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Steric Inhibition of Conjugation in Lowest Excited Singlet State of 9-Anthramide by Hydrogen Bond Donor Solvents: Role of Solvent in Chemical Structure

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Abstract □ 9-Anthramide has electronic absorption and fluorescence spectra that, in water, are similar to those of anthracene. This result is attributed to steric hindrance of the 9-carboxamido group with the *peri*-hydrogen atoms in the 1- and 8-positions of the anthracene ring. However, in aprotic solvents, although the absorption spectrum of 9-anthramide is anthracene-like, its fluorescence spectrum is red shifted and structureless. This finding is attributed to excited-state rotation of the 9-carboxamido group into coplanarity with the anthracene ring and indicates that, in water, the hydrogen-bonded solvent cage affects the steric inhibition of conjugation in excited 9-anthramide. These findings suggest that studies of structure and reactivity of drugs in nonaqueous or solid matrixes are probably of only limited value, since in the strongly interacting aqueous media the aqueous solvent cage plays a substantial role in determining molecular structure and reactivity.

Keyphrases □ 9-Anthramide—electronic absorption and fluorescence spectral study, effect of solvent on molecular structure □ Solvent—effect on molecular structure of 9-anthramide, electronic absorption and fluorescence spectral study □ Molecular structure—9-anthramide, effect of solvent, electronic absorption and fluorescence spectral study □ Conjugation—steric inhibition in 9-anthramide, effect of solvent, electronic absorption and fluorescence spectral study

9-Anthroic acid and many of its derivatives have absorption spectra that are very similar to those of anthracene in vibrational structure and position in the electromagnetic spectrum. However, in various solvents, these compounds demonstrate a fluorescence band that is unstructured and at considerably longer wavelengths than that of anthracene. This band has been explained in terms of rotation of the carboxyl group from a configuration perpendicular to that of the anthracene ring in the ground state to one coplanar with the anthracene ring in the thermally equilibrated lowest excited singlet state (1).

It has been suggested that the steric hindrance to coplanarity, exerted by the *peri*-hydrogen atoms in the 1- and 8-positions of the anthracene ring in the ground state, is circumvented by reduction of the O—C—O bond angle of the carboxyl group as a result of electronic excitation. In the 9-anthroate anion, however, the greater electron density at the carboxylate group has been suggested to prevent sufficient alteration of the structure of the latter to permit coplanarity, even in the excited state, because both the absorption and fluorescence spectra of the anion are anthracene-like in appearance (2).

Based on spectra of the ethyl esters of 1- and 2-naphthoic acids (3), it was thought that the inability of the 9-anthroate anion to conjugate in the lowest excited singlet state may not be purely a function of structure but may be due to environmental effects such as a tightly bound solvent cage producing the steric interference. This hypothesis is, however, rather difficult to test on the 9-anthroate anion, because the ion-pairs, upon which spectra would be taken in low dielectric media, would include cations; these cations would introduce further complications in the interpretation of the spectra.

The amide of the 9-anthroic acid affords at least a partial solution of this problem. The carboxamido group is intermediate between the carboxyl group and the carboxylate anion in its electronic distribution and, therefore, in its geometrical structure. Moreover, 9-

Table I—Absorption (Abs) and Fluorescence (Fl) of the Neutral and Cationic Species Derived from 9-Anthramide

Cation in	λ, Abs	λ, Fl^{max}	Neutral	λ, Abs	λ, Fl^{max}
Water	383	470	Water	385	407
Ethanol	382	442	Ethanol	385	404
Dioxane	384	440	Dioxane	384	440
Acetonitrile	382	448	Acetonitrile	382	448
Heptane	380	462	Heptane	380	451
Chloroform	384	461	Chloroform	384	461

anthramide is uncharged, so it can be studied in low dielectric media without having to account for ion-pairing phenomena. Consequently, to account for the possibility of solvation phenomena influencing the failure of the carboxamido group of 9-anthramide and, therefore, the carboxylate group of the 9-anthroate anion to achieve coplanarity in the lowest excited singlet state, electronic spectra of 9-anthramide were studied.

EXPERIMENTAL

Reagents—9-Anthroyl chloride[1] was recrystallized several times from absolute ethanol. 9-Anthramide was prepared from 9-anthroyl chloride by the method of Saare (4) and was recrystallized several times from hot water.

Analytical reagent grade sulfuric acid[2] was diluted with distilled, deionized water for the solutions used to study the Hammett acidity region. Solutions in the pH range were citrate and phosphate buffers and sodium hydroxide solutions in distilled, deionized water.

Each sulfuric acid or buffer solution in a 10-ml volumetric flask was injected with 100 μl of a 1.00×10^{-3} *M* stock solution of the appropriate 9-anthramide in absolute ethanol immediately prior to the taking of spectra to minimize decomposition errors. Nonaqueous solvent solutions were prepared by dissolving weighed amounts of the solid in 10.00 ml of the appropriate solvents.

Apparatus — Absorption spectra were taken on a spectrophotometer[3]. Fluorescence spectra were taken on a fluorescence spectrophotometer[4] whose monochromators were calibrated against the xenon line emission spectrum and whose output was corrected for instrumental response by means of a rhodamine-B quantum counter. The pH measurements were made on a pH meter[5] employing a silver–silver chloride–glass combination electrode.

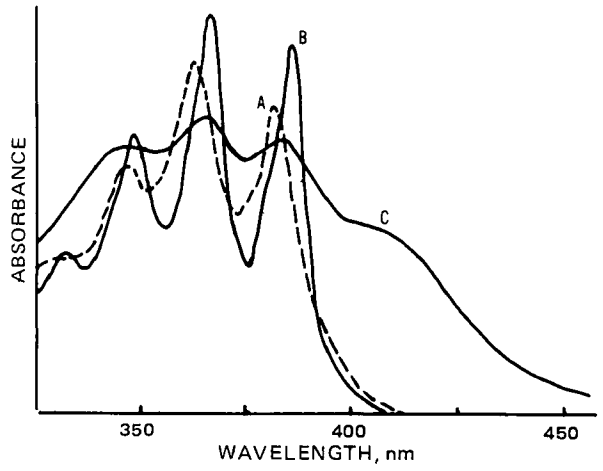


Figure 1—*Electronic absorption spectra of about* 1×10^{-5} M *9-anthramide in hexane (A), water at pH 7.9 (B), and Hammett acidity −4.0 (C).*

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] Mallinckrodt Chemical Works, St. Louis, Mo.
[3] Beckman DB-GT.
[4] Perkin-Elmer MPF-2A.
[5] Orion model 801.

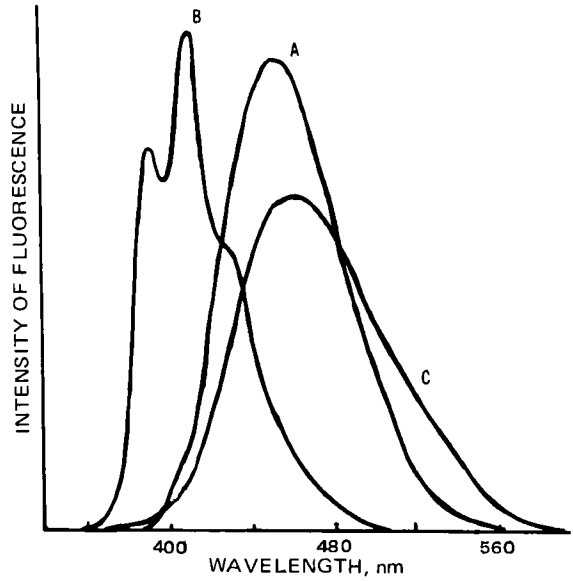


Figure 2—*Fluorescence spectra of about* 1×10^{-5} M *9-anthramide in hexane (A), water at pH 7.9 (B), and Hammett acidity −4.0 (C).*

RESULTS AND DISCUSSION

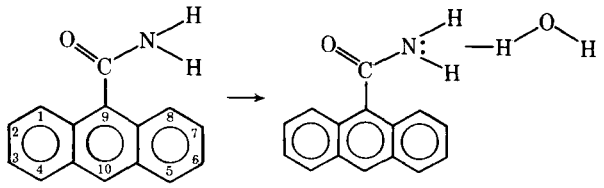
The principal absorption and fluorescence features of 9-anthramide in various solvents and at various pH's are presented in Table I. The ground-state pKa and excited-state pKa* values were −2.00 (determined absorptiometrically) and 1.50 (determined fluorometrically), respectively.

In anthracenes substituted in the 9-position with strongly interacting substituents, the transversely polarized $^1L_a \leftarrow {}^1A$ transition is more affected by intramolecular charge transfer than the longitudinally polarized $^1L_b \leftarrow {}^1A$ transition. As a result, the ^1L_a band tends to lose vibrational structure and shifts to longer wavelengths relative to its position in anthracene while the ^1L_b band is relatively unaffected (5). In 9-anthramide, steric hindrance in the ground state arising from the interactions between the bulky substituents in the 9-position and the *peri*-hydrogen atoms in the 1- and 8-positions of the anthracene ring prevents the conjugation (coplanarity) of the exocyclic group in the 9-position with the anthracene ring. Since the 9-substituents have little effect on the ^1L_a absorption bands of anthracene in this case, the absorption spectra of the 9-anthramides are almost identical with those of anthracene.

In the ground state of 9-anthramide in various solvents, steric hindrance is observed in the neutral and cationic species, as reflected by the highly structured absorption spectra at only slightly longer wavelengths than those of anthracene (Fig. 1). However, 9-anthramide exhibits an unstructured long wavelength fluorescence band (Fig. 2), indicating that in these solvents, in the lowest excited singlet state, the steric barrier to coplanarity is removed. Rotation of the 9-substituent into coplanarity with the ring occurs in the thermally equilibrated lowest excited singlet state. 9-Anthramide demonstrates this highly diffuse emission band with a maximum at 470 nm.

9-Anthramide, in hydrogen bond donor solvents (water and ethanol), shows no conjugation of the exocyclic group with the ring in the lowest excited singlet state, as reflected by the highly structured emission band with a maximum at 407 nm (Fig. 2). The assumption of the bond angle reduction of the carboxyl group or, in this case, the carboxamido group upon excitation is not sufficient to explain the observation of the structured, anthracene-like spectra of 9-anthramide in hydrogen bond donor solvents.

In the ground state of 9-anthramide in all solvents, the resonance-stabilization due to conjugation of the exocyclic group with the ring system is not large enough to overcome the steric interference from the *peri*-hydrogen atoms in the 1- and 8-positions of the ring. However, in the lowest excited singlet state, the conjugative interaction is much stronger than in the ground state, because of the greater electronic dipole moment of the ^1L_a state, which is stabilized by intramolecular charge transfer from the anthracene ring to the exocyclic group.



Scheme I

In aprotic solvents, this interaction is strong enough to overcome the steric barrier to it and allows the exocyclic group to attain a coplanar configuration. However, in water and ethanol, the carboxamido group is hydrogen bonded to the solvent (Scheme I), with the result that the group and its solvent cage become more bulky. The resonance interaction even upon excitation is not great enough to overcome the steric interference from the interaction between the *peri*-hydrogen atoms and the solvent cage.

Once 9-anthramide is protonated at the amido nitrogen, the effect of the hydrogen bond donor solvent cage is lost. This loss removes the possibility of hydrogen bonding at the carboxamido group and is observed as a loss of the mirror image relationship between the absorption and fluorescence spectra, with the result that the emission spectrum shifts to much longer wavelengths (Fig. 2).

While the ground-state pKa of 9-anthramide is −2.00, excited-state protonation occurs in this compound, as revealed by variations in the fluorescence spectra with pH or Hammett acidity. 9-Anthramide is more basic in the excited state and exhibits an excited-state pKa* value of 1.50. The decrease in acidity of the protonated amide in the lowest excited singlet state reflects the transfer of electronic charge from the anthracene ring to the exocyclic group upon excitation.

The effect of protonation on the conjugation of the exocyclic group can be observed by following the absorption and fluorescence band shapes and band maxima as they vary with pH or Hammett acidity. In the ground state, in the region below Hammett acidity of −2.0, protonation of the carboxamido group is observed as a slight smearing and red-shift in the absorption spectrum (Fig. 1). In the ground state, protonation apparently causes the resonance interaction to increase enough to allow the exocyclic group to reach a configuration that is nearly coplanar to the ring. The effect of protonation in the excited state is more dramatic, the large red-shift of the emission spectrum, on protonation, suggesting essentially complete conjugation in the excited state.

The solvents used in this study covered a wide range of polarity and hydrogen bond donor capability. It was found that excited-state conjugation in the neutral molecule can occur only in aprotic solvents (regardless of polarity). The hindrance observed in the excited state in hydrogen bond donor solvents is due to the solvent caging effect at the carboxamido group; this effect makes the group too bulky to overcome the steric interference from the *peri*-hydrogen atoms in the 1- and 8-positions of the anthracene ring.

The solvent cage has thus been shown to play an important role in chemical structure. A conclusion that may be drawn from these studies is that the chemical structure (and presumably the reactivity) of a compound may vary substantially from solvent to solvent. As illustrated by the differences in the spectra of 9-anthramide in water and heptane, strongly interacting solvents do affect chemical structure. These findings suggest that studies of structure and reactivity of drugs in nonaqueous solvents and solid matrixes may not always be validly applied to the interpretation of phenomena observed in strongly interacting solvents such as biological fluids because of the solvent caging effect.

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Effect of Variation in Compaction Force on Properties of Six Direct Compression Tablet Formulations

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Abstract □ The effect of variation in compaction force on six direct compression tablet matrixes was investigated. An instrumented tablet press allowed direct measurement of applied and ejection forces. Hardness, apparent tablet density, and disintegration times also were determined. The disintegration time of spray-dried lactose tablets was essentially independent of compaction force. However, in the other systems investigated, the properties studied showed varying types of dependence on compaction pressure. A direct compression formula was developed and exhibits a decrease in disintegration time as compaction force is increased.

Keyphrases □ Tablets—six matrixes, effect of various compaction forces on hardness, apparent density, and disintegration time □ Compaction force—effect on tablet hardness, apparent density, and disintegration time, six matrixes □ Hardness, tablet—six matrixes, effect of various compaction forces □ Density, apparent—six tablet matrixes, effect of various compaction forces □ Disintegration time, tablet—six matrixes, effect of various compaction forces □ Dosage forms—tablets, six matrixes, effect of various compaction forces on hardness, apparent density, and disintegration time

The production of pharmaceutical tablets by the direct compression technique has several advantages for many drugs in comparison with wet granulation or other methods. In particular, the relatively small labor content of this technique makes it increasingly attractive to the pharmaceutical industry (1).

Several well-proven materials can be used as tablet matrixes for direct compression, and some investigators