NMR δ 2.93 (d, 3, J = 5 Hz, -NHCH_3), 3.06 (d, 3, J = 5 Hz, -NHCH_3), 7.12 (br, 2, -NH), 7.34 (d, 1, J = 6 Hz, -NHCHO), 8.43 (s, 1, 2-H), 9.22 (br, 1, -NH), 9.40 (s, 1, -NH), and 9.73 (d, 1, J = 5 Hz, -NHC*H*O).

Attempted Ring Closure of 4,6-Dimethylureido-5-formylaminopyrimidine (XIII) to Give N^6-Di(N-methylcarbamoyl)adenine (40). To a mixture of 269 mg (1 mmol) of XIII and 852 mg (6 mmol) of phosphorous pentoxide cooled in an ice bath was added 1.20 mg of 85% phosphoric acid, and the mixture was stirred at 25 °C for 3 h and then at 150 °C for 3.5 h. The reaction mixture was cooled to room temperature and poured into 100 mL of ice water. The brown solution was carefully neutralized to pH 6.5, when a off-white solid slowly precipitated. This material was filtered, washed with water, and dried under vacuum: yield 85.0 mg; mp >350 °C dec. The product was identified as N^6-(N-methylcarbamoyl)adenine by comparison with the authentic material[8] in solvents A, B, and C in TLC and in UV spectra: λ max (nm) 269, 276 (water), 277 (0.1 N HCl), and 277 (0.1 N NaOH). TLC of the filtrate showed more of this material; however, no desired disubstituted product could be detected. A lower reaction temperature or time did not lead to the formation of the desired disubstituted product.

Growth Inhibition. These compounds were evaluated for their growth-inhibitory activity in cultured cells derived from the buffy coats of a normal individual (Nc 37) and a patient with myeloblastic leukemia (RPMI 6410) and also in cultures of L1210 mouse leukemia.[8] Compounds were dissolved in 0.5% Me_2SO in growth medium (RPMI 1640 + 10% fetal calf serum) at 10^{-4} M and the results are expressed as percent of viable cell number relative to controls containing 0.5% Me_2SO after 72 h of incubation. At the concentration used, Me_2SO did not affect cell growth. Results are shown in Tables I–VI.

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Synthetic Models of Deoxyribonucleic Acid Complexes with Antimalarial Compounds. 3. Forces Involved in the Stacking Interaction between Aminoquinoline and the Nucleotide Bases

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As an approach to the problem of the nature of the forces responsible for the stacking interactions between the aminoquinoline ring of the antimalarial chloroquine and the monomeric nucleotide bases, we have examined models in which the aromatic nucleus of the drug is linked to the nucleotide bases by a trimethylene chain. The degree of stacking of the models was determined in different conditions of solvent, pH, and temperature by hypochromism measurement in the UV. The results show that forces of the donor–acceptor type, due to the presence of a positive charge on the quinoline ring at neutral pH, do not bring an important contribution to the stacking interaction between the aminoquinoline and the nucleotide bases, while the influence of the solvent water is fundamental.

The antimalarial chloroquine (1) is one of a series of small, positively charged molecules which interact with nucleic acids.[1] Binding models have been proposed in which ionic interactions between the diethylamino nitrogen of the drug and the phosphate groups of DNA add to ring–ring stacking interactions between the aminoquinoline and the nucleotide bases to account for the complexation.[2]

In vitro the binding of chloroquine with nucleic acids is observed in water and the species which interacts is a diprotonated one in which the 4-aminoquinoline moiety

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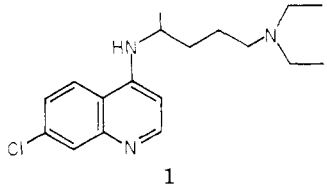
is protonated at the heterocyclic nitrogen,[3] the resulting charge deficiency being delocalized to the entire quinoline ring and to the 4-amino nitrogen.[4] From different studies including the effect of parameters such as medium, pH, and temperature, it was notably concluded that the presence of a positive charge on the ring nitrogen is essential for the binding. The thermodynamic properties of the association reaction were interpreted both in terms of "hydrophobic and/or ionic (charge transfer) interaction".[1d,5]

In order to obtain additional information pertaining to the specific forces of attraction which bind the planar aromatic part of chloroquine to the nucleotide base moieties, we have studied the interaction between aminoquinoline and the monomeric nucleotide bases in dilute aqueous solution, using simplified models. In preceding papers, we reported the preparation and UV examination of model compounds **2**–**4** in which the base and the quinoline are linked by a trimethylene chain.[6] These systems adopt a folded conformation in solution if attractive interactions between the aromatic rings do occur.



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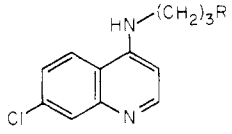
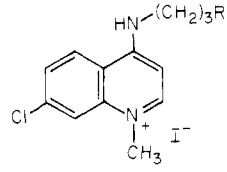


2, R = 9-Ade
3, R = 9-Gua
4, R = 1-Thy
5, R = H



6, R = 9-Ade
7, R = 1-Thy
8, R = H

We have thus shown notably that the purines stack with quinoline to a much greater extent (100% intramolecular stacking in water at 25 °C, pH 6.9, for **2** and **3**) than the pyrimidine thymine. In this paper we wish to focus on the nature of the forces responsible for this strong association by examining the folding–unfolding process of the models **2**–**4** in different conditions of pH, solvent, and temperature. The study was extended to compounds **6** and **7** in which the ring nitrogen has been methylated and carries therefore a positive charge in the whole pH range. The intramolecular stacking of the aromatic moieties was determined using the percent hypochromism, % H,[7] as a criterion, i.e., by comparing quantitatively the electronic absorption spectra of the models with the summation of the spectra of the corresponding constituent aromatic "half units". The method has been previously used in this laboratory and its applicability has been amply demonstrated, notably by Leonard.[8]

Effects of pH. 4-Amino-7-chloroquinoline is protonated at pH 7 and could thus act as an electron acceptor in a donor–acceptor pair with the neutral pyrimidines or purines.[4] If forces of the "donor–acceptor" type due to the presence of a positive charge on the quinoline ring contribute to the binding, they should be detectable by examining the variation of the degree of stacking of the models as a function of pH.

The UV spectra of the models B-C_3-Q (**2**–**4**, **6**, and **7**) and of the reference substances B-C_3 (9-propyladenine, 9-propylguanine, and 1-propylthymine) and Q-C_3 (**5** and **8**) were recorded at concentrations of 5×10^{-5} M in water at 25 °C at pH 6.9 (phosphate buffer) and at acidic (0.1 N HCl)[9] and basic (0.1 N NaOH) pH values. The percent hypochromism, % H, was calculated[10] (Table I). All of the compounds, within the range of pH used, showed significant hypochromism which proves that all adopt, to varying extents, the folded conformation. The variation of pH did not have a dramatic effect on the magnitude of H. These general remarks can be illustrated using Ade-C_3-Q (**2**), for which a sequential protonation of the rings can be observed (Figure 1). It is seen that at pH 13 when both rings are neutral, the value of H is high. The protonation of quinoline when passing at pH 6.9 (Q protonated, Ade neutral) does not bring a significant change in the magnitude of H.[11] But the percent hypochromism decreases when both rings are protonated at pH 1.[12] A comparable H decrease is observed in the guanine series when the monoprotonated species (pH 6.9, Gua neutral, Q protonated) gets diprotonated at pH 1 (the comparison with the value obtained in basic conditions is less direct, as two charge changes are induced on passing from pH 13 to 6.9; guanine loses a negative charge and quinoline acquires a positive one). For the thymine model 4, the value of H is smaller than for the preceeding compounds and no important variation is seen with pH (at pH 1 and 7, thymine is neutral, whereas it bears a negative charge at pH 13).

Table I. Computed Percent Hypochromism Values (% H) for the Base-Quinoline Interaction Models in Different Conditions of pH, in H_2O, 25 °C, 5×10^{-5} M[a]

		pH 1	pH 6.9	pH 13
Ade-C_3-Q (2)	(a)	16 ± 2	20 ± 2	21 ± 1
	(b)	19.5 ± 0.7	25.5 ± 0.5	23 ± 1
Gua-C_3-Q (3)	(a)	13 ± 2	16 ± 2	11 ± 1
	(b)	22.4 ± 0.7	25.9 ± 0.7	13 ± 1
Thy-C_3-Q (4)	(a)	5 ± 2	5 ± 2	8 ± 2
	(b)	11 ± 1	10 ± 1	9 ± 1
Ade-C_3-Q^+CH_3 (6)[b]	(a)	12 ± 1	18 ± 1	
	(b)	17 ± 1	23 ± 1	
Thy-C_3-Q^+CH_3 (7)[b]	(a)	6 ± 2	7 ± 2	
	(b)	12 ± 1	12 ± 1	

[a] (a) 230–300 nm (quinoline and base absorption); (b) 300–380 nm (quinoline absorption only; the corresponding % H values are therefore more precise). [b] See ref 16.

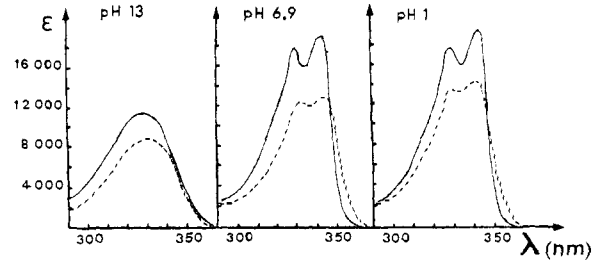


Figure 1. UV spectra of Ade-C_3-Q (---) and Q-C_3 (—) at different pH values in the 300–380-nm range (quinoline absorption only): water, 5×10^{-5} M, 25 °C. Left, pH 13 (NaOH, 0.1 N); center, pH 6.9 (phosphate buffer); right, pH 1 (HCl, 0.1 N).

The main conclusion of this study is that the effects of the charge on the magnitude of H, i.e., on the degree of stacking, are relatively low, as best exemplified in the adenine series: (1) no significant contribution to the stacking when the quinoline ring becomes protonated; (2) a repulsive effect when both rings are protonated. This is observed for the adenine (% H, 25.5 → 19.5) and guanine (25.9 → 22.4) models and for the analogous methylated compound **6** (23 → 17) when passing from pH 6.9 to 1. However, this decrease of the percent hypochromism is relatively small (Δ % H = 6) and it is necessary to question its real significance and verify that it reflects a difference

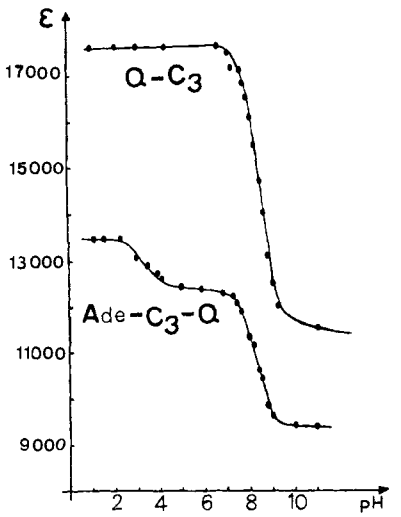


Figure 2. Variation of the molecular extinction coefficient (ϵ_{max}) of quinoline (330 nm, adenine does not absorb) as a function of pH for Ade-C_3-Q (2) (lower curve) and for Q-C_3 (5) (upper curve), in water, 5×10^{-5} M, 25 °C.

of intramolecular stacking. Toward this end, we have examined in particular the adenine model 2.

Variation of ε as a Function of pH for Ade-C_3-Q (2). To see whether the variation of H between pH 6.9 and 1 is really due to the protonation of adenine (and not to undefined secondary effects), the UV spectra of Q-C_3 and Ade-C_3-Q were measured between pH 1 and 11. Figure 2 shows the variation of the molecular extinction (ϵ) at 330 nm (quinoline absorption only). The two curves exhibit the expected inflection point near pH 8.5, the pK of aminoquinolines.[3] Between pH 1 and 6, where the quinoline is 100% protonated, a decrease in ϵ is now observed for Ade-C_3-Q, corresponding to an increasing hypochromic effect. The point of inflection indicates a pK near 3.5, corresponding to adenine alkylated in position 9. This is therefore a titration curve, but now it is the adenine, which does not absorb at this wavelength, which is being titrated. The decrease of the percent hypochromism previously described on passing from pH 6.9 to 1 is thus a direct consequence of the protonation of adenine in the model. (The variation of ϵ as a function of pH represents a directly observable proof of the existence of interactions between the two aromatic rings.)

Variation of H with Temperature. It has been shown that the percent hypochromism H can be taken as a measure of the interaction, but it is not precise, being dependent upon the degree and orientation of intramolecular stacking.[7] A temperature study was then made to see whether the variation of H on passing from pH 6.9 to 1 (Δ % H = 6) reflects a difference in the degree of stacking and is not due to a change in the intrinsic electronic properties of the chromophores as a result of protonation. In earlier work[6a] we have shown that the stacking of this model increases when the temperature is lowered to reach 100% at 20 °C, pH 6.9, as indicated by the curve % $H = f(T)$ (a maximum constant value of 26 being observed for % H from +20 to 0 °C). The study was repeated in acid medium (Figure 3). The value of H is lower than at pH 6.9 at any temperature and no asymptotic value is reached at low temperatures. This can be interpreted as a proof that the degree of intramolecular stacking is lower in acidic conditions when the two rings of the model are protonated.

It is now clearly established that the affinity of quinoline for adenine decreases when the latter is also protonated, and this can be attributed to the mutual repulsion of the positive charges. This conclusion can also be applied to the guanine model. However, the stacking remains substantial. Base–quinoline interactions can be compared to base–base interactions. For dinucleosides larger differences are observed: H goes from 6.8 to −0.5 for ApA, from 9 to −1 for GpG, and from 6 to 3 for GpA on passing from pH 7 to 1.[13] Similarly for dinucleoside models in which the two bases are linked by a trimethylene chain, % H, under the same conditions, goes from 16 to 3 for Ade-C_3-Ade, from 15 to 6 for Gua-C_3-Ade, and from 16 to 2 for Gua-C_3-Gua.[14]

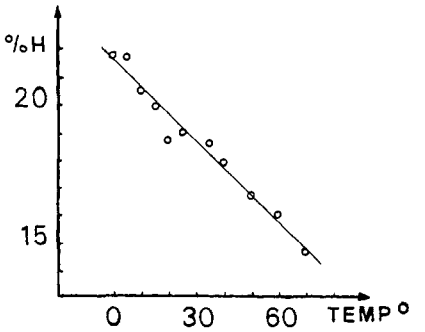


Figure 3. Variation of the percent hypochromism (% H) as a function of temperature for Ade-C_3-Q (2) in water, 5×10^{-5} M, pH 1 (HCl, 0.1 N); both chromophores protonated.

Variations in the pK of Quinoline. Additional information about the influence of the charge present on the quinoline ring near pH 7 upon the stacking was obtained from the comparative measurement of the pK of quinoline in the model and in the reference compound. By UV spectroscopy, close pK values were found (8.35 ± 0.06 for Ade-C_3-Q and 8.52 ± 0.03 for Q-C_3), the pK of quinoline being slightly lowered when it is incorporated in the model system.[15] This result is rather contrary to the expectation that the folded conformation of Ade-C_3-Q would be significantly stabilized by charge-transfer interaction (adenine → quinoline) and that this would be more pronounced when the quinoline is protonated (in which case a larger pK could be expected).

This confirms the previous observation that forces of the "donor–acceptor type" between the charged quinoline ring and neutral adenine do not intervene to a very significant extent.

Effects of the Solvent. The models were studied in various organic solvents. In ethanol, dimethyl sulfoxide, and dimethylformamide, no measurable hypochromism could be observed; the spectra of the B-C_3-Q systems are similar to the summation of the spectra of the constituent monomeric units B-C_3 and Q-C_3. Hypochromism appears only in the presence of water. For example, Ade-C_3-Q^+-CH_3 (6) exhibits a % H equal to 11 in a 50:50 mixture of dimethyl sulfoxide and water.[16] The influence of the addition of ethanol to aqueous solutions of the models was examined in different conditions of pH (Figure 4): Ade-C_3-Q (2) was studied in acidic conditions (the two rings being protonated); Ade-C_3-Q^+-CH_3 (6) in a neutral medium (Adenine neutral, the quinoline carries one positive charge); and Thy-C_3-Q (4) in acidic medium (Thymine neutral, quinoline protonated). All the systems behave similarly; up to 15% ethanol, hypochromism is slightly affected and at greater ethanol concentrations, the hypochromic effect decreases rapidly, although at 50% ethanol, H is 7% for Ade-C_3-Q and 4% for Thy-C_3-Q.

Water is therefore essential for the B-C_3-Q molecules to adopt a folded conformation. This result indicates that some solvent-induced bonding of the hydrophobic type contributes to the intramolecular stacking, and in view of

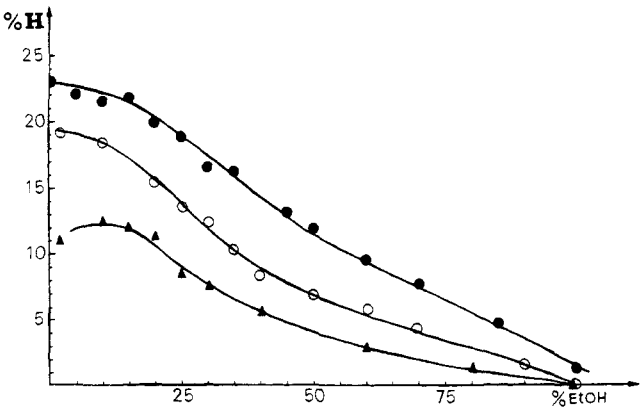


Figure 4. Variation of the percent hypochromism (% *H*) as a function of the ethanol content in a water–ethanol solution (volume of ethanol/total volume of solution), 5×10^{-5} M, 25 °C: (●——●) Ade-C_3-Q^+CH_3 (6), neutral medium; (○——○) Ade-C_3-Q (2), acidic medium (HCl, 0.1 M); (▲——▲) Thy-C_3-Q (4), acidic medium (HCl, 0.1 M).

the thermodynamic characteristics of the process ($\Delta H°$ = −9 kcal/mol; ΔS = −24 eu for Ade-C_3-Q and Gua-C_3-Q in water, pH 6.9[6b]) it seems that the bonding can be discussed in terms which are comparable to the interpretations given for the molecular interactions between stacked bases in nucleosides, nucleotides, and oligo- and polynucleotides.[17] (For example, base–base stacking for ApA is observed in water and is characterized by a decrease in enthalpy and entropy: $\Delta H°$ = −10 kcal/mol; $\Delta S°$ = −30 eu.[18])

Discussion

The stacking interactions between monomeric nucleotide bases and 4-aminoquinoline have been examined by linking the rings covalently by a trimethylene bridge. The method implies obvious limitations which are inherent to the conceptual approach itself, as the aromatic moieties are geometrically constrained by the bridge. However, it enabled the study of the influence of solvent, pH, and temperature on the stacking, all informations which may be obtained, but with other limitations, by different experimental approaches; the intermolecular stacking interaction between quinoline and the bases is too weak to be significantly studied as a function of different parameters.[1d,2b,6] (Even with dinucleotides, the interaction of chloroquine is still negligible, as determined spectrophotometrically.)[2b] On the other side, binding of chloroquine with nucleosides, nucleotides, and polynucleotides leads to observations which are the result of a number of contributing factors, of which ring–ring interaction is only one component, and which may be sensitive themselves to changes of solvent, pH, and temperature.[2b,19]

From the examination of the binding of chloroquine to DNA and other polymers[1,2] to oligonucleotides and various monomeric base moieties,[1d,19] it was notably concluded that (a) binding is most extensive with ordered polynucleotide structures, (b) it is specific for the protonated form of the drug and does not occur at low pH when purines are protonated, (c) it decreases with temperature, and (d) methylation of the ring nitrogen does not diminish the interaction. These various results were interpreted in terms of ring–ring attraction forces added to electrostatic interactions between the side chain of the drug and the phosphates, according to the intercalation model as proposed by Hahn and Waring or to the stacking model of Yielding.[2]

In the compounds reported here (with the limitations already quoted), we have shown that ring–ring stacking forces are strong enough to lead to a total association between a quinoline moiety and a purine residue, when these are held in close proximity by an additional type of force (covalent link). The interaction decreases with temperature and shows no important variation when the quinoline nitrogen is methylated. The interaction is determined to a major extent by the presence of water. This role of water overwhelms the effects of charge; no significant change of the percent hypochromism is observed in the adenine model when quinoline is neutral or protonated. In the interaction of chloroquine with nucleic acids it has been observed that the presence of a charge on the quinoline ring is an essential factor for binding to occur (it was concluded that the charged ring is involved in the electrostatic attraction with the phosphate groups).[2,5] As far as comparisons can be made between the intramolecular interactions as observed in our models and stacking interactions in the polymer, it seems that the charge present on the drug does not contribute significantly to the ring–ring attraction with the neutral bases.

In the models the percent hypochromism decreases, although remaining at a high value when the two rings carry a positive charge, as is apparent for Ade-C_3-Q and Gua-C_3-Q, and is confirmed for the N-methylated analogue. The detailed analysis of the Ade-C_3-Q model indicates that this % *H* decrease reflects a difference in the intramolecular interaction. This substantial interaction at pH 1 is reminiscent of the behavior of cationic dyes which aggregate in water and for which it has been proposed that the minimum coulombic repulsion between two cations requires the delocalized charges to be alternately at each end of the planar ions.[20] In the models, the actual centers of charge may well be far from each other, so that the repulsion is minimized and the contribution of the solvent water is strong enough to keep the interaction at a substantial level. (This situation is, of course, quite different for chloroquine in its interaction with nucleic acids at low pH when purines are protonated.)

Experimental Section

Chemistry. Where analysis are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values. All melting points are uncorrected. NMR spectra were recorded using Me_4Si (δ = 0.000) as internal standard.

The synthesis of the model compounds **2–4** and of the reference compounds has been described.[6]

1-Methyl-4-[3-(Aden-9-yl)propylamino]-7-chloroquinolinium Iodide (6). To a solution of 2.3 g (12 mmol) of 9-(3-aminopropyl)adenine[21] in 30 mL of methanol was added slowly, at room temperature, 1.5 g (4.6 mmol) of 1-methyl-4,7-dichloroquinolinium methyl sulfate.[22] After 2 h, the mixture was filtered, and the filtrate was treated with a portion of 3.0 g (18 mmol) of IK dissolved in 5 mL of water. The mixture was cooled to −30 °C, and the precipitate was filtered and crystallized from water and then from methanol yielding 2.1 g (89%) of **6**: mp 254–254.5 °C; NMR (CF_3CO_2H) δ 9.48 (s, 1 H, AdC_2H or AdC_8H), 8.83 (s, 1 H, AdC_8H or AdC_2H), 8.41 (d, 1 H, J = 9 Hz, QC_5H), 8.31 (d, 1 H, J = 7 Hz, QC_2H), 8.0 (s, 1 H, QC_8H), 7.8 (d, 1 H, J = 9 Hz, QC_6H), 6.88 (d, 1 H, J = 7 Hz, QC_3H), 4.9 (m, 2 H, $QNHCH_2CH_2CH_2$-Ad), 4.2 (s, 3 H, QN_1CH_3), 3.9 (m, 2 H, Q-$NHCH_2$), 2.8 (m, 2 H, Q-$NHCH_2CH_2CH_2$-Ad); IR (KBr) 3420, 3300, 3160, 3120, 1620, 1565, 1460, 1450, 1365, 1325, 1230, and 860 cm^{-1}; UV (EtOH) λ_{max} 261 nm (ϵ 36 800), 338 (22 600), 351 (23 300). Anal. ($C_{18}H_{19}N_7ClI \cdot H_2O$) C, H, N.

1-Methyl-4-[3-Thym-1-yl)propylamino]-7-chloroquinolinium Iodide (7). 1-(3-Aminopropyl)thymine hydrochloride[14] (1.3 g, 6 mmol) and 1.5 g (4.6 mmol) of 1-methyl-4,7-dichloroquinolinium methyl sulfate were dissolved in 40 mL of water and allowed to stand 48 h at room temperature. The mixture was heated to reflux and neutralized with NH_4OH. A 1.6-g (0.1 mol) portion of IK was added. The precipitate formed was filtered and recrystallized from water and then from methanol yielding 1.65 g (85%) of desired product: mp 280–281 °C; NMR

(Me_2SO-d_6) δ 11.1 (s, 1 H, ThN_3H), 9.3 (m, 1 H, QC_4NH), 8.75 (d, 1 H, J = 7 Hz, QC_2H), 8.65 (d, 1 H, J = 9 Hz, QC_5H), 8.22 (d, 1 H, J = 2 Hz, QC_8H), 7.86 (dd, 1 H, J = 2 and 9 Hz, QC_6H), 7.6 (s, 1 H, ThC_6H), 7.0 (d, 1 H, J = 7 Hz, QC_3H), 4.17 (s, 3 H, QN_1CH_3), 4–3 (m, 4 H, Q-$CH_2CH_2CH_2$Th), 2.1 (m, 2 H, Q-CH_2CH_2), 1.75 (s, 3 H, ThC_5CH_3); IR (KBr) 3440, 3200, 3000, 2310, 1690, 1670, 1610, 1560, 1460, 1365, 1355, 1230, 1215, 865, and 800 cm^{-1}; UV (EtOH) λ_{max} 262 nm (ϵ 24600), 340 (18400), 353 (20100). Anal. ($C_{18}H_{20}N_4O_2ClI$) C, H, N, Cl.

1-Methyl-4-propylamino-7-chloroquinolinium Iodide (8). A mixture of 2.0 g (9.1 mmol) of 4-propylamino-7-chloroquinoline prepared according to **6b** and 16 g (110 mmol) of ICH_3 was refluxed for 5 min. After cooling, the precipitate was filtered and recrystallized from ethanol to yield 2.6 g (79%) of the desired product 8: mp 242–243 °C; NMR (Me_2SO-d_6) δ 9.25 (s, 1 H, QN_9H), 8.7 (d, 1 H, J = 7 Hz, QC_2H), 8.65 (d, 1 H, J = 9 Hz, QC_5H), 8.18 (d, 1 H, J = 2 Hz, QC_8H), 7.85 (dd, 1 H, J = 9 and 2 Hz, QC_6H), 6.98 (d, 1 H, J = 7 Hz, QC_3H), 4.12 (s, 3 H, QN_1CH_3), 3.5 (m, 2 H, $QNHCH_2CH_2CH_3$), 1.7 (m, 2 H, $QNHCH_2CH_2CH_3$), 1.0 (t, 3 H, J = 8 Hz, $QNHCH_2CH_2CH_3$); IR (KBr) 3250, 3100, 3000, 2980, 1610, 1560, 1530, 1465, 1455, 1360, 1225, 1140, 865, and 805 cm^{-1}; UV (EtOH) λ_{max} 261 nm (ϵ 17600), 339 (18400), 352 (20200). Anal. ($C_{13}H_{16}N_2ClI$) C, H, N, Cl, I.

Ultraviolet Spectroscopy. The measurements were obtained on a Cary Model 15 spectrophotometer. The spectra were recorded and the percent hypochromism was calculated as previously described.[6,10] pK measurements of the quinoline moiety in Q-C_3 and Ade-C_3-Q were based on the different UV absorptions of the acidic and basic forms, as measured by the oscillator forces. f_{Q^+} is the oscillator force for the acid form and f_Q for the basic form, between 300 and 370 nm. f_Q was measured in 0.1 N NaOH for Q-C_3 and Ade-C_3-Q. f_{Q^+} was measured in 0.1 N HCl for Q-C_3 and at pH 5.0 (KH_2PO_4 buffer) for Ade-C_3-Q, in the pH zone where adenine is not protonated. The value of f was then measured, between pH 7 and 9, every 0.2 unit. pH was measured using a Tacussel pH meter accurate within 0.01 pH unit. The pH was adjusted by mixing two solutions of identical concentration in Q-C_3 or Ade-C_3-Q, one in 0.1 N HCl and the other in 0.1 M tris(hydroxymethyl)aminomethane. All pH values at which the percentages of the two forms were significant were used in the calculation.

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(9) No significant special effect of the anion was noted; switching from 0.1 N HCl to 0.1 N $HClO_4$ does not bring any noticeable change in the spectra. Even the addition of salts such as LiCl and NaI leads to no significant changes.

(10) In the variation of the absorption intensity between the model and reference compounds, the "hypochromism" was expressed by $H = 1 - f(\text{B-C}_3\text{-Q})/[f(\text{B-C}_3) + f(\text{Q-C}_3)]$. The oscillator forces, $f = 4.32 \times 10^{-9} \int \epsilon(\lambda)/\lambda^2 \, d\lambda$, were taken as a measure of absorption intensity, and were calculated from optical density measured every 2.5 nm, on a "Wang" calculator programmed using Simpson's rule.

(11) This is observed for the 300–380-nm range (quinoline absorption) and for the 230–300-nm range as well (adenine and quinoline absorption).

(12) (a) As pointed out by one referee, the H values measured for **2** and **3** at pH 1 could be the result of a true (and high) hypochromism to which could add an hyperchromic perturbation. Craig et al.[12b] have shown in a series of quaternized bis(nicotinamides) that hyperchromism arises as a result of bringing a charged ring close to a charged ring. In **2** and **3**, it does not seem that H can be notably affected by hyperchromism; the UV curve for Ade-C_3-Q at pH 1 (Figure 1) drops immediately to the base line and does not show hyperchromism as extended to longer wavelength (see for comparison ref 12c). In acidic ethanol, hypochromism disappears and no hyperchromism can be detected. (b) J. H. Craig, P. C. Huang, T. G. Scott, and N. J. Leonard, *J. Am. Chem. Soc.*, **94**, 5872 (1972); (c) J. A. Secrist III and N. J. Leonard, *ibid.*, **94**, 1702 (1972).

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(15) In addition to solvation factors, variations in the pK values between Q-C_3 and Ade-C_3-Q may also arise from the stacking properties of the model, which may interfere with the coplanarity required at N-4 of quinoline for the quinonoid "structure" of the resonance hybrid.

(16) (a) The iodides were prepared in a search for an eventual contribution of the base to a charge transfer between the quinolinium and the halide.[16b] However, in the concentration range used (10^{-5} M) and with the limitations due to solubility, no charge transfer could be detected. The spectra of Ade-C_3-Q^+-CH_3 I^- and C_3-Q^+-CH_3 I^- were not sensitive to I^- (0.1 N) addition both in H_2O and EtOH. Switching from I^- to ClO_4^- for C_3-Q^+-CH_3 did not bring any significant change in the spectrum. (b) E. M. Kosower and J. A. Skorcz, *J. Am. Chem. Soc.*, **82**, 2195 (1960), and references cited therein.

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