

The Solvent and Concentration Dependence of the Nuclear Magnetic Resonance Spectra of Indoles¹

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Abstract: The effect of solvent and concentration on the nmr spectra of several indoles has been investigated. Dilution of a carbon tetrachloride solution of an indole or replacement of this solvent with a more polar one such as tetrahydrofuran causes a selective paramagnetic shift of the signals of the hydrogen or methyl substituents at the 2 and 7 positions. These shifts are rationalized by a self-association of indoles in carbon tetrachloride solution which is broken up on dilution or by hydrogen bonding to more polar solvents. The self-association appears to arise from a combination of hydrogen bonding and local dipole interactions. Possible models for the association complexes are discussed.

The nmr spectra of aromatic compounds often display unusual solvent and concentration effects.^{3,4} Several explanations for these phenomena have been suggested,⁵⁻⁷ and additions or modifications to these theories are still forthcoming.⁸⁻¹¹ Our own interest in this area¹ developed during investigations on the structure of the indole Grignard reagent by nmr spectroscopy¹² when it was noted¹³ that the 2- but not the 3-proton resonance of indole occurs at considerably lower fields in tetrahydrofuran than in carbon tetrachloride. Similar selective, paramagnetic solvent shifts of the 2-proton resonance were observed with other polar solvents both by us (Table I) and by Jardine and Brown¹⁴ who proposed this phenomenon as a useful tool for distinguishing 2 and 3 substitution in indoles.¹⁵

Table I. Chemical Shifts (τ) of 10% Solutions of Indole

Solvent	τ_2	τ_3
Carbon tetrachloride	3.38	3.67
Tetrahydrofuran	2.89	3.62
1,2-Dimethoxyethane	2.82	3.57
Dimethoxymethane	2.85	3.52
Diethyl ether	2.87	3.57
Dioxane	2.80	3.50
Dimethyl sulfoxide	2.67	3.54

(1) Portions of this paper have previously appeared in: (a) Abstracts of the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 56Q; (b) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *Chem. Ind.* (London), 151 (1964); (c) Ph.D. Dissertation of J. F. Sebastian, University of California, Riverside, 1965.

(2) To whom inquiries should be sent at Texas Christian University.

(3) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 424.

(4) P. Laszlo, *Progr. Nucl. Magnetic Resonance Spectry.*, 3, 348 (1967).

(5) T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, 32, 1218 (1960).

(6) W. G. Schneider, *J. Phys. Chem.*, 66, 2653 (1962).

(7) J. Ronayne and D. H. Williams, *J. Chem. Soc., B*, 540 (1967).

(8) D. H. Williams, J. Ronayne, and R. G. Wilson, *Chem. Commun.*, 1089 (1967).

(9) D. J. Barraclough, P. W. Hickmott, and O. Meth-Cohn, *Tetrahedron Letters*, 4289 (1967).

(10) Y. Ichikawa and T. Matsuo, *Bull. Chem. Soc. Japan*, 40, 2030 (1967).

(11) T. Ledaal, *Tetrahedron Letters*, 1683 (1968).

(12) M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *ibid.*, 1183 (1963).

(13) Reference 12, footnote 9.

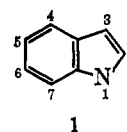
(14) R. V. Jardine and R. K. Brown, *Can. J. Chem.*, 41, 2067 (1963).

(15) As has been pointed out,¹⁵ this method of structural elucidation is valid only if concentrations are also taken into consideration.

Further studies in our laboratory established that the 7-proton resonance in certain substituted indoles also undergoes a paramagnetic solvent shift in tetrahydrofuran^{1a} and that the 2- but not the 3-proton resonance of indole, either in tetrahydrofuran or carbon tetrachloride, is remarkably concentration dependent.^{1b} The present paper will combine, extend, and explain these observations on the solvent and concentration dependence of the nmr spectra of several simple indoles.

Results

The nmr spectrum of indole (1) in carbon tetrachlo-



ride contains two, well-separated, one-proton peaks at approximately τ 3.3 and 3.6 which have been assigned to the 2- and 3-protons, respectively.¹⁶ The resonance of the latter proton is readily identified in the nmr spectra of all compounds and in all solvents utilized in this study. As previously noted,^{1,13} however, the 2-proton resonance shifts downfield sufficiently in tetrahydrofuran that it often overlaps the complex, benzenoid proton multiplet. In these cases the location of the 2-proton resonance was usually determined by decoupling it from the 1-proton by rapid, base-catalyzed exchange of the latter with a trace of indolylsodium¹⁷ and observing which peak in the nmr spectrum collapsed from a quartet ($J_{1,2} = 2.4$ cps; $J_{2,3} = 3.3$ cps)^{18,19} to a doublet.²⁰

With 1-methylindole, where this technique could not be used, the 2-proton resonance was located by observing its shift to progressively lower fields as the solvent

(16) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, 82, 2184 (1960).

(17) S. Gronowitz, A. Hornfeldt, B. Gestblom, and R. Hoffman, *Arkiv Kemi*, 18, 133 (1961).

(18) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

(19) P. J. Black and M. L. Heffernan, *Australian J. Chem.*, 18, 353 (1965).

(20) The reported coupling ($J = 0.4$ cps) of the 2- and the 6-proton of some indoles²¹ was not observed. As expected the 3-proton resonance also collapsed under the exchange conditions to a quartet ($J_{3,7} = 0.7$ cps).¹⁸

(21) M. Martin-Smith, S. T. Reid, and S. Sternhell, *Tetrahedron Letters*, 2393 (1965).

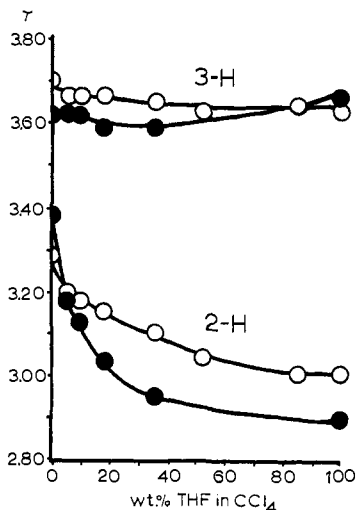


Figure 1. Chemical shifts of the 2- and 3-protons of indole, —●—, and 1-methylindole, —○—, in 10 wt % solutions of carbon tetrachloride and tetrahydrofuran of varying composition.

was changed in increments from pure carbon tetrachloride to pure tetrahydrofuran (Figure 1). The chemical shifts of the 4-, 5-, 6-, and 7-protons were obtained by a first-order analysis^{22,23} of the nmr spectra of the benzene ring methylated indoles.

Representative chemical shifts obtained in this manner are collected in Tables I-III and compared in

Table II. Chemical Shifts of Several Indoles in Tetrahydrofuran and Carbon Tetrachloride^a

Compound	Solvent	τ_2	τ_3	τ_4	τ_5	τ_6	τ_7
Indole	CCl ₄	3.38	3.67				
	THF	2.89	3.62				
1-Methylindole	CCl ₄	3.29	3.70				
	THF	3.03	3.60				
2-Methylindole	CCl ₄	7.97	4.00				
	THF	7.65	3.93				
3-Methylindole	CCl ₄	3.55	7.78				
	THF	3.11	7.72				
5-Methylindole	CCl ₄	3.25	3.66	2.67	7.58	3.07	3.07
	THF	2.88	3.64	2.65	7.60	3.09	2.75
7-Methylindole	CCl ₄	3.33	3.65				7.82
	THF	2.88	3.60				7.55
2,5-Dimethylindole	CCl ₄ ^b	7.72	4.01	2.83	7.58	3.16	3.16
	THF	7.66	4.02	2.85	7.66	3.23	2.94
2,6-Dimethylindole	CCl ₄	7.91	4.01	2.75	3.23	7.63	3.48
	THF		4.00	2.77	3.26		3.03
2,7-Dimethylindole	CCl ₄	7.78	3.92				7.75
	THF	7.60	3.87				7.57

^a All solutions 10% by weight unless otherwise noted. ^b 3% solution. Italics indicate methyl group.

Figure 2 as solvent shifts ($\Delta_s = \tau_{\text{THF}} - \tau_{\text{CCl}_4}$) and in Figure 3 as dilution shifts ($\Delta_d = \tau_{10\%} - \tau_{0\%}$). The effect of concentration on the chemical shifts of the 2- and 3-hydrogen atoms of indole in carbon tetrachloride and tetrahydrofuran is illustrated in Figures 4 and 5, respectively.

(22) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 89 ff.

(23) This approximation is justified since the errors so introduced are small compared to the effects under consideration and because the values so obtained are in reasonable agreement with literature values^{19,24} if the effects of the added methyl groups²⁴ are taken into account.

(24) R. Romanet, A. Chemizart, S. Cuhoux, and S. David, *Bull. Soc. Chim. France*, 1048 (1963).

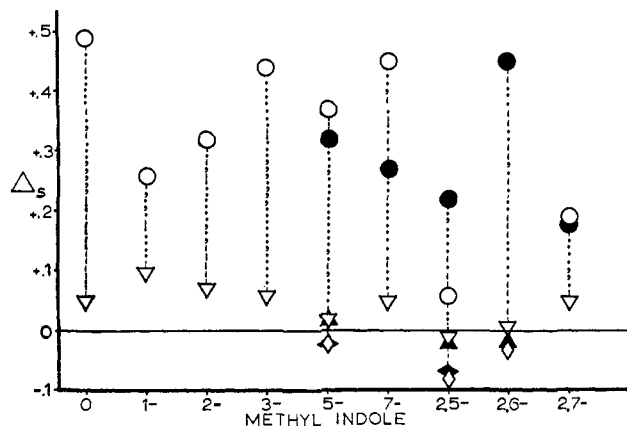


Figure 2. Solvent shifts ($\Delta_s = \tau_{\text{THF}} - \tau_{\text{CCl}_4}$) of protons or methyl groups at selected positions (2, ○; 3, ▽; 4, ▲; 5, ◇; 6, ◆; 7, ●) of several methylindoles.

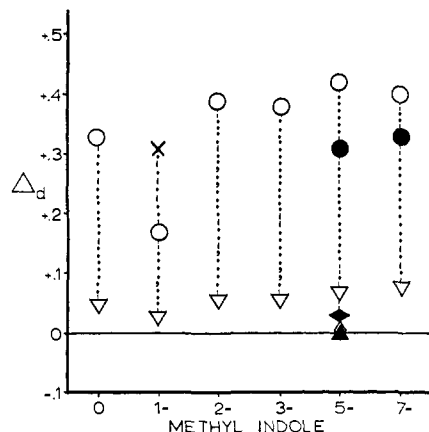


Figure 3. Dilution shifts ($\Delta_d = \tau_{10\%} - \tau_{0\%}$) of proton or methyl groups at selected positions (1, ×; 2, ○; 3, ▽; 4, ▲; 5, ◇; 6, ◆; 7, ●) of several methylindoles in carbon tetrachloride.

These data substantiate the selective solvent^{13,14} (Figure 2) and concentration^{1b} (Figure 3) dependence of the 2-proton chemical shift of indoles and also reveal a

Table III. Hydrogen Chemical Shifts of Several Indoles in Carbon Tetrachloride at Selected Concentrations

Compound	Position	τ at mol % indole concn of	
		10 ^a	0 ^a
Indole	2	3.26	2.92
	3	3.62	3.55
1-Methylindole	1	6.46	6.15
	2	3.24	3.07
2-Methylindole	3	3.68	3.65
	2	7.93	7.55
3-Methylindole	3	3.95	3.90
	2	3.50	3.12
5-Methylindole	3	7.73	7.68
	2	3.34	2.92
7-Methylindole	3	3.71	3.63
	4	2.70	2.69
7-Methylindole	5	7.60	7.60
	6	3.20	3.17
7-Methylindole	7	3.05	2.74
	2	3.38	2.96
7-Methylindole	3	3.66	3.57
	7	7.82	7.50

^a These values were obtained from a plot of concentration vs. chemical shift similar to that in Figure 4. Italics indicate methyl group.

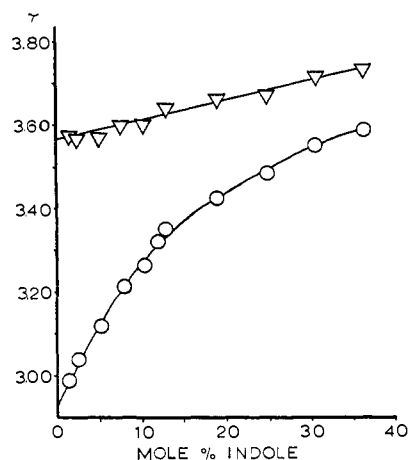


Figure 4. Concentration dependence of chemical shifts of 2-(—○—) and 3-(—▽—) protons of indole in carbon tetrachloride.

similar effect for the resonances of the 7-proton^{1a,25} and, to a lesser extent, of the 2- and 7-methyl groups. The only compounds where the 2- and/or 7-proton resonances themselves fail to show a solvent or dilution shift of the usual magnitude (0.3–0.5 ppm) are 1-methylindole and 2,5-dimethylindole. In the latter case the small solvent shift is probably due to the low solubility of 2,5-dimethylindole in carbon tetrachloride; thus, the 7-proton signal already may be shifted downfield to an appreciable extent by the concentration effect because a 3% instead of the usual 10% solution was used. The halving of the solvent and dilution shifts of the 2-proton resonance of 1-methylindole compared to indole itself is not due to low solubility, however, and must arise from perturbations in the ultimate phenomena responsible for these shifts.

Although the 2-proton resonance of indoles is concentration dependent in either carbon tetrachloride (Figure 4) or tetrahydrofuran (Figure 5), the nature of the dependence is reversed in the two solvents; the greatest change in chemical shift occurs at low concentrations in the former solvent and at high concentrations in the latter.

Another noteworthy feature of the concentration-dependence curves is that for all the indoles investigated, except 1-methylindole, the curves for the 2- and 7-protons or methyl groups are essentially similar in shape but different from those of the protons or methyl groups at the other positions.

Discussion

The solvent and concentration effects described above must arise from either solvent–solute or solute–solute interactions. The dilution studies carried out in pure solvents serve as useful starting points for a discussion of these interactions.

The most obvious explanation for the concentration effects in carbon tetrachloride would be the characteristic, nonspecific dilution shift of aromatic molecules.³ Such a process is consistent with the decreased dilution shift of 1-methylindole, since substituents increase the

(25) A selective solvent shift of the resonance of the analogous 8-proton of several tetrahydrocarbazole derivatives has been reported by (a) G. Van Binst, C. Danheux, C. Hootele, J. Pecher, and R. H. Martin, *Tetrahedron Letters*, 973 (1964); (b) G. Van Binst, C. Danheux, and R. H. Martin, *Bull. Soc. Chim. Belges*, 75, 181 (1966).

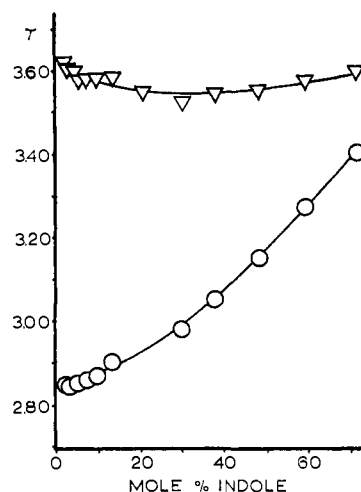


Figure 5. Concentration dependence of chemical shifts of 2-(—○—) and 3-(—▽—) protons of indole in tetrahydrofuran.

molecular volume which in turn is inversely proportional to the magnitude of the dilution shift.²⁶ However, since several other methylindoles have dilution shifts greater than indole itself (Figure 3), this phenomenon cannot be solely responsible for the concentration effects in carbon tetrachloride.

Although specific solvent–solute interactions are usually considered to be absent in carbon tetrachloride, this assumption is not necessarily correct.²⁷ Such effects can be neglected in this case since the greatest change in chemical shift occurs in dilute solutions of the indoles in carbon tetrachloride (Figure 4) which is exactly the reverse of what would be expected for a solute–solvent interaction. Therefore it appears that specific solute–solute interactions must be involved.

Self-association of five-membered, nitrogen heterocycles is well known for pyrroles^{28–35} and purines.^{36,37} Because of the similarity in structure of these compounds and indole, the occurrence of a related phenomenon is not unexpected. The diamagnetic shift of the 2-proton resonance of indole as the temperature is decreased (Table IV) is consistent with an exothermic

Table IV. Temperature Dependence of the 2- and 3-Proton Signals of 10% Indole in Carbon Tetrachloride

°C ± 2	τ ± 0.02	
	2-H	3-H
32	3.25	3.58
14	3.29	3.59
0	3.37	3.60

(26) A. A. Bothner-By and R. E. Glick, *J. Chem. Phys.*, 26, 1651 (1957).

(27) Reference 4, p 244.

(28) M. Josien, P. Pineau, M. Paty, and N. Fuson, *J. Chem. Phys.*, 24, 1261 (1956).

(29) J. A. Happe, *J. Phys. Chem.*, 65, 72 (1961).

(30) M. Gomel and H. Lumbroso, *Bull. Soc. Chim. France*, 220 (1962).

(31) H. J. Anderson, *Can. J. Chem.*, 43, 2387 (1965).

(32) H. Lumbroso, *J. Chim. Phys.*, 61, 132 (1964).

(33) A. Weisbecker, *ibid.*, 63, 838 (1966).

(34) M. T. Chenon and N. Lumbroso-Bader, *Compt. Rend.*, 266, 293 (1968).

(35) D. M. Porter and W. S. Brey, Jr., *J. Phys. Chem.*, 72, 650 (1968).

(36) S. I. Chan, M. P. Schweizer, P. O. P. Ts'o, and G. K. Helmkamp, *J. Am. Chem. Soc.*, 86, 4182 (1964).

(37) N. S. Kondo, *Dissertation Abstr.*, 28B, 4067 (1968).

association in which the average distance between indole molecules decreases at reduced temperatures. The small dilution shift of 1-methylindole suggests that the N-H group of indole may be involved in the self-association process. This is supported by analogy to related systems^{28-30, 32, 33} and by the observation of two concentration-dependent bands at 3490 cm⁻¹ (sharp, free N-H) and 3420 cm⁻¹ (broad, bonded N-H) in the infrared spectra of indole in carbon tetrachloride. As expected the relative intensity of the former increases on dilution.

In contrast to the situation in carbon tetrachloride, the nature of the concentration dependence of the nmr spectra of indoles in tetrahydrofuran (Figure 5) is typical for a solvent-solute interaction (very little change in chemical shift at lower concentrations). By analogy to pyrrole-ether systems,^{30, 32, 38-41} this interaction probably involves hydrogen bonding of the indole N-H to the ether oxygen atom. At very high concentrations of indole (50-70 mol %), the high-field position of the 2-proton signal suggests that some solute-solute interaction may also be occurring.

These two types of interactions of indoles in different solvents can explain the solvent shifts, Δ_s (Figure 2, Table II). In carbon tetrachloride 10% solutions of indoles are associated, while at the same concentrations in tetrahydrofuran they are not. Therefore a decrease in shielding by adjacent indole molecules takes place when tetrahydrofuran breaks up these aggregates. The fact that dilution in carbon tetrachloride (Figure 3) affects the same proton resonances in the same way constitutes a strong argument for this interpretation.

Hydrogen bonding between indole and tetrahydrofuran also could be responsible for at least a portion of the solvent shifts. If the stretched and hence polarized N-H bond in an hydrogen-bonded complex is assumed to approximate a nonbonded electron pair or a carbon-metal bond, then a calculation of the chemical shift of various protons⁴² using the point anisotropy approximation^{43, 44} reveals that only the 2- and 7-proton resonances will appear at appreciably lower fields than in indole itself. This agrees with observation (Figure 2, Table II).

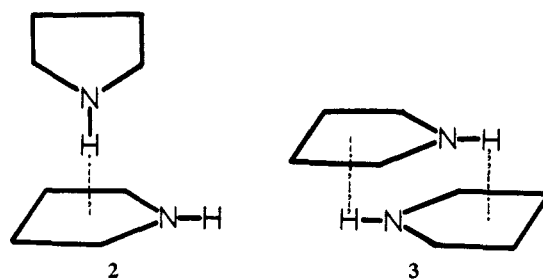
The mixed solvent studies (Figure 1) suggest some additional features of these interactions. At that solvent composition (7 wt % tetrahydrofuran) where the number of tetrahydrofuran molecules is equal to the number of indole molecules, the chemical shift of the 2-hydrogen atom is exactly half way between its values in the two pure solvents. It therefore appears that in carbon tetrachloride the tendency for indole to associate with itself and with tetrahydrofuran is approximately equal.

The 2-proton resonance of 1-methylindole is not as sensitive to solvent composition as that of indole. In 6% tetrahydrofuran the number of 1-methylindole molecules is equal to the number of tetrahydrofuran

molecules and the chemical shift of the 2-proton resonance is significantly closer to its value in pure carbon tetrachloride than was the 2-proton resonance of indole. This suggests that in carbon tetrachloride 1-methylindole prefers to associate with itself rather than with tetrahydrofuran.

The difference in the tendencies of indole and 1-methylindole to associate with themselves *vs.* tetrahydrofuran is consistent with a hydrogen-bonding interaction between indole and tetrahydrofuran.^{30, 32, 38-41} However, the apparent ability of 1-methylindole to self-associate is not consistent with hydrogen bonding being the *exclusive* mechanism for the self-association of indole.

The ability of an indole type N-H to participate in hydrogen bonding is supported by a large number of studies^{30, 32, 38-41} including our own results in tetrahydrofuran. Although the nitrogen atom in such a molecule would not be expected to be a good hydrogen-bond acceptor, the π system of aromatic compounds can function in this way.^{45, 46} In the case of pyrrole this type of interaction would lead to one of two types of complexes (only dimers shown), open (2) or closed (3).



The preponderance of available evidence favors the latter of these.^{29, 30} Since the strength of a nonlinear hydrogen bond as in 3 would be expected⁴⁷ to be substantially lower than normal, other forces must be at least partially responsible for this type of self-association. This conclusion is supported in the pyrrole case by the observation that 1-methylpyrrole probably associates in the same way and to the same extent as pyrrole itself.³¹ In the indole series, hydrogen bonding may be more important since 1-methylindole displays decreased solvent and dilution shifts compared to indole. An alternative explanation for this decrease would be steric hindrance to association by the 1-methyl group. Why 1-methylpyrrole or the other methylindoles are not similarly affected might be due to the detailed configuration of the complex. Whichever explanation is correct it is clear that the self-association of indole must involve other forces in addition to hydrogen bonding.

A consideration of the nature of these forces therefore seems in order. At least four different processes can be envisioned for the specific solute-solute interactions of aromatic compounds: π complexing, charge-transfer complexing, hydrophobic (apolar) interactions, and van der Waals forces.

The association of a specific proton in a solute with the π electrons of either another solute molecule or an aromatic solvent molecule (π complexing) was postu-

(38) M. Gomel and H. Lumbruso, *Bull. Soc. Chim. France*, 2212 (1962).

(39) M. Veyret and M. Gomel, *Compt. Rend.*, 258, 4506 (1964).

(40) M. Gomel, *ibid.*, 261, 403 (1965).

(41) F. Strobusch and H. Zimmermann, *Ber. Bunsenges. Phys. Chem.*, 71, 567 (1967).

(42) J. F. Sebastian, M. G. Reinecke, and H. W. Johnson, Jr., *J. Phys. Chem.*, 73, 455 (1969).

(43) G. Fraenkel, D. G. Adams, and R. R. Dean, *ibid.*, 72, 944 (1968).

(44) H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).

(45) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 202.

(46) Z. Yoshida and E. Osawa, *J. Am. Chem. Soc.*, 87, 1467 (1965) 88, 4019 (1966).

(47) Reference 45, p 242.

lated to rationalize anomalous solvent effects in the nuclear magnetic resonance spectra of substituted benzenes.⁵ Although this hypothesis subsequently was abandoned in favor of a dipole-induced dipole model,⁶ it was considered, and rejected, as an explanation for the association of purines.^{36,37} The basis for rejection was that the strength of such an association should be dependent on the relative acidities of the protons being complexed, yet ring protons and alkyl group protons displayed the same concentration shifts. A similar argument can be constructed from our data (Table III, Figure 3).

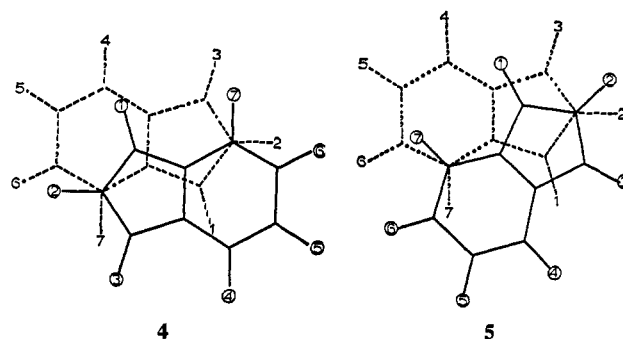
Charge-transfer complexing among biologically important molecules⁴⁸ such as purines,⁴⁹ pyrimidines,⁴⁹ and indoles⁵⁰⁻⁵⁴ is well known. Several different lines of evidence have suggested that in the latter molecules the donation of π electrons is localized over the C-3 position.⁵¹⁻⁵³ A recent nmr study of the interactions of indole with nitrobenzene derivatives⁵⁰ has substantiated this hypothesis and shown that the 3- and not the 2-proton resonance is most sensitive to added acceptors. Since the reverse is true for the dilution shifts in our studies (Table III, Figure 3), charge-transfer complexation does not appear to be important in the self-association of indoles.

An important driving force for the well-demonstrated association of purines and pyrimidines in aqueous solution^{36,37,55-57} is postulated to be some form of apolar bonding. Regardless of the mechanism (hydrophobic⁵⁸ or hydrotactoid⁵⁹) for this type of bonding, it ultimately is a manifestation of the strong solvent-solute interaction of water. Since carbon tetrachloride does not possess a strong tendency to associate with itself, apolar interactions should be unimportant for solutes in this solvent.

The remaining forces which lead to molecular association are known as van der Waal's forces and consist of three components: the dipole orientation force, the induction force, and the dispersion force.⁶⁰ The first of these appears to correlate well with the benzene-induced nmr solvent shifts of aliphatic molecules containing one polar group^{6,61} but not with those of aromatic solutes⁶ or with the relative ability of purines and pyrimidines to associate.^{56,62} The correlation of the latter phenomenon with the polarizability of the bases⁵⁶ suggests⁶⁰ that either induction or dispersion forces are the chief mechanism for association. The latter forces have

been implicated in the stability of the DNA helix⁶³ and the former are the basis for current theories⁶⁻¹¹ on the nature of benzene-induced nmr solvent shifts of both aliphatic and aromatic molecules. These same theories⁶⁻¹¹ involving nonplanar, local dipole-induced dipole complexes seem to offer the best explanation for the self-association of indole as well. A final, most persuasive argument in favor of this view is that the magnitude and direction of the solvent and dilution shifts of the nmr signals of the various positions in indole as revealed in the present study are essentially parallel to those of the benzene-induced solvent shifts previously reported.⁶⁴

One of the remaining questions concerning the self-association of indole is the relative orientation of the indole molecules in the complex. According to Williams' theory on the origin of benzene-induced solvent shifts,⁷ the favored orientation of these complexes is one in which the benzene molecules associate with the positive ends, and as far as possible from the negative ends, of local dipoles in the solute molecule. In the case of indole, this would require association over the nitrogen atom and away from position 3 similar to the benzene-pyrrole complex.^{7,11} Although such complexes are often nonplanar,^{7,11} the fact that the self-association of indole is a reciprocal interaction, as well as the probability that this association goes beyond the dimer stage,²⁸⁻³³ would tend to favor planar complexes. In order to accommodate the selective solvent and dilution shifts of the 2- and 7-proton resonances, only these positions along with the nitrogen atom must lie in the region of maximum shielding⁶⁵ above the plane of an adjacent indole ring. The above considerations lead to two approximate time-averaged orientations for associated indole, 4 and 5. Either of these rationalizes the de-



creased solvent shift of the 2- and 7-methyl resonances of 2,7-dimethylindole (Table V), since substituents at the

(48) A. Szent-Györgyi, "Introduction to a Submolecular Biology," Academic Press, New York, N. Y., 1960, pp 54-91.

(49) B. Pullman and M. Weissbluth, "Molecular Biophysics," Academic Press, New York, N. Y., 1965, pp 141-170.

(50) R. Foster and C. A. Fyfe, *J. Chem. Soc., B*, 926 (1966).

(51) A. Szent-Györgyi and I. Isenberg, *Proc. Natl. Acad. Sci. U. S. A.*, 46, 1334 (1960).

(52) A. Szent-Györgyi, I. Isenberg, and J. McLaughlin, *ibid.*, 47, 1089 (1961).

(53) J. P. Green and J. P. Mabrieu, *ibid.*, 54, 659 (1965).

(54) R. Foster and P. Hanson, *Trans. Faraday Soc.*, 60, 2189 (1964).

(55) M. P. Schweizer, S. I. Chan, and P. O. P. Ts'o, *J. Am. Chem. Soc.*, 87, 5241 (1965).

(56) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *ibid.*, 89, 3612 (1967).

(57) M. P. Schweizer, A. D. Brown, P. O. P. Ts'o, and D. P. Hollis, *ibid.*, 90, 1042 (1968).

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Table V. Selected Solvent Shifts (Δ_s) of Several Methylindoles^a

Δ_s for	Methylindole			
	5	2	7	2,7
2-position	0.37	0.32	0.45	0.18
7-position	0.32		0.27	0.18

^a Data taken from Table II.

2 and 7 positions would increase the distance between the associated indole molecules.

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Analogy to pyrrole association^{29,30} and local dipole-dipole considerations favor **5** as does the fact (Table V) that in 7-methylindole the solvent shift of the 2-proton resonance is exceptionally high and that of the 7-proton is somewhat low. This may be rationalized by orientation **5** if the mutual repulsion of the adjacent 7-methyl groups would force them further from, and the 2 positions closer to, the aromatic rings of the adjacent indole molecule in the complex. A similarly convenient rationalization for **4** is not available.

Further information on the preferred orientation of indole complexes may be available from studies of substituted derivatives similar to those in the purine series.³⁷

Experimental Section

Equipment. The nmr spectra were taken at $38 \pm 2^\circ$ on a Varian Associates A-60 spectrometer operating at 60 Mcps. Chemical shifts were obtained from precalibrated chart paper with the internal tetramethylsilane reference signal set at τ 10.00. The calibration was checked frequently with a chloroform-tetramethylsilane standard. A variable-temperature probe regulated with a Varian V-6040 variable-temperature controller was used for the temperature studies.

Infrared spectra were taken on a Perkin-Elmer 421 grating spectrophotometer. Band positions were checked against the 1028, 1603, and 3083 cm^{-1} absorption bands of a polystyrene film.

All melting points (corrected) were determined on a Thomas-Hoover capillary melting point apparatus.

Solvents. Tetrahydrofuran was stored over potassium hydroxide and distilled immediately before use from lithium aluminum hydride. Dioxane, dimethoxymethane, 1,2-dimethoxyethane, and diethyl ether were distilled from sodium. Dimethyl sulfoxide was treated with molecular sieves and then vacuum distilled. Carbon tetrachloride was of reagent quality and stored in dark bottles.

Indoles. With two exceptions noted below the indoles used in this study were obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis. Indole, mp $52-53^\circ$ (lit.⁶⁶ $52-53^\circ$), 2-methylindole, mp $59-61^\circ$ (lit.⁶⁷ 62°), 3-methylindole, mp $94-96^\circ$ (lit.⁶⁷ 96.5°), 7-methylindole, mp $81-83^\circ$ (lit.⁶⁷ 85°), and 2,7-dimethylindole, mp picrate $154-155^\circ$ (lit.⁶⁷ 156.5°), were used without further purification. 5-Methylindole, mp $58-60^\circ$ (lit.⁶⁷ 59.5°), and 2,5-dimethylindole, mp $114-115^\circ$ (lit.⁶⁷ 115°), were sublimed before use. 1-Methylindole was prepared by the method of Potts and Saxton⁶⁸ and purified by elution from a neutral alumina column with high-boiling petroleum ether (bp $60-90^\circ$). 2,6-Dimethylindole was prepared by the method of Marion and Oldfield⁶⁷ and purified by sublimation, mp $85-86^\circ$ (lit.⁶⁷ 88.5°), mp picrate $137-138^\circ$ (lit.⁶⁷ 138.5°).

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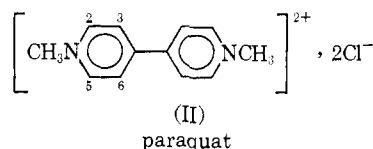
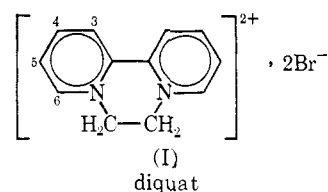
Nuclear Magnetic Resonance Studies of Diquat, Paraquat, and Their Charge-Transfer Complexes¹

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Abstract: The proton magnetic resonance spectra of two quaternary pyridinium salts, diquat (I) and paraquat (II), in D_2O solution have been reported. A complete analysis of the spectra has been carried out, and the coupling constants and the chemical shifts for various protons are reported. These studies have indicated a strong tendency for ion association of these cations with electron-donating anions. Iodide and ferrocyanide ions form charge-transfer-type complexes with diquat and paraquat, while ferricyanide ions form an outer-sphere-type ion pair. The association constant for the ion association has been measured using nuclear magnetic resonance and absorption spectrophotometry. The results obtained by the two methods are in good agreement.

Diquat (I) and paraquat (II), also known by the name viologens, are employed as herbicides.³ In solution they form free radicals, either by the action of sunlight or by the presence of reducing agents. They also form charge-transfer complexes in the presence of various anions. The formation of free radicals and charge-transfer complexes plays an important role in determining their biological activity.⁴ The electron spin resonance spectra^{5,6} of the diquat and paraquat



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free radicals and a preliminary investigation of the charge-transfer complexes of paraquat and potassium ferrocyanide have been reported.⁷ In this paper we

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