$

where $[A]_0$ and $[D]_0$ are initial concentration of acceptor and donor in mol/kg; K is the association constant for complex formation; Δ^A_{obs} or Δ^D_{obs} is the observed chemical shift of acceptor or donor protons in the presence of excess concentrations of donor or acceptor relative to the chemical shift of the particular protons in acceptor or donor in the absence of D or A; and Δ^A_{DA} or Δ^D_{DA} is the chemical shift of the measured protons in the acceptor or donor moiety in the pure complex

TABLE 1. *Elemental analyses of solid complexes*

Complex	mp	Calculated			Found		
		C	H	N	C	H	N
5-Methoxyindole–$(NO_2)_3Bz$	148	50.00	3.33	15.55	49.86	3.45	15.42
7-Methoxyindole–$(NO_2)_3Bz$	169	50.00	3.33	15.55	50.06	3.54	15.25
4,7-Dimethoxyindole–$(NO_2)_3Bz$	170	49.23	3.59	14.36	49.08	3.56	14.01
5,6-Methylenedioxyindole–$(NO_2)_3Bz$	150	48.13	2.67	14.97	47.86	2.73	14.57
5,7-Dimethoxyindole–$(NO_2)_3Bz$	190	49.23	3.59	14 36	49.30	3.70	14.00
6,7-Dimethoxyindole–$(NO_2)_3Bz$	118	49.23	3.59	14.36	49.43	3.69	14.35

DA. A plot of $\Delta^A_{obs}/[D]_0$ against Δ^A_{obs} or $\Delta^D_{obs}/[A]_0$ against Δ^D_{obs} should be linear, with gradient $-K$ in kg/mol. All NMR measurements were made on materials weighed into 0.45-cm diameter tubes and dissolved on a Varian HA-100D spectrometer with probe at 30.8°. Line positions of the proton resonance of the acceptor or donor molecule were measured relative to an internal tetramethylsilane reference. Each position was determined six times with a frequency counter, to an accuracy of ±0.1 Hz. The values of K and Δ^A_{DA} were determined by observation of the chemical shift of the protons in acceptor $(NO_2)_3Bz$ in dichloromethane, and also in 1,2-dichloroethane for some of the donors. The values of K and Δ^D_{DA} were determined by observation of the chemical shifts of the protons in donor (methoxyindoles) in 1,2-dichloroethane.

Spectrophotometric Method. The association constants, K, and molar absorptivity, ϵ_{DA}, were determined by the method of Benesi and Hildebrand (13) of the form:

$$\text{when } [D]_0 \gg [A]_0 \quad \frac{[A]_0 l}{d} = \frac{1}{[D]_0} \cdot \frac{1}{K\epsilon_{DA}} + \frac{1}{\epsilon_{DA}} \qquad [3]$$

$$\text{when } [A]_0 \gg [D]_0 \quad \frac{[D]_0 l}{d} = \frac{1}{[A]_0} \cdot \frac{1}{K\epsilon_{DA}} + \frac{1}{\epsilon_{DA}} \qquad [3a]$$

where $[A]_0$ and $[D]_0$ are initial concentration of acceptor and donor in mol/liter; d is the absorbance for an l-cm light path taken at maximum absorption; ϵ_{DA} is the molar absorptivity for the complex; and K (in liter/mol) is the association constant for complex formation. A plot of $[A]_0 l/d$ against $1/[D]_0$ should be linear, and yield ϵ_{DA} as the reciprocal of the intercept and the product $K\epsilon_{DA}$ as the reciprocal of the slope. For all complexes in this study, fairly good straight lines were obtained on absorbance plots. The absorption measurements were made with a Cary 14 recording spectrophotometer, equipped with a thermostatable sample-cell jacket. The measurements of absorption maximum were made either at a fixed acceptor concentration with different amounts of excess donor, or at a fixed donor concentration and various excess acceptor concentrations.

RESULTS AND DISCUSSION

Complexes between methoxyindoles and 1,3,5-trinitrobenzene

The association constants and relative chemical shifts, Δ^A_{DA} and Δ^D_{DA}, for complexes of various substituted indoles with $(NO_2)_3Bz$ in dichloromethane and in 1,2-dichloroethane, from measurements of the shifts of particular protons in the acceptor or donor, are shown in Table 2 and Table 3, respectively. The various proton chemical shifts of methoxyindoles are shown in Table 4. The dielectric constant of dichloromethane (9.08) is slightly lower than that of 1,2-dichloroethane (9.96) (14). In Table 2, the association constants are slightly higher in dichloromethane than in 1,2-dichloroethane and are similar to other charge-transfer complexes, in that the K values are decreased by a change of the solvent to one with a higher dielectric constant (1). The disubstituted indoles show higher association constants than mono- and trisubstituted indoles. For the same conditions, the association constants determined by NMR measurements are very close to the values determined by the spectrophotometric method, as shown in Table 5. The fact that there is no relationship between K and λ_{max} indicates that the binding forces of the molecular complexes are due to electrostatic or van der Waals forces and a minor charge-transfer force (15, 16). Increasing the methoxy

TABLE 2. *Equilibrium constants K and relative chemical shifts Δ^A_{DA} for complexes of methoxyindoles with $(NO_2)_3Bz$* in dichloromethane from measurements of the shifts of protons in the $(NO_2)_3Bz$ at 30.8°*

Donor compound	Δ^A_{DA}(Hz)	K (kg/mol)
Indole	169.9	0.886
N,N-Dimethyltryptamine	186.4	0.925
5-Methoxyindole	144.4 (140.5)†	1.189 (1.149)†
5-Methoxy-*N,N*-dimethyltryptamine	167.0	1.154
5-Benzyloxyindole	150 8	1.099
N-Methyl-5-methoxyindole	149.9	1.334
N-Ethyl-5-methoxyindole	153.0	1.120
2-Methyl-5-methoxyindole	133.5	1.923
6-Methoxyindole	142.3	1.202
7-Methoxyindole	151.7	1.743
4-Benzyloxyindole	146.0	1.518
4,5-Dimethoxyindole‡	93.6	1.874
4,6-Dimethoxyindole	121.7	2.054
4,7-Dimethoxyindole	122.9	3.680
5,6-Methylenedioxyindole	122.4 (120.0)†	1.110 (1.040)†
5,6-Dimethoxyindole‡	113.0	1.810
5-Methoxy-6-benzyloxyindole	128.8	1.460
5-Benzyloxy-6-methoxyindole	145.1	1.223
5,7-Dimethoxyindole	129.5 (126 3)†	2.401 (2.336)†
6,7-Dimethoxyindole	117.9 (115.0)†	1.540 (1.455)†
4,5,6-Trimethoxyindole	101.1	1.264
5,6,7-Trimethoxyindole	114.4	1.118

* Chemical shift of $(NO_2)_3Bz$ is 9.36 and 9.326 ppm in dichloromethane and 1,2-dichloroethane, respectively.

† In 1,2-dichloroethane.

‡ Low solubility.

TABLE 3. *Equilibrium constants, K, and relative chemical shifts, Δ^D_{DA}, for complexes of methoxyindole with $(NO_2)_3Bz$ in 1,2-dichloroethane from measurements of the shifts of protons in donors at 30.8°*

Donor compound	K (kg/mol)						Δ^D_{DA} (Hz)					
	H-2	H-3	H-4	H-5	H-6	H-7	H-2	H-3	H-4	H-5	H-6	H-7
5-Methoxyindole	2.440	1.573	1.412	—	1.202	1.744	27.0	63.1	95.4	—	75.2	63.6
N-Methyl-5-methoxyindole	2.885	1.799	2.081	—	*	2.209	30.5	62.1	90.5	—	*	62.9
6-Methoxyindole	2.165	1.446	1.414	1.170	—	1.586	29.2	66.0	88.4	79.5	—	70 0
7-Methoxyindole	3.372	2.142	2.596	*	*	—	34 4	62.1	70.5	*	*	—
4,5-Dimethoxyindole	2.048	1.710	—	—	1.750	1.720	24.9	63.1	—	—	47 8	50.2
4,6-Dimethoxyindole	3.313	2.266	—	2.299	—	2.825	39.6	87 6	—	69.6	—	66.2
4,7-Dimethoxyindole	4.530	2.810	—	3.975	3.786	—	41.5	81.0	—	49.1	53.2	—
5,6-Methylenedioxyindole	1.817	1.238	1.236	—	—	1.255	28.4	69.3	96.7	—	—	71.7
5,6-Dimethoxyindole	1.890	1.715	1.810	—	—	1.940	36.2	65.6	88.2	—	—	66.7
6,7-Dimethoxyindole	2.170	1.394	1.479	1.938	—	—	29.0	62.7	74.8	48.5	—	—
4,5,6-Trimethoxyindole	1.510	1.440	—	—	—	1.660	32.3	61.3	—	—	—	53.2
5,6,7-Trimethoxyindole	1.344	1.138	1.368	—	—	—	39.2	71.9	80.5	—	—	—

The solid complex of 5,7-dimethoxyindole was formed immediately.
* Overlap with other proton resonance.

or benzyloxy groups on the donor will increase the strength of the binding forces by increasing the polarizability and the electron-donating ability of the donor. It has been reported that bulky substituents on π-donors or π-acceptors markedly reduce their complexing ability (17). Since the methoxy or benzyloxy group is not in the plane of the indole ring, the lower association constants for trimethoxyindoles are probably due to a steric-hindrance effect. This effect may also play an important role on the disubstituted indoles. It is shown that the closer the disubstituent groups on the indole, the lower the association constant, and also, the larger the substituent group, the lower the association constant. The benzyloxy group is larger than the methoxy group; therefore, 5-methoxy-6-benzyloxyindole and 6-methoxy-5-benzyloxyindole show lower K values than 5,6-dimethoxyindole. The introduction of a methyl group in the *N*-, 2-, or 3-position moderately increases the association constant, but introduction of groups sterically larger than methyl does not cause much of an effect (11).

The protons in $(NO_2)_3Bz$ are shifted upfield in the presence of an excess of methoxyindoles; likewise, the various indole protons are shifted upfield in the presence of an excess of $(NO_2)_3Bz$. However, the latter shifts are less than the former. The charge-transfer effect may have a minor contribution. If charge-transfer is important in complex formation, the donor protons should be shifted downfield in the presence of an excess of the acceptor and the acceptor proton shift should go to a higher field as the complexes become stronger. The upfield shifting is believed to be due to ring-current effect of the aromatic structure in either the $(NO_2)_3Bz$ or the methoxyindole. The magnitude of Δ^A_{DA} shown in Table 2 decreases as the number of methoxy groups increases in the indole. This decrease may be the result of the combination of upfield shift due to ring-current effect and downfield shift due to electric-field effects of the donor on acceptor protons and alteration of the paramagnetic contribution to the acceptor proton shifts,

TABLE 4. *The chemical shift (ppm) of various protons for methoxyindoles* in 1,2-dichloroethane at 30.8°*

Compound	Chemical shift					
	H-2	H-3	H-4	H-5	H-6	H-7
5-Methoxyindole	7.17	6.42	7.05	—	6.79	7.28
N-Methyl-5-methoxyindole	7.01	6.33	7.02	—	6.80	7.19
6-Methoxyindole	7.08	6.41	7.44	6.72	—	6.88
7-Methoxyindole	7.17	6.45	7.19	6.96	6.62	—
4,5-Dimethoxyindole	7.14	6 54	—	—	6.93	7.04
4,6-Dimethoxyindole	6.92	6.46	—	6.18	—	6.49
4,7-Dimethoxyindole	7.09	6.23	—	6.50	6.34	—
5,6-Methylenedioxyindole†	7.06	6.36	6.96	—	—	6.86
5,6-Dimethoxyindole	7.05	6.37	7.03	—	—	6.90
5,7-Dimethoxyindole	7.12	6.38	6.63	—	6.31	—
6,7-Dimethoxyindole	7.11	6.41	7.21	6.81	—	—
4,5,6-Trimethoxyindole	7.02	6.49	—	—	—	6.65
5,6,7-Trimethoxyindole	7.11	6.37	6.80	—	—	—

* The chemical shifts of methoxy groups for various methoxyindoles are in the range of 3.78–4.01 ppm.
† The chemical shift of a methylene group is 5.89 ppm.

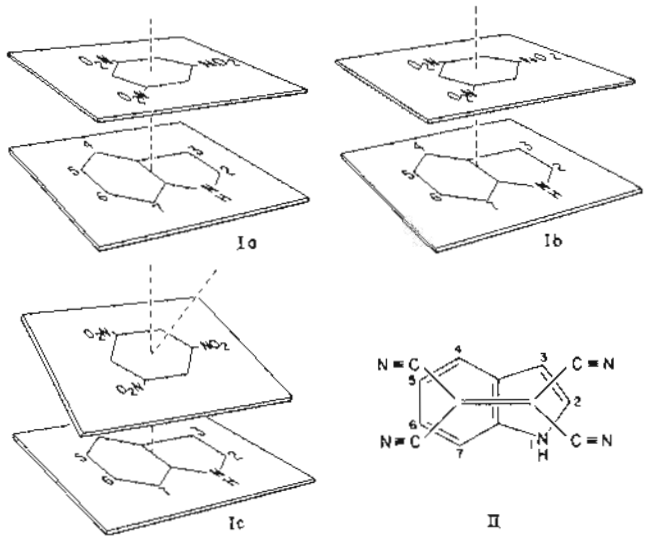
TABLE 5. *The wavelength of maximum absorption, molar absorptivity, and association constant of molecular complexes between methoxyindoles and $(NO_2)_3Bn$ in dichloromethane at 30.8°*

Donor compound	Optical method			NMR method
	λ_{max} (nm)	ϵ_{DA}*	K†	K†
Indole	375	2550	0.690	0.687
5-Methoxyindole	414	2500	0.981	0.922
6-Methoxyindole	400	2000	0.907	0.932
7-Methoxyindole	430	2000	1.35	1.351
4,7-Dimethoxyindole	496	1560	2.574	2.853
5,6-Methylenedioxyindole	413	2222	0.853	0.860
5,6-Dimethoxyindole	430	1818	1.492	1.403
5,7-Dimethoxyindole	420	2105	2.094	1.861
6,7-Dimethoxyindole	460	1500	1.180	1.194

* In liter mole^{-1} cm^{-1}.
† In liter mole^{-1}.

as discussed by Hanna and Ashbaugh (5) on molecular complexes between aromatic hydrocarbons and 7,7,8,8-tetracyanoquinodimethane. These downfield shifts become increasingly important as the number of methoxy groups on the indole increases.

One of the objectives of this work is to obtain information about the structure of the molecular complexes. The association constants and Δ^D_{DA} determined by different protons on indole are different (Table 3). The association constants determined from H-2 on the indole are always higher than values calculated with H-3, and the values of K determined from H-4 are always lower than the values of K determined from H-7. The relative chemical shifts Δ^D_{DA} for H-2 and H-7 are always smaller than the values of H-3 and H-4, respectively. The structure of the molecular complexes has been suggested from these data. The upfield shifts of both acceptor and donor protons in the formation of complex is mainly due to ring-current effect. The acceptor molecule must be parallel to the donor molecule, as shown in Structure I*a*. It is assumed



that the protons most perturbed, i.e., those having the largest Δ^D_{DA} value, are those lying closest to the center of the other component of the complex. The relative chemical shift Δ^D_{DA} for H-3 and H-4 of the indole in the formation of complex is larger than the chemical shift of H-2 and H-7, respectively; therefore, the protons 3 and 4 must be closer to the center of the $(NO_2)_3Bz$ ring (Structure I*b*). The fact that the association constants determined from H-2 and H-7 are higher than the K values determined from H-3 and H-4, respectively, implies that in the formation of complex the binding has some localization over positions 2 and 7 compared with positions 3 and 4, respectively. Structure I*c* is suggested as the geometrical orientation between methoxyindoles and $(NO_2)_3Bz$, with the plane of donor and acceptor inclined and laterally displaced. The *N*-, 1-, and 7-positions of the indole are closer to the acceptor molecule. It is possible that the interaction of an indole with a $(NO_2)_3Bz$ molecule is localized over the nitrogen atom of the indole that has the highest electrical charge (19). It is not possible to predict the degree of inclination and displacement of the two components. It might be different for each of the complexes, because the relative association constants determined from various protons of the indole differ for different complexes.

Complexes between methoxyindoles and tetracyanoethylene

Tetracyanoethylene does not contain a hydrogen atom. The molecular complexes between methoxyindoles and tetracyanoethylene were studied by spectrophotometric measurements. The wavelength of absorption maximum, association constants, and molar absorptivity for all complexes were determined in dichloromethane at room temperature (24.5 ± 0.5°), and are summarized in Table 6. The association constants determined in the presence of an excess of acceptor agree with the values determined in the presence of an excess of donor. The decomposition rate of the complex between indole and $(CN)_4C_2$ is faster in the higher concentration of the indole (8). The determination must be made immediately after mixture of the two components if a higher concentration of donor is used. Some of the complexes were not stable, so it was not possible to determine the association constant at room temperature. The dimethoxyindoles show higher association constants than mono- or trimethoxyindoles with $(CN)_4C_2$, as they did with $(NO_2)_3Bz$. It may be that the steric-hindrance effect also plays an important role, even though $(CN)_4C_2$ is a planar molecule. In the complexes, the $(CN_4)C_2$ molecule may be located above the indole nucleus, as shown in Structure *II*. The steric requirements are stronger where both 4,5- or 6,7-positions are substituted. The effect can explain the

TABLE 6. *The wavelength of maximum absorption, molar absorptivity, and association constant of molecular complexes between methoxyindoles and $(CN)_4C_2$ in dichloromethane at room temperature (24.5 ± 0.5°)*

Donor compound	λ_{max} (nm)	$[A]_0 \gg [D]_0$ ϵ_{DA}	$[A]_0 \gg [D]_0$ K	$[D]_0 \gg [A]_0$ ϵ_{DA}	$[D]_0 \gg [A]_0$ K
Indole	550	2000	2.97	2100	2.79
5-Methoxyindole	630	2940	5.07	3300	5.05
2-Methyl-5methoxyindole	665	—	—	4200	9.40
6-Methoxyindole	720	2325	5.68	2000	6.60
	565	2048	5.49	—	—
7-Methoxyindole	680	2040	7.43	1820	8.20
	555	1700	7.31	—	—
4,5-Dimethoxyindole	730	2130	5.63	unstable	
4,6-Dimethoxyindole	775	3080	11.32	—	—
4,7-Dimethoxyindole	790	3921	11.78	3640	11.30
	525	1785	12.29	—	—
5,6-Methylenedioxyindole	710	—	—	3300	4.30
5,6-Dimethoxyindole	725	3378	10.28	unstable	
5,7-Dimethoxyindole	690	2860	13.02	2500	14.71
6,7-Dimethoxyindole	750	2500	5.71	2720	4.30
	550	—	—	—	—
4,5,6-Trimethoxyindole	710	2222	5.82	—	—
5,6,7-Trimethoxyindole	675	2222	5.33	2222	5.05

Units of constants as in Table 5.

lower K values of 4,5- and 6,7-dimethoxyindoles, as compared with other dimethoxyindoles.

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