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Structural differences in solutions derived from polymorphic modifications of aspirin

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Differences in the structure of solutions derived from two polymorphic modifications of aspirin were demonstrated through differences in apparent pK_a values. The apparent pK_a's were determined in dimethylformamide using tetrabutyl-ammonium hydroxide as the titrant. The pK_a differences were ascribed to differences in intra- and intermolecular hydrogen bonding of the solute.

While polymorphic modifications of a substance have the same chemical properties, they may have different physical properties. It has been generally accepted that once in solution, all polymorphic modifications are identical; that is, there is no structuring of the solute that can be related to the original structure of the polymorph. However, solutes such as benzoic acid and salicylic acid are known to associate in certain solvents through hydrogen bonding, as do some solvents themselves. It is not surprising therefore that Urazovskii and co-workers (Urazovskii & Chetaev, 1949; Urazovskii & Kogan, 1950; Urazovskii, Kotlyarenko & Kuris'ko, 1959) were able to show differences in solutions derived from different polymorphic modifications. The present report utilizes similar methods to demonstrate structural differences in solutions derived from polymorphic modifications of apirin. The polymorphs are those whose dissolution properties from single crystals (Tawashi, 1968) and thermal properties (Tawashi, 1969; Summers, Carless & Enever, 1970) have recently been reported.

METHODS

Two polymorphic modifications of aspirin were prepared as described by Tawashi (1968). Polymorph I was prepared by slow crystallization at room temperature from a saturated solution of aspirin U.S.P. in 95% ethanol. Polymorph II was prepared by crystallization from a saturated solution of aspirin U.S.P. in n-hexane at room temperature.

The polymorphs were titrated in dimethylformamide using 0·1N tetrabutylammonium hydroxide in methanol-benzene as the titrant. A glass-modified calomel electrode system containing a saturated solution of potassium chloride in anhydrous methanol was used. Micro melting points were determined using a Mettler FP-2 hot stage.

RESULTS AND DISCUSSION

The two polymorphic forms of aspirin had melting points of 140° to 142° for polymorph I and 121·5° to 124° for polymorph II. The structural energy of the polymorph is reflected in the melting point, the intermolecular forces of the lower melting polymorph being of lesser magnitude than the forces present in the higher melting

polymorph. In aspirin it is possible to account for the difference in melting points by considering the effect of intra- and inter-molecular hydrogen bonding. Wheatly (1964) has shown that an aspirin structure crystallized from benzene and melting at 143° has a dimeric structure in the solid state. This is most likely polymorph I. Polymorph II would then be expected to have a lesser degree of intermolecular hydrogen bonding or increased intramolecular hydrogen bonding which is possible between the ester carbonyl and the hydroxyl hydrogen.

The solvation of two such polymorphic structures in the dissolution process could lead to solutions differing in acidic properties, provided the structures of the polymorphs were maintained on a molecular level during solvation and dissolution. That the solutions obtained from the two polymorphic forms of aspirin have different structural characteristics is demonstrated by the significant differences in apparent pK_a values obtained from these solutions. (Figs 1 and 2). Two structures for the

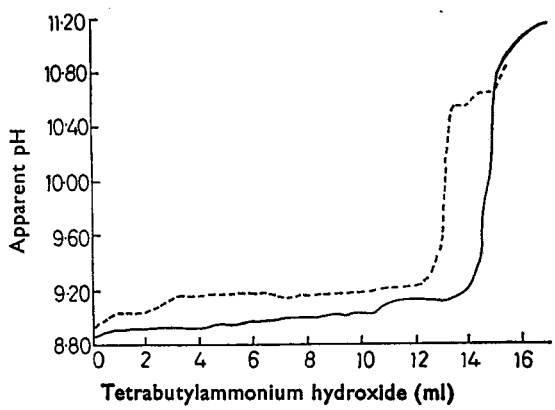


FIG. 1. Titration of aspirin polymorphs with 0·1N tetrabutylammonium hydroxide in dimethylformamide Polymorph I ——, II– – –.

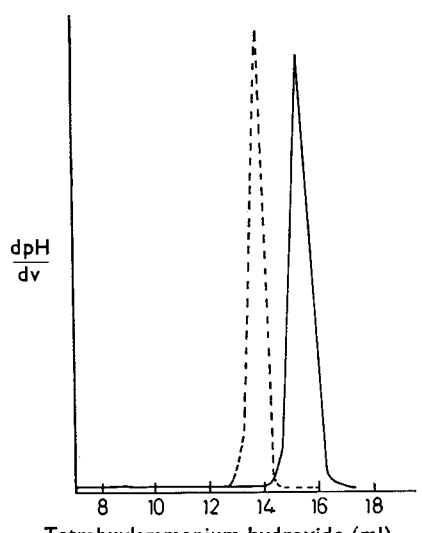
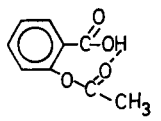
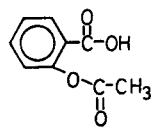


FIG. 2. First derivative plot of the titration of aspirin polymorphs. Polymorph I——, II – – –.

solute, aspirin, in solution are postulated to account for these differences in apparent pK_a (Structures A and B). Based on these two structures, it would be expected that structure A would have the highest pK_a value, and extrapolating to the solid polymorph, the lowest melting point because of the intramolecular hydrogen bonding. This is indeed the case of polymorph II, having a melting point of 121° to 124° is the weaker acid having an apparent pK_a of 9·19 in this solvent.



A



B

Polymorph I would be expected to be a stronger acid if its solvated structure involves little intramolecular hydrogen bonding, even if some dimer or higher forms exist in solution. In his *X*-ray analysis, Wheatly (1964) detected a great deal of angular distortion centered about the carboxyl and acetyl oxygen attached to the ring. Because of these stresses in the dimeric structure of the solid and because of the lower pK_a value obtained for polymorph I, it would appear that the solvated structure of this polymorph should be represented by structure B. Polymorph I was found to have an apparent pK_a of 8·99 representing a pK_a difference of 0·20. This is consistent with the above theory.

CONCLUSIONS

The concept of structured solutions resulting from polymorphic modifications could have profound implications in considerations of drug-receptor interactions and in drug availability from a dosage form in general. Many of the steroids, capable of existing in a large number of polymorphic forms under conditions of standard temperature and pressure, may be capable of forming structured solutions due to the presence of hydroxyl and carbonyl groups. These groups are most likely responsible for many of the polymorphic modifications. Differences in the properties of these and other polymorphic materials, as affected by the structure of their solutions, are being investigated further.

Acknowledgement

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