Ultrasonic Relaxation Studies of Antihistamine Type Drugs

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Summary Ultrasonic measurements on several antihistamines have revealed the presence of an interionic proton transfer mechanism and two competing association phenomena.

THE significance of the biological activity of many drugs has been discussed in relation to their colloidal behaviour.[1] The association, and in particular micellar, behaviour of several antihistamines has recently been studied by equilibrium methods.[2-4] In order to obtain a better understanding of the solution properties of these compounds, with particular reference to the mechanistic details of the reactions, these equilibrium studies should be complemented with kinetic data. For this purpose we have carried out ultrasonic relaxation measurements on aqueous solutions of these compounds. The main reason for employing the ultrasonic technique is that it has previously been used successfully to study the kinetics and mechanisms of association phenomena.[5]

The relaxation behaviour of the antihistamine solutions was found to depend on both the counterion and the structure of the nucleus on which the antihistamines are based. A single relaxation of weak amplitude was found in all the compounds which contain a chloride counterion; a typical relaxation spectrum is shown in the Figure (curve A). It was found that those drugs based on a pyridine type nucleus and containing a maleate counterion showed intense relaxation spectra, as shown in the Figure (curve B). This relaxation is characterized by more than one relaxation time. In attempts to determine the molecular origin of these relaxations, extensive studies have shown that the main molecular interaction which contributes to the intense relaxation in these maleates is a proton transfer process involving the maleate counterion and the pyridine ring of the antihistamine nucleus. The existence of this proton transfer mechanism was confirmed by measurements of the ultrasonic relaxation spectrum of aqueous solutions of pyridine–sodium maleate mixtures at the same pH as the antihistamine maleates, as shown in the Figure (curve C).

The above proton transfer contribution to the relaxation spectra can be eliminated at pH *ca.* 1·8. Indeed, at this pH the ultrasonic relaxation associated with these pyridine based antihistamine maleates is characterized by a single relaxation time of comparable amplitude and concentration dependence to those found for the hydrochloride antihistamines as shown in the Figure (curve D). The origin of this relaxation must be associated with the aggregation behaviour of these antihistamines. An examination of the structures of these compounds indicates that two association phenomena can take place. Firstly, a π-electron cloud density associated with the aromatic ring nucleus will promote a 'base stacking' type of association. Secondly,

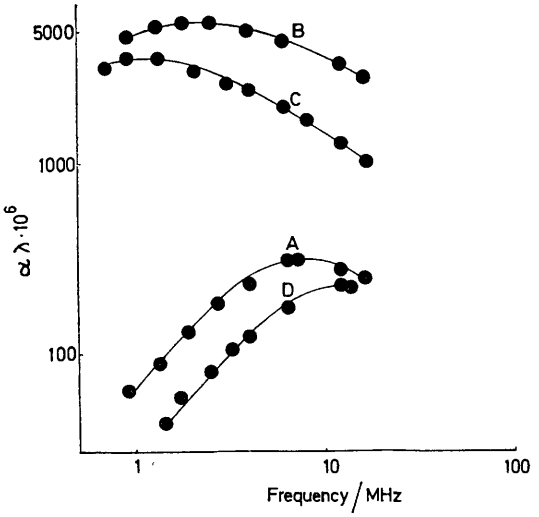

FIGURE. Plots of relaxation spectra of (A) 0·1 M tripelennamine hydrochloride, (B) 0·1 M chlorpheniramine maleate, pH 4·9, (C) 0·1 M pyridine + 0·05 M sodium maleate, pH 5·0, and (D) 0·1 M chlorpheniramine maleate, pH 1·8.

the amphiphilic nature of these antihistamines gives rise to micellar type aggregation behaviour. Indeed, equilibrium measurements on some of these compounds have shown the presence of a critical micelle concentration (c.m.c.),[2,4] however a debate still exists as to the exact nature of the association phenomena.[4] In the present work the concentration dependence of the relaxation times are not

consistent with only one of these mechanisms taking place[5] and one must therefore assume that both of the phenomena are occurring at the same time. Thus when antihistamine is dissolved in water base-stacking initially occurs; this process is accompanied by the monomer concentration increasing with overall antihistamine concentration. Eventually this monomer concentration will reach a constant value, the c.m.c., when presumably micelles will be formed.

It is of interest to note that the amplitudes of the ultrasonic relaxation spectra of the antihistamine maleates at their normal pH, which is dominated by the interionic proton transfer process, increase with increasing antihistamine concentration. This implies that proton transfer is taking place even though aggregates are present in solution. Thus the structure of the aggregates must be such that the acceptor sites are available for this proton transfer with the maleate counterion. A proton transfer process on micellar surfaces has also been observed using n.m.r. spectroscopy.[6]

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