Hydrophobic Self-Association of *d*-Propoxyphene Hydrochloride and the Effect of Urea: A Nuclear Magnetic Resonance Study

Keyphrases □ *d*-Propoxyphene HCl—hydrophobic self-association □ Urea effect—*d*-propoxyphene HCl self-association □ NMR spectroscopy—molecular interaction

Sir:

d-Propoxyphene is an important nonnarcotic analgesic agent. In a previous study from our laboratories, Conine has reported that aqueous solutions of *d*-propoxyphene hydrochloride[1] possess the ability to solubilize sparingly water-soluble organic acids (1). Conine's data have strong parallels to the phenomenon of micellar solubilization; he observed an apparent solute critical micelle concentration (SCMC). The amount of organic acid solubilized per mole of *d*-propoxyphene hydrochloride increased appreciably once the SCMC had been exceeded. Formation of aggregates of some type by propoxyphene ions was suggested but no direct evidence for this phenomenon was presented. Other reports (2, 3) in the literature also show that pharmacologically active amines form aggregates in aqueous solutions of their salts. It was of interest to us to develop a more definitive understanding of the aggregation phenomenon in aqueous *d*-propoxyphene hydrochloride solutions.

Nuclear magnetic resonance (NMR) spectroscopy can provide much detailed information about molecular interactions. In recent years NMR has been utilized for this purpose in such diverse areas as micelle formation (4), micellar solubilization (5), drug-protein interactions (6), and enzyme-substrate interactions (7). Applications of this versatile tool to research problems in physical pharmacy are not well documented in the literature. In this communication we wish to describe the findings of a preliminary NMR spectroscopic study of the self-association of *d*-propoxyphene hydrochloride in aqueous solutions.

The effect of concentration on the high resolution NMR spectrum of *d*-propoxyphene hydrochloride in D_2O is illustrated in Fig. 1. Assignments of the various signals, based on a first-order analysis, are also indicated in the figure.[2] As the concentration is increased, the signals of the aromatic and C-1 methylene protons are the most strongly affected. The fine structure in the aromatic region, apparent at low concentrations, is gradually lost as the solute concentration is increased.

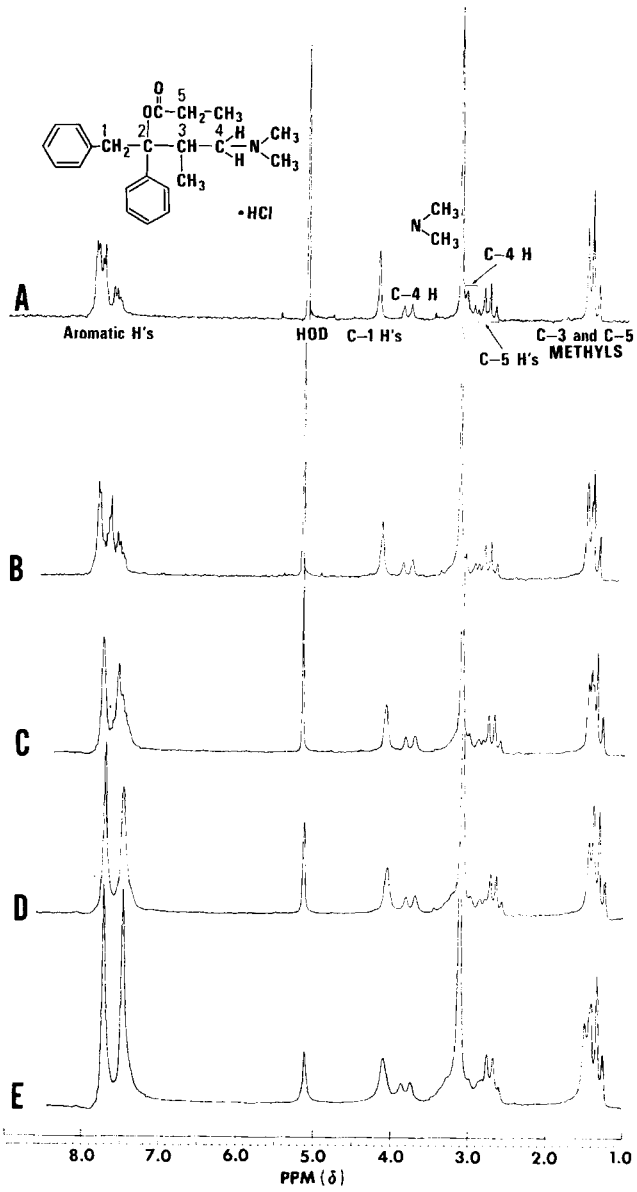

Figure 1—*Effect of concentration on 100-Mc.p.s. NMR spectrum of* d*-propoxyphene hydrochloride in D_2O at 30°. The scale is referred to external TMS which was used as the source of a lock signal. Key:* A, *0.1* M; B, *0.2* M; C, *0.3* M; D, *0.5* M; and E, *1.0* M.

In a 1 *M* solution, two rather broad singlets appear for the aromatic protons. The signal at 4.22 p.p.m. due to the C-1 methylene group is also appreciably broadened as indicated by its linewidth at half-height. The width of the sharp singlet due to the dimethylamino protons appears to be the least affected.

In addition to line broadening, all the signals move upfield as the concentration is increased; however, those due to the aromatic and the C-1 methylene protons undergo the most pronounced upfield shifts. It thus appears that aggregation in aqueous *d*-propoxyphene

[1] Marketed as Darvon by Eli Lilly and Co.
[2] The C-3 proton multiplet coincides with the *N*-methyl singlet and therefore it cannot be observed directly.

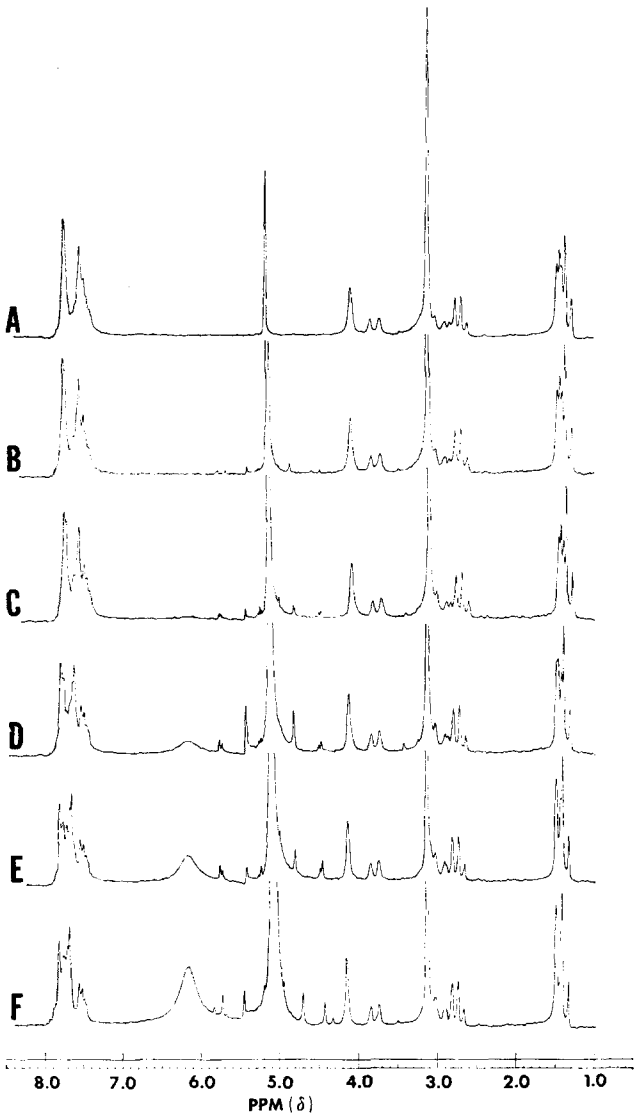

Figure 2—*Effect of urea on 100-Mc.p.s. NMR spectrum of 0.3* M d-*propoxyphene hydrochloride in D_2O at 30°. The scale is referred to external TMS which was used as the source of a lock signal. The peaks symmetrically placed on either side of the HOD peak are spinning sidebands. The rather broad peak at 6.16 p.p.m. is due to the unexchanged amide protons of urea. Key:* A, *0.0* M *urea;* B, *0.5* M *urea;* C, *1.0* M *urea;* D, *2.0* M *urea;* E, *3.0* M *urea;* F, *4.0* M *urea.*

hydrochloride solution takes place primarily through hydrophobic interactions of the aromatic systems. Further evidence supporting the proposed hydrophobic nature of this self-association comes from the fact that the concentration effects are absent in acetone and methanol solutions. It has been shown before that hydrophobic aggregation does not take place in these solvents (8, 9).

One of the factors causing such hydrophobic bonding would be the highly ordered water structure around the nonpolar moieties of the solute molecule. This ordered, cooperative, or iceberg-like structure of water may be altered by the addition of urea which has a strong potential to interact with water. There appears to be some controversy about the effect of urea on water structure as to whether it acts as a structure breaker or as a structure maker (10); however, the hydrophobic bond-weakening effect of urea is generally recognized.

Increasing the addition of urea to *d*-propoxyphene hydrochloride solutions (at a given concentration) should weaken the hydrophobic interactions of the aromatic moieties. This predicted effect was observed when the NMR spectra of a 0.3 *M d*-propoxyphene hydrochloride solution were examined (Fig. 2). This particular concentration was chosen to demonstrate the effect of urea since it appeared, from chemical shift *versus* concentration plots, to be just above the concentration at which aggregation is complete. Weakening of hydrophobic bonding can be seen by the progressive reappearance of the fine structure of aromatic multiplets and by the increasing sharpness of C-1 methylene proton singlet as the urea concentration is increased from 0.5–4 *M*. The protons which are responsible for the intermolecular hydrophobic interactions also show the most significant downfield shifts indicating that as hydrophobic bonds are weakened, solute structure becomes less ordered. To our knowledge this is the first direct NMR demonstration of the hydrophobic bond-weakening effect of urea.

We are, at present, studying in detail the effect of hydrophobic self-association on chemical shifts and spin-spin relaxation rates. We are also examining, by NMR spectroscopy, aqueous *d*-propoxyphene hydrochloride solutions containing solubilized aromatic molecules. Results of these studies will be reported in future, more complete papers.

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