Molecular Complexing Ability of Quinoline and Its Simple Derivatives

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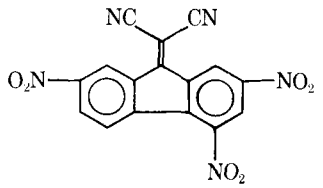
Abstract □ Electron donor–acceptor complexes for a group of quinolines and naphthalenes with 9-(dicyanomethylene)-2,4,7-trinitrofluorene in 1,2-dichloroethane were studied by optical absorption methods. Association constants, molar absorptivities, and charge-transfer transition energies were evaluated for each system, together with theoretically calculated orbital energies and complex geometries. In contrast to the association constants and structures reported for *N*-heterocycle–halogen complexes, these studies indicate that, with a moderately large π-electron acceptor, quinolines function as π- rather than *n*- (lone-pair) donors. These results support intercalation models for drug–receptor interactions involving the quinoline moiety.

Keyphrases □ Molecular complexing—various quinoline and naphthalene derivatives with 9-(dicyanomethylene)-2,4,7-trinitrofluorene, mechanism of π-electron donation □ Complexing, molecular—various quinoline and naphthalene derivatives with 9-(dicyanomethylene)-2,4,7-trinitrofluorene, mechanism of π-electron donation □ Quinolines, various—mechanism of π-electron donation in molecular complexing with 9-(dicyanomethylene)-2,4,7-trinitrofluorene □ Naphthalenes, various—mechanism of π-electron donation in molecular complexing with 9-(dicyanomethylene)-2,4,7-trinitrofluorene □ 9-(Dicyanomethylene)-2,4,7-trinitrofluorene—mechanism of π-electron donation by various quinolines and naphthalenes in molecular complexing

The possible role of electron donor–acceptor complexes in drug–receptor binding processes as well as in many other biological reactions has been widely discussed (1–5). For example, in the intercalation model (6–8) of antimalarial drug interactions, the parallel planar arrangement of DNA base pairs and the quinoline moiety of drugs such as pamaquine and chloroquine almost certainly involves some degree of π-electron interaction.

The ubiquitous occurrence of *N*-heterocyclic compounds in living systems has prompted several investigations into the nature of their complexes with various compounds (9–13). Although molecules such as pyridine and quinoline may function as either *n*- or π-electron donors, with σ-acceptors, particularly iodine and iodine monochloride, binding is through the nitrogen lone-pair electrons (11, 13–17). However, with π-acceptors, the results are by no means as certain; conflicting interpretations have been reported (18–21).

This study was initiated to: (*a*) discover the mode of binding of quinoline and its simple derivatives to a moderately large π-electron acceptor, (*b*) determine the effects of different substituents on the complexing ability of quinoline, and (*c*) examine the implications of the resulting donor–acceptor model in drug–receptor interactions. The present report describes optical absorption studies combined with theoretical calculations for complexes of amino- and hydroxyquinolines and their naphthalene analogs with 9-(dicyanomethylene)-2,4,7-trinitrofluorene (I).



I

EXPERIMENTAL

Materials—Quinoline[1] was dried over potassium hydroxide and fractionally distilled at reduced pressure. 8-Hydroxyquinoline[1] was recrystallized from toluene. 8-Aminoquinoline[2], 5-aminoquinoline[1], 1-hydroxynaphthalene[2], and 1-aminonaphthalene[1] were purified by vacuum sublimation. Naphthalene[1] was twice recrystallized from absolute ethanol. Isoquinoline[1] was fractionally distilled at reduced pressure. 9-(Dicyanomethylene)-2,4,7-trinitrofluorene[2] was twice recrystallized from acetonitrile. 1,2-Dichloroethane[3] was purged with dry nitrogen (dew point less than −40°) immediately before use.

Spectroscopic Measurements—Optical absorption spectra for solutions with a fixed concentration of I and different donor concentrations were recorded[4] at 20 and 40°. Spectral data were collected using 1-, 2-, or 5-cm matched quartz cells with either the pure solvent or an equimolar solution of I as reference. Absorption, if any, of the free donor was subtracted from the measured absorbance during the data analysis step. For each system, absorbance measurements were reproducible to ±0.002 absorbance unit.

Data Analysis—The reversible association of an electron donor, *D*, with an electron acceptor, *A*, to form a 1:1 molecular complex, *AD*, may be written as $A + D \rightleftharpoons AD$. The association constant, *K*, for this reaction is given by:

$$K = \frac{[AD]}{([A]_0 - [AD])([D]_0 - [AD])} \quad \text{(Eq. 1)}$$

where $[A]_0$ and $[D]_0$ represent initial concentrations of *A* and *D*, respectively; and $[AD]$ is the equilibrium concentration of *AD*. If Beer's law is obeyed by *AD* in a wavelength region where free donor and acceptor do not absorb or where their contributions have been subtracted, the complex absorbance, A_{AD}, will be:

$$A_{AD} = [AD]\epsilon_{AD}b \quad \text{(Eq. 2)}$$

where ϵ_{AD} is the molar absorptivity of the complex and *b* is the pathlength. Equations 1 and 2 can be combined to yield a modification of the Scatchard (22) equation:

$$\frac{A_{AD}}{[A]_0[D]_0b} = -K\left[\frac{A_{AD}([A]_0 + [D]_0 - [AD])}{[A]_0[D]_0b}\right] + K\epsilon_{AD} \quad \text{(Eq. 3)}$$

In this work, association constants and molar absorptivities for each donor–acceptor complex were computed[5] by means of an iterative least-squares curve-fitting procedure (23). For each system, a Scatchard plot was generated from eight or more data sets, which consisted of initial donor and acceptor concentrations along with the absorbances at the charge-transfer band maximum. Values of *K* and ϵ_{AD} were determined from the slopes and intercepts of these linear plots.

Theoretical Calculations—The Hückel molecular orbital (HMO) method (24) was applied to I and to each aromatic donor molecule. Heteroatom parameters used in this work followed closely the values recommended by Streitwieser (25). The HMO atomic orbital coefficients and π-orbital energies were then used in a second-order perturbation

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] Eastman Organic Chemicals, Rochester, N.Y.
[3] Spectral grade, Eastman Organic Chemicals, Rochester, N.Y.
[4] Cary model 14 spectrophotometer.
[5] XDS Sigma 9 computer.

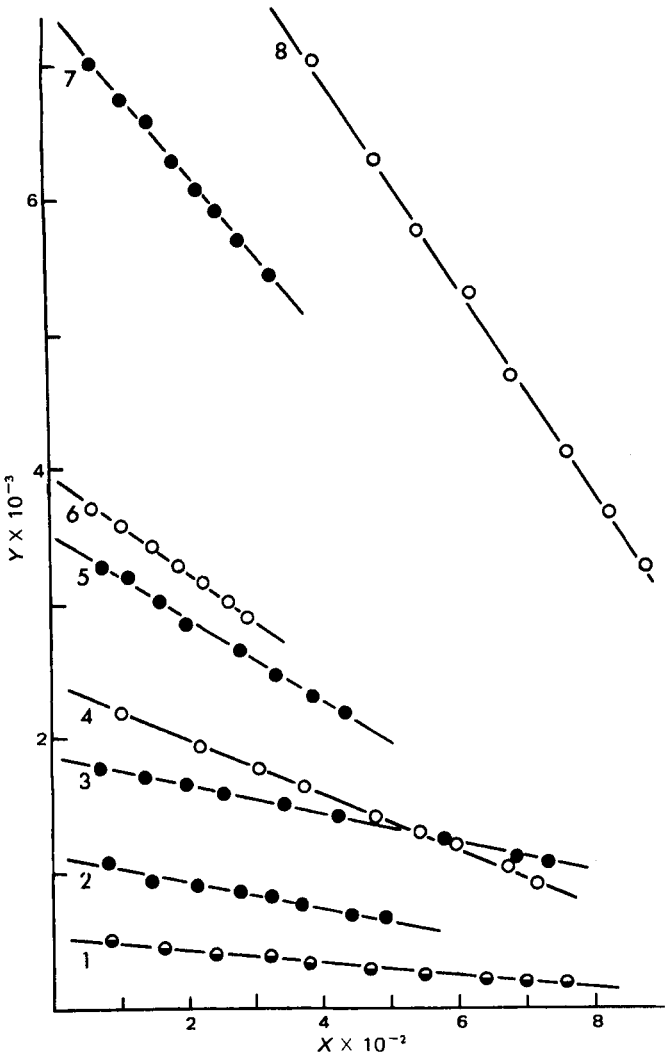


Figure 1—*Scatchard plots with* $X = A_{AD}([A]_0 + [D]_0 - [AD])/([A]_0[D]_0b)$ *and* $Y = A_{AD}/([A]_0[D]_0b)$ *for complexes of I with isoquinoline (1), quinoline (2), 8-hydroxyquinoline (3), naphthalene (4), 5-aminoquinoline (5), 1-hydroxynaphthalene (6), 8-aminoquinoline (7), and 1-aminonaphthalene (8) in 1,2-dichloroethane at 20°.*

treatment (26) to obtain binding energies and the most favorable geometries for the different complexes.

RESULTS AND DISCUSSION

Intensely colored mixtures are formed immediately upon combining 1,2-dichloroethane solutions of the quinolines or naphthalenes with I.

Table II—Association Constants for Iodine and Iodine Monochloride Complexes

Complex	Solvent	Temperature	K, M^{-1}	Reference
Benzene–iodine	Carbon tetrachloride	25°	0.15	16
Naphthalene–iodine	Carbon tetrachloride	25°	0.25	16
Pyridine–iodine	Carbon tetrachloride	25°	101	17
	Cyclohexane	25°	107	27
	Heptane	25°	140	14
	Heptane	16.7°	290	11
	Chloroform	28°	43.7	15
2,6-Lutidine–iodine	Chloroform	28°	26.2	15
Quinoline–iodine	Heptane	25°	114.6	28
	Chloroform	28°	69	15
Benzene–iodine monochloride	Carbon tetrachloride	25°	0.54	16
Naphthalene–iodine monochloride	Carbon tetrachloride	25°	1.39	16
Pyridine–iodine monochloride	Carbon tetrachloride	25°	483,000	17
2,6-Lutidine–iodine monochloride	Carbon tetrachloride	25°	89,000	17

Visible absorption spectra of these mixtures are characterized by broad featureless absorption bands, typical of electron donor–acceptor complexes. For each complex system, absorption data were collected near the wavelength maximum of the charge-transfer band for solutions covering a reasonably wide donor concentration range. From these absorbance values, association constants, K, and molar absorptivities, ϵ, were computed using Eq. 3. Figure 1 shows typical Scatchard plots for several complex systems. Donor and acceptor concentrations, absorption maxima, and computed K and ϵ values are given in Table I.

For comparison, association constants previously reported for aromatic hydrocarbon and N-heterocyclic donors with iodine and iodine monochloride are listed in Table II. The large variations in K for the halogen complexes are readily attributable to different modes of binding for the two donor types. X-ray diffraction studies (29, 30) of the N-heterocyclic complexes have shown a planar colinear arrangement of the interatomic axis of halogen acceptors with the nitrogen atom of the donors. This configuration is due to a relatively strong interaction of the nitrogen lone-pair electrons with an antibonding σ-orbital of the acceptor. In the case of the hydrocarbons, only the comparatively less favorable π-electron donation is possible.

In contrast to the marked increase in K for halogen–heterocycle over halogen–aromatic hydrocarbon complexes, association constants for interactions of the quinolines with I are somewhat lower than those of their naphthalene analogs. These results immediately suggest that, with I, both quinolines and naphthalenes form sandwich-type π–π complexes and that the presence of a nitrogen atom reduces slightly the donor ability of the π-system. This interpretation is further substantiated by other similarities between the two classes of donors.

Substitution of both quinoline and naphthalene by electron-releasing groups is accompanied by increased association constants and by shifts in the charge-transfer absorption maxima to longer wavelengths. Effects of the amino group on both K and λ_{max} are more pronounced than for the

Table I—Experimental Details, Association Constants, and Molar Absorptivities of I[a] Complexes in 1,2-Dichloroethane

Donor	Donor Concentration, M	Temperature	λ_{max}, nm	K, M^{-1}	ϵ, M^{-1} cm^{-1}
Naphthalene	0.05–0.72	20°	488	1.98 ± 0.03	1150 ± 60
		40°	485	1.52 ± 0.04	1150 ± 70
Quinoline	0.08–0.72	20°	440[b]	0.90 ± 0.04	1500 ± 40
Isoquinoline	0.02–1.90	20°	475[b]	0.54 ± 0.006	1130 ± 100
1-Hydroxynaphthalene	0.02–0.09	20°	560	3.64 ± 0.04	1060 ± 30
		40°	555	3.28 ± 0.11	910 ± 40
8-Hydroxyquinoline	0.02–0.83	20°	495	1.03 ± 0.07	1570 ± 120
		40°	490	0.77 ± 0.08	1600 ± 50
1-Aminonaphthalene	0.03–0.27	20°	660	7.95 ± 0.12	1280 ± 10
		40°	665	5.56 ± 0.09	1220 ± 10
5-Aminoquinoline	0.02–0.20	20°	600	3.02 ± 0.06	1130 ± 10
		40°	595	2.70 ± 0.16	1000 ± 50
8-Aminoquinoline	0.007–0.05	20°	645	5.94 ± 0.07	1230 ± 20
		40°	640	4.03 ± 0.11	1200 ± 20

[a] Concentrations of I are 0.001 M for all systems except 8-aminoquinoline for which the concentration is 0.003 M. [b] Shoulder.

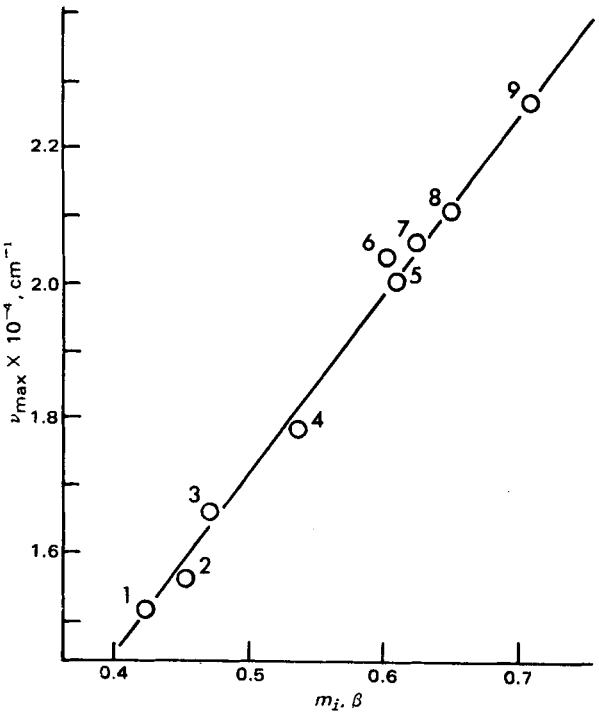
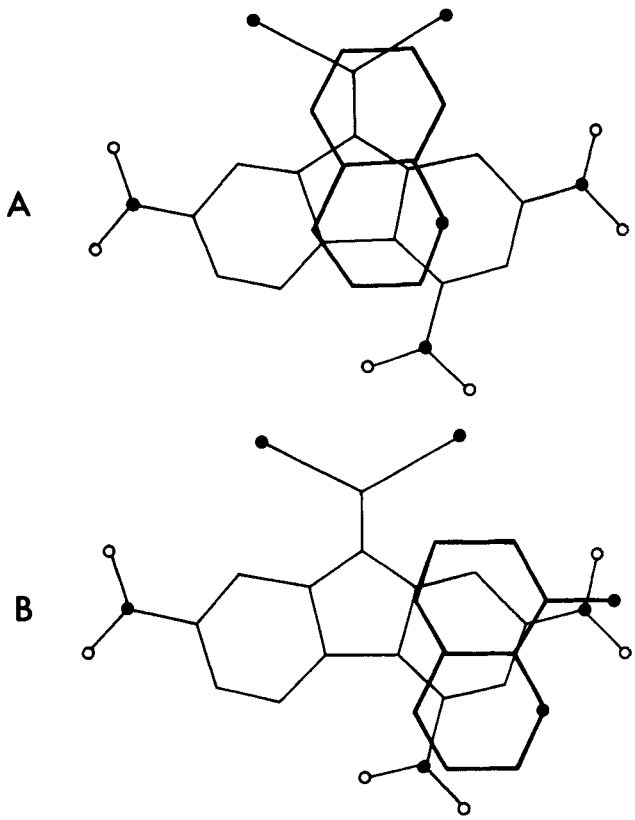


Figure 2—*Charge-transfer transition energies* versus *energies (in β units from the Hückel molecular orbital method) of the highest occupied donor orbitals for complexes of I with 1-aminonaphthalene (1), 8-aminoquinoline (2), 5-aminoquinoline (3), 1-hydroxynaphthalene (4), 5-hydroxyquinoline (5), 8-hydroxyquinoline (6), naphthalene (7), isoquinoline (8), and quinoline (9).*



hydroxyl group. These trends are consistent with a greater electron-releasing tendency of the amino group as reflected by the respective Hammett σ constants, $\sigma_{NH_2} = -0.660$ and $\sigma_{OH} = -0.357$. Molecular orbital calculations for amino- and hydroxyquinolines also show a greater electron-releasing effect for the amino derivatives, thereby making them better electron donors.

Association constants for complexes of 8- and 5-aminoquinoline (Table I) indicate that the position of substitution also has a significant influence on donor strength. If, as a first approximation, the energy of the highest occupied π-molecular orbital is taken as a measure of donor ability, HMO calculations predict electron donor strengths in the order: 8 > 5 > 6 > 3 > 4 > 7 > 2 > 0 for aminoquinolines and 8 > 5 > 4 > 6 > 3 > 7 > 2 > 0 for hydroxyquinolines.

Linear relationships between ionization potentials or orbital energies for a series of donors with a common acceptor were found in numerous cases (3). Figure 2 shows a plot of highest occupied donor orbital energies *versus* charge-transfer transition energies for the complexes in this work. Points for both the quinolines and naphthalenes fall on a single straight line, indicating that the same mode of electron donation is operative in the two systems.

Although molar absorptivities for the quinoline and 8-hydroxyquinoline complexes show some enhancement, no systematic variations are apparent throughout the series. This behavior again differs from that of the halogen complexes, which show greatly increased absorptivities with *N*-heterocyclic donors. For example, a value of ϵ_{max} approaching 50,000 M^{-1} cm^{-1} was reported for the pyridine–iodine complex (11).

Since electron donor–acceptor complexes of the type discussed here involve weak interactions, typically 5–6 kcal/mole or less, even a moderate amount of steric hindrance near the binding site can lead to substantially reduced association constants. For complexes of iodine with methyl-substituted pyridines and quinolines, a two- to fivefold decrease between *K*'s for the parent compound and 2,6-lutidine and complete suppression of complex formation with 7,8-benzoquinoline were reported (15, 17). If complexation through the nitrogen lone pair is important, substitution at the 8-position of quinoline would sterically hinder the approach of an acceptor, especially a molecule as large as I. Association constants for the complexes in the present work show no evidence of steric hindrance by substituents in the 8-position. In fact, just the reverse trend is noted (Table I).

Stabilization energies computed by a second-order perturbation method (26) indicate that the most favorable geometry occurs for each complex system when donor and acceptor molecules are stacked in parallel planes at an intermolecular distance of 3.3–3.4 Å. Theoretical binding energies ranged from −3.7 kcal/mole for quinoline–I to −8.5 kcal/mole for 5-aminoquinoline–I. Minimum energy configurations for the quinoline and 8-aminoquinoline complexes with I are shown in Structures A and B, respectively, where dark circles represent nitrogen and open circles represent oxygen. The intermolecular distance is 3.35 Å in both cases, and the binding energies are −3.7 kcal/mole for Complex A and −5.7 kcal/mole for Complex B. Calculations for both in-plane and perpendicular orientations of the interacting species result in net positive binding energies.

CONCLUSIONS

Molecular complexation through the π-electron system of quinolines is indicated by the following evidence.

Association constants and molar absorptivities for quinoline complexes with I are of the same order of magnitude as those for naphthalenes where only π-donation is possible.

A linear correlation is found between the highest occupied molecular orbital (HOMO) energies and charge-transfer band energies for each complex. Such correlations are characteristic of π–π complexes.

A decrease in charge-transfer transition energies and an increase in association constants result from substitution of the quinoline or naphthalene ring with electron-releasing groups.

Little, if any, steric hindrance to complex formation is experienced on substitution at the 8-position in quinoline.

Perturbation calculations favor a stacking of donor and acceptor molecules in parallel planes separated by 3.3–3.4 Å.

The π-complexing mode of quinolines in their interaction with the acceptor lends support to intercalation models of drug activity of quinoline-based compounds (6–8). However, caution must be exercised in assigning mechanistic importance to these interactions until more substantive evidence for the role of charge-transfer complexes in biological systems is demonstrated.

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Kinetics and Mechanism of Oxidation of Promazine and Promethazine by Ferric Perchlorate

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Abstract □ The equilibrium constants, kinetics, and mechanism of promazine and promethazine oxidation by ferric perchlorate were investigated at different temperatures and acidities using a stopped-flow spectrophotometric technique. The overall reaction can be represented as follows:

$$Fe(III) + P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Fe(II) + P^{\cdot+}$$

where $P^{\cdot+}$ represents the radical cation corresponding to the phenothiazine derivative. The equilibrium quotients were evaluated at 1.00 *M* $HClO_4$, 25.0°, and ionic strength 1.0 *M*. The kinetics of reaction follow the equation:

$$-\frac{d[P]}{dt} = k_1[Fe^{3+}][P] - k_{-1}[Fe^{2+}][P^{\cdot+}]$$

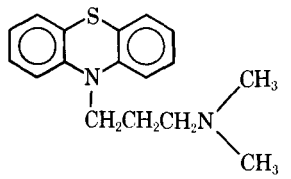
The rate constants k_1 and k_{-1} are independent of acidity and are related to the corresponding equilibrium quotients.

Keyphrases □ Promazine—kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Promethazine—kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Phenothiazines—promazine and promethazine, kinetics and mechanism of oxidation by ferric perchlorate, various temperatures and pH values □ Oxidation—kinetics and mechanism, promazine and promethazine by ferric perchlorate, various temperatures and pH values □ Ferric perchlorate—oxidation of promazine and promethazine, kinetics and mechanism, various temperatures and pH values

Free radicals of dialkylaminoalkylphenothiazine derivatives have been found in the urine of patients receiving phenothiazine drugs (1). Studies were carried out to elucidate both the role of such free radicals in biotransformation and structure–activity relationships.

Using electron spin resonance, Fenner (2, 3) noted the influence of the electron-donating and electron-withdrawing groups on the ring, as well as that of the side chain bonded to the nitrogen (in position 10), on radical formation. Investigation of the oxidation by inorganic agents also showed the large influence of the side chain (4, 5). In particular, the oxidation of the two isomers promazine[1] [10-(3-dimethylaminopropyl)phenothiazine] (I) and promethazine[2] [10-(2-dimethylaminopropyl)phenothiazine] (II), both with ammonium persulfate and ceric sulfate in aqueous solution at different pH values, gave different oxidation products (6, 7). Moreover, I and II show different pharmacodynamic properties; I is an antidepressant and II is an antihistaminic.

The differences in the behavior of these compounds toward oxidation suggested an investigation of the kinetics



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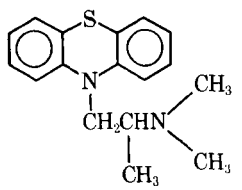

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