the generation of **2b** was indicated by the transient appearance of a green intermediate. Although its isolation was not successful, the radical anion derived from **3b** in HMPA by the method of Sakurai[12] was detected by ESR. The spectrum consisted of 19 binomial lines appropriate for 18 equivalent protons (a^H = 0.308 G).

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(1) T. Fukunaga, *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) All new compounds analyzed satisfactorily unless otherwise stated.
(3) Tris(dimethylamino)cyclopropenium hexafluorophosphate[2] was used as the cationic source; for the tetrafluoroborate salt, see Z. Yoshida, *Top. Curr. Chem.*, **40**, 48 (1973).
(4) Other salts of **2a** described also showed similar absorptions.
(5) Mixtures of THF and hexamethylphosphoramide as solvents for radical anions were found to afford ESR spectra of greatly enhanced resolution compared to common solvents. Relatively concentrated solutions can be studied without appreciable line broadening allowing the easy examination of isotopic species in natural abundance.
(6) C. J. Vetee, *J. Chem. Phys.*, **43**, 1080 (1965).
(7) (a) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Am. Chem. Soc.*, **90**, 4201 (1968); (b) d(CC ring) = 1.445 Å, d(CC methylene) = 1.395 Å, d(CC cyano) = 1.420 Å, d(CN) = 1.165 Å, d(CH) = 1.08 Å.
(8) (a) The methylene ^{13}C splittings for the related TCNE and TCNQ radical anions are not known with certainty. Our measurements on TCNE$^{\cdot-}K^+$ in THF–HMPA revealed that the value of 2.92 G suggested for this splitting[8b] is in error. The difficulty arises from overlapping lines. From a careful analysis of the relative intensities of the cyano-^{13}C and ^{15}N satellite lines, we conclude that a^C(methylene) = 6.27 G in this radical anion. For TCNQ$^{\cdot-}$, the reported value of 7.18 G[8c] must also be questioned in the light of a more recent paper;[8d] (b) P. H. Rieger, I. Bernal, W. H. Reinmuth, and G. K. Fraenkel, *J. Am. Chem. Soc.*, **85**, 683 (1963); (c) P. H. H. Fischer and C. A. McDowell, *ibid.*, **85**, 2694 (1963); (d) M. T. Jones and W. R. Hertler, *ibid.*, **86**, 1881 (1964).
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Synthetic Models of Deoxyribonucleic Acid Complexes with Antimalarial Compounds. I. Interaction of Aminoquinoline with Adenine and Thymine

Sir:

Chloroquine (**1**) is an antimalarial drug which inhibits the DNA and RNA polymerase reactions in vitro and the DNA replication and RNA transcription in susceptible cells.[1] The existence of a strong interaction between chloroquine and nucleoproteins has been demonstrated and the complex seems to be best described in terms of at least two distinct classes of DNA binding sites: the diethylamine of the diaminoaliphatic chain interacts ionically with the anionic phosphate groups, while a more specific interaction is involved between the aromatic portion of the drug and the nucleotide bases.[2] It has been proposed that the protonated aminoquinoline ring[3] is intercalated between the base pairs of double stranded DNA.[4]

In order to study *ring–ring interactions* between the drug and the bases in the absence of complicating factors, we devised the "simplified" models "B-C_3-Q": **2** and **3**. These molecules include the aromatic part of the drug bound to a purine (adenine) or a pyrimidine (thymine), through a trimethylene chain (which is of sufficient length to allow a vertical, intramolecular stacking of the rings).[5] The spectroscopic behavior of such models in solution, compared to that of the corresponding reference compounds **4**, **5** and **6**, should reflect the stacking ability of the systems and hence should give rough information about the affinity of the aminoquinoline portion of chloroquine for a purine or pyrimidine type receptor.

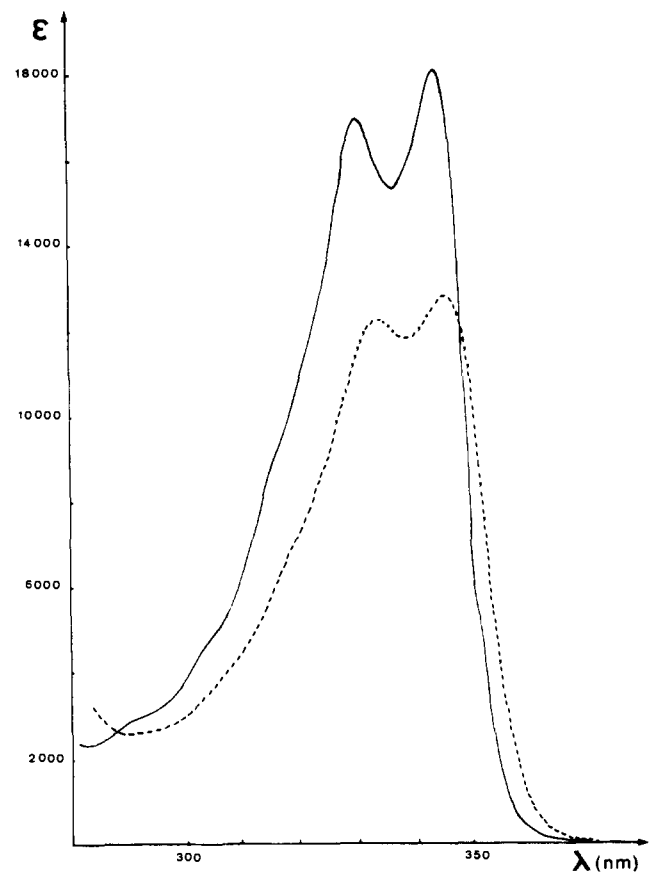
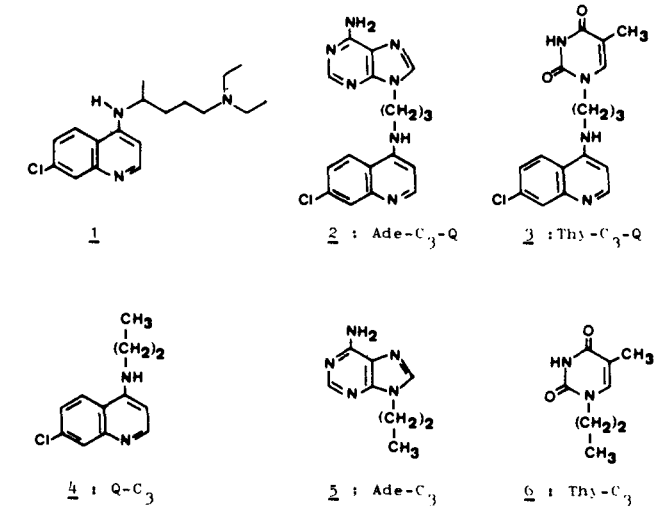


Figure 1. Comparative ultraviolet spectra of **2**, Ade-C_3-Q (- - -), and **4**, Q-C_3 (—), in water, pH 6.9, 5 × 10^{-5} M, 25 °C.



Model compounds **2** (Ade-C_3-Q) and **3** (Thy-C_3-Q)[6] were obtained from 4,7-dichloroquinoline through a nucleophilic substitution reaction by the primary amino function of the appropriate aminopropylnucleotide base. Thus, 9-(3-aminopropyl)adenine (Ade-C_3-NH_2)[7] was treated with 4,7-dichloroquinoline in DMSO at 120°, to afford **2** (Ade-C_3-Q) (mp 255–256°, yield 60%). Reaction of 1-(3-aminopropyl)thymine formate (Thy-C_3-NH_3^+, $HCOO^-$)[8] with the same dichloroquinoline in DMSO in the presence of

Table I. Computed Percent Hypochromism (% H) for the 230–300-nm and 300–380-nm Absorption Bands of Model Systems 2 (Ade-C_3-Q) and 3 (Thy-C_3-Q) in water,[12] 25 °C, at different pH's

	230–300 nm[b]		300–380 nm[b]	
	2	3	2	3
pH 1[a]	16 ± 2	5 ± 2	19.5 ± 0.7	11 ± 1
pH 6.9[a]	20 ± 2	5 ± 2	25.5 ± 0.5	10 ± 1
pH 13[a]	21 ± 1	8 ± 2	23 ± 1	9 ± 1

[a] pH 1, 0.1 N HCl; pH 6.9, phosphate buffer; pH 13, 0.1 N NaOH. [b] In each model, both chromophores quinoline and base show an absorption in the 230–300-nm range; in the 300–380-nm region, quinoline is the only absorbing chromophore; the corresponding H% values are therefore more precise.

diazabicyclooctane led to compound **3** (Thy-C_3-Q) (mp 236–237°). The reference compound **4** (Q-C_3) (mp 148–149°) was prepared by a similar reaction using propylamine. Compounds **5** (Ade-C_3) and **6** (Thy-C_3) were synthetized by alkylation of the corresponding bases.[7-9]

These models were examined by uv absorption spectroscopy, as this technique had been used successfully to detect the interactions of chloroquine with DNA.[10] We recorded the spectrum of an equimolecular solution (5×10^{-5} M) of both "half molecules" **4** (Q-C_3) and **5** (Ade-C_3) in water. This uv spectrum appeared to be superimposable with the summation curve of the spectra of the two individual components. The same observation was made in the thymine case. On the contrary, very large perturbations were observed in the spectrum of the model compounds **2** and **3**, as can be seen, in Figure 1, which shows the uv spectra of neutral aqueous solutions of Ade-C_3-Q (**2**) and Q-C_3 (**4**) (equimolar in quinoline residues), in the 300-360-nm region, in which quinoline is the only absorbing chromophore. The most important feature is the very strong decrease in intensity in the region of the two absorption bands for which the molar extinction coefficients decrease respectively from 18 900 and 17 600 to 12 800 and 12 200. Similar spectral shift and hypochromic effects have indeed been observed for chloroquine in its interaction with DNA.[2c] This "hypochromic effect" exhibited by the model compounds is a proof of the existence of attractive interactions between the two aromatic rings. This hypochromic effect is common to systems which are stacked with the chromophores one on top of another and it has been shown to be proportionate to the degree of stacking.[11] It is generally expressed by the quantity "hypochromism H" by the equation

$$\%H = \{1 - f(\text{B-C}_3\text{-Q})/(f(\text{B-C}_3) + f(\text{Q-C}_3))\}100$$

where f stands for the corresponding oscillator strengths: $f = 4.32 \times 10^{-9} \int \epsilon(\lambda)/\lambda^2 d\lambda$. Table I shows the values calculated for models **2** and **3** for the 230-300-nm region, where both nucleotide bases and quinoline show an absorption, and in the 300-370-nm region, where quinoline is the only chromophore.

Both models exhibit an important hypochromic effect. The H values are always higher for Ade-C_3-Q at any wavelength range and pH, indicating that this system is stacked to a greater extent than Thy-C_3-Q.

Although hypochromism is considered as a semiquantitative measure of the degree of stacking, one may question the validity of this direct comparison of H values calculated for systems with intrinsically different chromophores (adenine and thymine). We therefore developed a temperature method which gave a definite answer. Figure 2 shows the variations of H for both models as a function of temperature. The behavior of compounds **2** and **3** is clearly different; hypochromism (which reflects the degree of stacking)

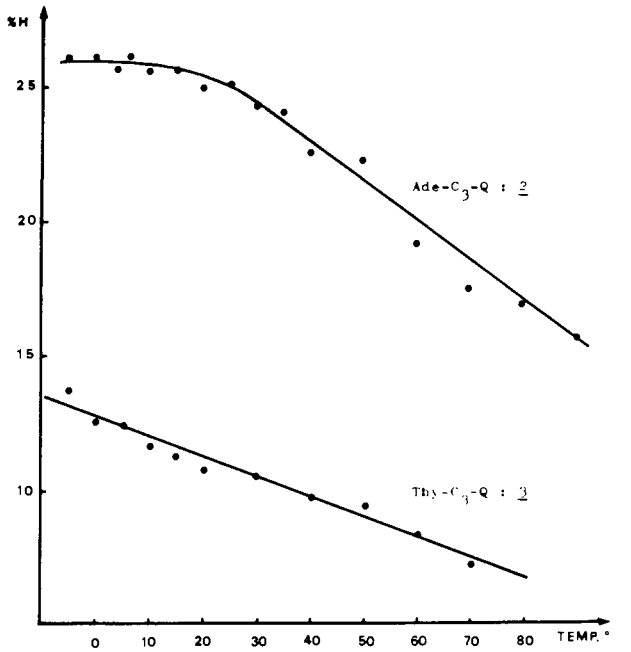


Figure 2. Variation of hypochromism values (% H) with temperature, for model systems **2** (Ade-C_3-Q) and **3** (Thy-C_3-Q) in water, pH 5.

regularly increases for both models as the temperature is lowered, but a maximum constant value is observed in the case of Ade-C_3-Q from +20 to −5 °C, the lowest temperature. This may be interpreted in terms of the existence of the molecule in an essentially stacked conformation, in this temperature range. The recognition of this maximum hypochromism value H_{max} constitutes a powerful tool for the study of the system; the percentage of stacked conformation can be calculated at any temperature, being equal to $100(H/H_{max})$: 20 °C, 100%; 40 °C, 88%; 60 °C, 75%. The thermodynamic parameters can be determined ($\Delta H° = -9$ kcal/mol; $\Delta S° = -24$ eu). It also becomes possible to obtain an estimate of the degree of stacking for the Thy-C_3-Q (**3**) model, if one makes the assumption that the corresponding H_{max} value is intermediate between 14 (highest value experimentally obtained for Thy-C_3-Q) and 26 (maximum value observed for Ade-C_3-Q). This gives a degree of stacking of 40–80% at 20 °C, the lower value being more likely.

The present study shows a higher affinity of chloroquine for adenine than for thymine. This is in good agreement with the result described for the complex formation between this drug and nucleic acids, for which it has been shown that purines constitute preferential binding sites.[1]

A useful comparison can also be made with the hypochromism values calculated by N. J. Leonard and co-workers for a series of dinucleotide analogues B-C_3-B′[13] (B,B′ being purines or pyrimidines), as it appears that hypochromism is greater for Ade-C_3-Q than for any of the other models. This suggests that the attractive interactions between the aromatic ring of chloroquine and adenine are *stronger* than those existing between nucleotide bases, whatever their nature. This observation is of obvious biological interest.[14]

Acknowledgments. We wish to thank the Organon Co. for its support and interest.

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(5) This chain length appears to be the most favorable for interactions between two linked aromatic rings to be observed. The influence of the number of linking methylene groups has been examined notably by N. J. Leonard and co-workers who studied a number of comparable "spectroscopic models related to coenzymes and base pairs": N. J. Leonard and K. Ito, *J. Am. Chem. Soc.*, **95**, 4010 (1973), and references therein. This study has recently been extended to indole–base interactions, see M. Mutai, B. A. Gruber, and N. J. Leonard, *J. Am. Chem. Soc.*, **97**, 4095 (1975).

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(11) For a recent review, see C. A. Bush in "Basic Principles in Nucleic Acid Chemistry", Vol. II, P. O. Ts'o, Ed., Academic Press, New York, N.Y., 1974, p 102; P. O. Ts'o, *ibid.*, p 332.

(12) Water plays a fundamental role in the interaction process as no hypochromic effect can be detected in ethanol. Ionic interactions intervene to a fairly small extent, as no dramatic change is observed when the pH is varied; Ade-C_3-Q shows a maximum *H* value (25.5%) under neutral conditions (Ade, neutral; Q, protonated). At pH 1, when both rings are protonated, the hypochromic effect remains large (19.5%).

(13) See ref 5 and 8. The following % *H* values were found by the authors: Ade-C_3-Ade, 14.8; Ade-C_3-Thy, 11.7; Ade-C_3-Gua, 14.9; Ade-C_3-Cyt, 13.9; Gua-C_3-Gua, 15.8.

(14) These results have been confirmed by a preliminary NMR study carried out under the same conditions of solvent, pH, and concentration.

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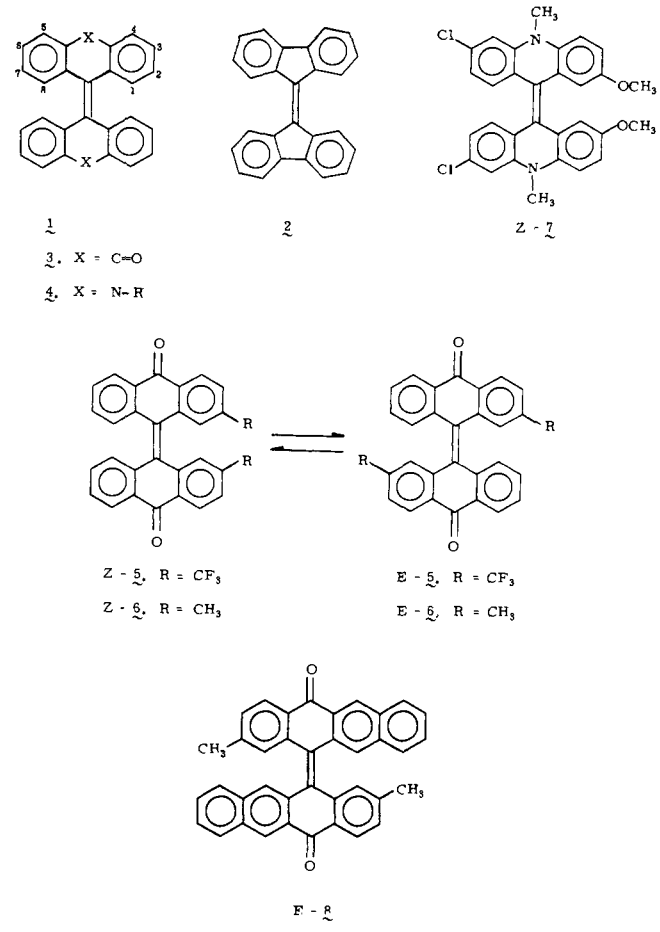
Fast Thermal *Z,E* Isomerization in Symmetrical Overcrowded Ethylenes. Low Barriers Due to Ground-State Destabilization[1]

Sir:

The study of the mechanisms of uncatalyzed thermal *Z,E* isomerizations around carbon-carbon double bonds has been focused mainly on polarized ethylenic systems and on electronic effects.[2,3] Very little attention has been drawn to *Z,E* isomerizations in *symmetrical overcrowded ethylenes*, in which steric effects might become decisive.[2,3] In this series, a dominant role has been played by the bis-tricyclic systems **1**. The strain built in **1**, by the considerable overlap of the van der Waals radii in the region of the central double bond ("pinch"), leads to deviations from planarity and to various distortions, e.g., folding of the benzene rings, and twisting and stretching of the "pinch".[4-6] Fast diastereomerizations were observed in 1,1′-disubstituted $\Delta^{9,9'}$-bisfluorenylidenes carrying bulky groups,[7] but it was not clear whether these exchange processes represented *Z,E* isomerizations or the interconversion between twisted and folded ethylenes of the chiral *E* conformation.[2] In any event, these phenomena are not an intrinsic feature of the bisfluorenylidene system (**2**).[8] We report fast true *Z,E* isomerizations in



the bianthrone (**3**) and the biacridan (**4**) series. We ascribe the unusual low energy barriers in these systems predominantly to a destabilization of strained ground-state conformations. Hitherto, the existence of *Z,E* isomers and thermal isomerizations in these series has hardly been established.[9-12] These aspects have been overlooked in the extensive studies of the origin of the photochromic, thermochromic, and piezochromic properties of the bianthrones.[5,9,13-15]

Bianthrone and biacridan derivatives seemed to be promising substrates for the present investigation because of the higher degree of overcrowding (in the ground state planar model) relative to **2**. The following unconventional tailor-made substituted bianthrones and biacridan were studied: 2,2′-bis(trifluoromethyl)bianthrone (**5**), 2,2′-dimethylbianthrone (**6**), and 6,6′-dichloro-2,2′-dimethoxy-*N,N′*-dimethylbiacridan (**7**). The introduction of "tag" substituents (CF_3, CH_3, OCH_3) at positions 2 and 2′ does not effectively change the ground-state steric overcrowding around the "pinch" relative to the parent compound, and yet permits an NMR study of *Z,E* isomerism and isomerization. Tag substituents in the conventional 3 and 3′ positions of bianthrone, proved to be too far removed from the other half of the molecule and unsuited as probes for detection of inequivalent magnetic environment in the two geometrical isomers.

Compound **5** was synthesized as follows.[16] A Grignard reaction of phthalic anhydride and α,α,α-trifluoro-*m*-tolylmagnesium bromide gave *o*-(α,α,α-trifluoro-*m*-toluyl)benzoic acid[17] which was hydrogenated (Pd/C) to *o*-(α,α,α-trifluoro-*m*-tolyl)benzoic acid (mp 111°). HF cyclization of the latter acid afforded 3-trifluoromethyl-10-anthrone (mp 144-145°), which was converted by ferric chloride to the corresponding 9,9′-bianthronyl (mp 235-238°). Enolization (KOH in ethanol) and dehydrogenation ($K_2S_2O_8$) led final-