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Structure and interactions of aspirin-like drugs

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Abstract. A pre-requisite for the elucidation of the mechanism of action of aspirin-like drugs, which are believed to exert their pharmacological effects through the inhibition of prostaglandin biosynthesis, is an understanding of their molecular geometry, the non-covalent interactions they are likely to be involved in, and the geometrical and the electronic consequences of such interactions. This has been sought to be achieved through the x-ray analysis of these drug molecules and their crystalline complexes with other suitable molecules. The results obtained from such studies have been discussed in terms of specific typical examples. For instance, antipyrine can form metal and hydrogen-bonded complexes; phenylbutazone can form ionic complexes with basic molecules. Complex formation is accompanied by characteristic changes in the molecular geometry and the electronic structure in both the cases. The results obtained so far appear to indicate that the important common invariant structural features of the fenamates, deduced from crystal structures, are retained even when complexation takes place.

Keywords. Aspirin-like drugs; prostaglandin biosynthesis; non-covalent interactions; crystalline complexes; pyrazole derivaties; fenamates.

1. Introduction

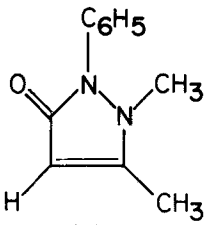
Nonsteroid anti-inflammatory analgesics like salicylates, aniline derivatives, pyrazole derivatives and fenamates, which are effective in varying degrees against pain, inflammation and fever, have been among the most commonly used drugs for several decades. Hardly anything was known about the molecular mechanism of their pharmacological action until the early seventies when it was discovered that all these drugs, despite their widely different chemical structures, inhibit prostaglandin biosynthesis (Vane 1971). They are now believed to act through the inhibition of the system of enzymes responsible for the biosynthesis of prostaglandins (Flower 1974). In this context, a pre-requisite for the elucidation of the molecular details of the action of these compounds is a thorough understanding of (a) their molecular geometry, (b) the non-covalent interactions they are likely to be involved in and (c) the changes introduced in their molecular and electronic structure as a result of these interactions. One of the x-ray crystallographic projects in our laboratory seeks to achieve this through the x-ray analysis of these drug molecules as well as their crystalline complexes with other suitable molecules. The focus of attention in these studies has been on pyrazole derivatives and fenamates, and the structures analysed include drugs such as antipyrine (Singh and Vijayan 1973), amidopyrine (Singh and Vijayan 1976), metamizol (analgin or novalgin) (Krishna Murthy *et al* 1979), phenylbutazone (Singh and Vijayan 1977), oxyphenbutazone (Krishna Murthy and Vijayan 1981a), niflumic acid (Krishna Murthy and Vijayan 1979), meclofenamic acid (Krishna Murthy and Vijayan 1981b), flufenamic acid (Krishna Murthy *et al* 1982) and some of their complexes (Singh and Vijayan 1974, 1977; Dhanaraj and Vijayan 1983). These analyses have produced a wealth of information on the structure and interactions of the concerned drug

molecules, but we shall confine ourselves here to a few representative results to illustrate the type of information that could be obtained from studies of this nature.

2. Pyrazole derivatives

2.1 *Pyrazolone derivatives*

Pyrazole derivatives with aspirin-like action can be classified into two groups, namely, pyrazolone derivatives and pyrazolidinedione derivatives. Antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) (I) was the first pyrazolone derivative to be introduced into



(I)

medical practice, and the better known amidopyrine and metamizol (analgin or novalgin) are its derivatives. It is therefore perhaps appropriate to take antipyrine as an example of the drugs in this family.

The molecular structure of antipyrine, as derived from the x-ray analysis of its crystals, is shown in figure 1 (Singh and Vijayan 1973). The five-membered and the six-membered rings, connected through a N–C bond, are inclined with respect to each other at 52°. The two nitrogen atoms are pyramidal, and the phenyl and the methyl groups attached to them lie on the opposite sides of the plane of the five-membered

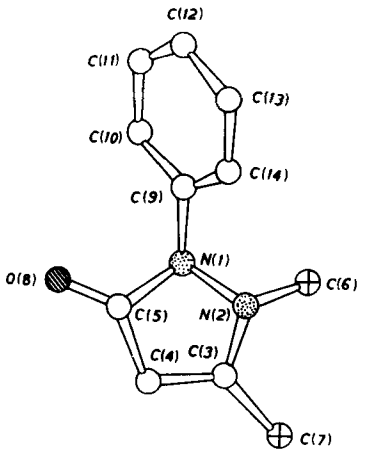


Figure 1. Geometry of the antipyrine molecule (Singh and Vijayan 1973).

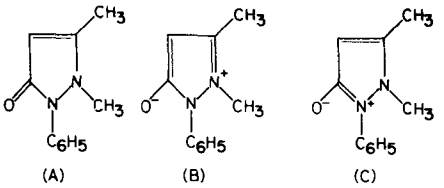


Figure 2. Canonical structures of antipyrine.

ring. To a good approximation, the molecule can be considered to be a resonance hybrid of the three canonical forms shown in figure 2. The observed bond lengths in the molecule can be satisfactorily explained, using standard bond length-bond order curves, if the contributions of A, B and C are taken to be 66, 22 and 12% respectively.

The crystal structures of a number of metal complexes of antipyrine are available and coordination is achieved in all of them through the carbonyl oxygen atom (Vijayan and Viswamitra 1966, 1967, 1968; Cingi *et al* 1972; Brassy, *et al* 1974a, b, c, d). The bond lengths and angles in the pyrazolone moiety in the metal complexes have similar values in general. But they differ systematically from those found in free antipyrine. It turns out that the observed bond lengths in the metal complexes can be accounted for if the contributions from the canonical forms A, B and C (figure 2) are taken to be 41, 37 and 22% respectively. Thus, while the neutral form predominates in free antipyrine, the polar forms do in the metal complexes. Another difference between the molecular geometries of antipyrine in the uncomplexed state and in the metal complexes pertains to the hybridisation state of the hetero nitrogen atoms. The two nitrogen atoms are more pyramidal in the free molecule than in the metal complexes. Consequently, the geometry of the molecule is substantially different in the two cases. This is illustrated in figure 3 which shows the uncomplexed molecule as well as that in a metal complex, viewed along comparable directions. This represents an interesting situation in which a perturbation at one end of the molecule, namely, association of a metal ion at the carbonyl oxygen atom, induces striking changes in its over all geometry.

In addition to metal complexes, antipyrine is known to form hydrogen-bonded complexes as well. The 1 : 1 complex between antipyrine and salicylic acid (generally

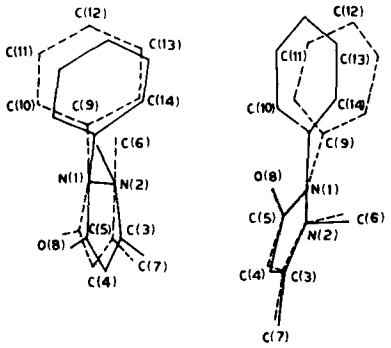


Figure 3. Two views of the molecule in free antipyrine and in its metal complexes along comparable directions (Singh and Vijayan 1973). Solid and broken lines correspond to free antipyrine and calcium hexa-antipyrine perchlorate respectively.

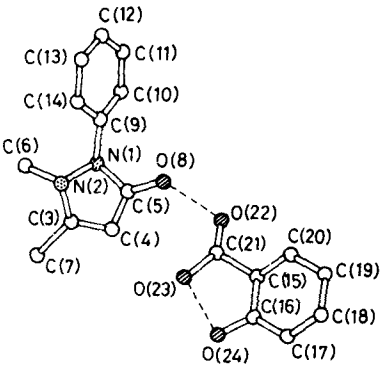


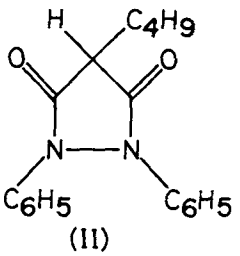
Figure 4. Molecular structure of salipyrine.

known as salipyrine) is typical of the latter. The structure of this complex, determined by x-ray crystal structure analysis, is shown in figure 4 (Singh and Vijayan 1974). Complexation is achieved through an intermolecular O–H . . . O hydrogen bond with a carboxyl oxygen of the salicylic acid molecule as the donor and the carbonyl oxygen of the antipyrine molecule as the acceptor. In the antipyrine molecule in the complex, the pyramidal nature of the hetero nitrogen atoms is intermediate between those observed in free antipyrine and in the metal complexes. The bond lengths in the pyrazolone moiety in the complex indicated the contributions of forms A, B and C to be 45, 34 and 21 % respectively, suggesting thereby that the antipyrine molecule in salipyrine is more polar than in free antipyrine but less so compared to the molecule in the metal complexes.

It has been possible to define the molecular geometry of antipyrine in different states of association, from the studies outlined above. The molecule can take part in metal coordination or hydrogen bonding. Association is achieved by an interaction at the carbonyl group in both the cases and its effect is (i) to make the hetero nitrogen atoms more planar and consequently to introduce substantial changes in molecular geometry; and (ii) to increase the polar nature of the molecule. The interaction of a metal ion with the carbonyl group is expected to be stronger than that arising from a hydrogen bond and hence the planarity of the nitrogen atoms and the polar nature of the molecule are more pronounced in metal complexes than in salipyrine.

2.2 *Pyrazolidinedione derivatives*

Phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidine-dione) (II) and its hydroxy



(II)

derivative oxyphenbutazone are the best known pyrazolidinediones with aspirin-like activity. The three-dimensional structures of the two crystallographically-independent molecules in the crystals of phenylbutazone are shown in figure 5 (Singh and Vijayan 1977). The two molecules have essentially the same structure except for the differences in the conformation of the butyl group. The two nitrogen atoms in the five-membered ring are pyramidal and the attached phenyl rings lie on opposite sides of the plane of the pyrazole ring. But for the presence of the butyl group, the molecule could have had two-fold symmetry about an axis passing through the tetrahedral carbon at the 4-position and the mid-point of the N–N bond. This symmetry is, however, prevented by the

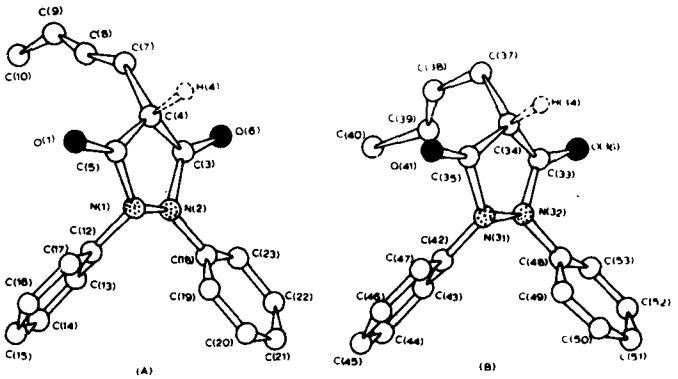


Figure 5. Geometries of the two crystallographically independent molecules in the structure of phenylbutazone (Singh and Vijayan 1977).

substitution of the butyl group at the tetrahedral carbon atom. The environments of the two phenyl groups are also now dissimilar and their orientations with respect to the five-membered ring are different.

The phenylbutazone molecule, being acidic, may be expected to interact with basic amino acid residues. Attempts were made to co-crystallize it with basic amino acids and their derivatives, but these attempts were not successful. It was, however, possible to prepare a 2 : 1 crystalline complex of phenylbutazone with the basic compound, piperazine. The ring carbon atom C(4) in phenylbutazone is deprotonated when complexation takes place. The structure of the resulting anionic molecule is shown in figure 6 (Singh and Vijayan 1977). The complex is stabilized by ionic and hydrogen bonded interactions with the cationic piperazine molecules. There are significant structural differences between the neutral phenylbutazone molecule and the deprotonated anionic molecule in the complex. The carbon atom C(4) is tetrahedral in the former whereas it is trigonal in the latter resulting in different orientations of the butyl group in the two cases. The excess electron in the anionic molecule is delocalised over the two C–O and the two C–C bonds whereas these bonds are double and single respectively in the neutral molecule, as can be seen from the bond lengths given in figure 7. As C(4) is sp^2 in the anion, the C(4)–C(7) bond lies in the plane of the five-membered ring and the butyl group has no preferred orientation with respect to this plane; therefore, unlike in the case of free phenylbutazone, the two phenyl rings are

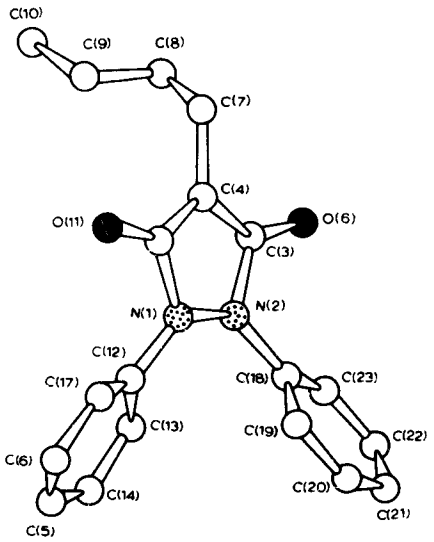


Figure 6. Molecular geometry of the anionic phenylbutazone in its complex with piperazine (Singh and Vijayan 1977).

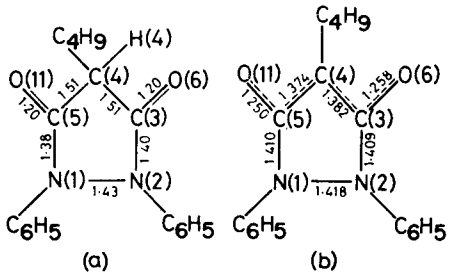


Figure 7. Bond lengths of the pyrazolidinedione moiety in the crystals of phenylbutazone and those of the phenylbutazone-piperazine complex.

structurally indistinguishable and are oriented with respect to the five-membered ring at nearly equal angles. Therefore, the two-fold symmetry of the molecule is almost restored on account of the deprotonation of C(4).

The results outlined above, which have been corroborated by those of the x-ray analysis of 1:1 complex between phenylbutazone and N-methyl piperazine (Toussaint *et al* 1974), indicate that C(4) is deprotonated, with accompanying changes in the molecule, when phenylbutazone interacts with a basic molecule or chemical group. Obviously then, deprotonation of the phenylbutazone molecule is likely to occur when it approaches carrier proteins or the prostaglandin synthatase system as a result of its interaction with basic amino acid residues. The consequent characteristic changes in the geometry and the electronic structure of the molecule is likely to be of importance in its protein binding properties and its inhibitory action against prostaglandin synthatase.

2.3 *Fenamates*

Fenamates (figure 8) form an important recently developed group of non-steroidal analgesics. The molecules of this family of compounds essentially consist of three planar groupings, namely, two six-membered rings and a carboxyl group. The important members of this family are mefenamic acid, flufenamic acid, meclofenamic acid and niflumic acid. The crystal structures of all these compounds have been determined (Krishna Murthy and Vijayan 1979, 1981a; Krishna Murthy *et al* 1982; McConnell 1973; McConnell and Company 1976). A striking common feature of all these structures is the coplanarity of the six-membered ring carrying the carboxyl group, the carboxyl group and the imino nitrogen atom. The internal N–H . . . O hydrogen bond with the imino nitrogen as the donor and one of the carboxyl oxygens as the acceptor, also exists in all the structures. This hydrogen bond, along with resonance interactions between the six-membered ring and the carboxyl group, presumably stabilise the coplanar arrangement. The variations in the geometry of the molecules arise almost exclusively on account of the differences in the orientation of the second six-membered ring with respect to the rigid coplanar moiety.

The crystal structure of a 1:1 complex between one of the fenamates, namely, niflumic acid, and ethanolamine has been determined recently (Dhanaraj and Vijayan 1983). As can be seen from the perspective view of the complex, shown in figure 9, the interactions between the two molecules involve primarily, though not exclusively, the deprotonated negatively charged carboxylate group of niflumic acid and the protonated positively charged amino group of ethanolamine. It is interesting to note that the invariant structural features of the fenamates observed in their crystal structures are retained in the complex also.

The work on fenamates, particularly that involving complexes, is still in progress. From the results obtained so far, it would appear that the only invariant features of the fenamates is the rigid coplanar geometry of the six-membered ring carrying the carboxyl group, the carboxyl group and the imino nitrogen atom, and also the internal

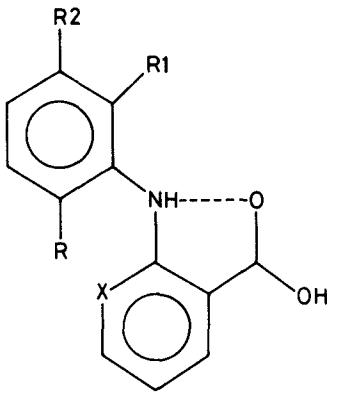


Figure 8. General formula of fenamates.
Mefenamic acid: R=H; R1=R2=CH_3; X=CH
Flufenamic acid: R=R1=H; R2=CF_3; X=CH
Niflumic acid: R=R1=H; R2=CF_3; X=N
Meclofenamic acid: R=R1=Cl; R2=CH_3; X=CH

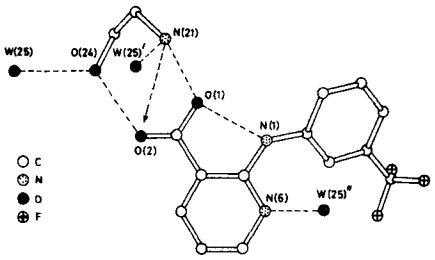


Figure 9. Molecular structure of the 1 : 1 complex between niflumic acid and ethanolamine (Dhanaraj and Vijayan 1983).

hydrogen bond connecting the imino and the carboxyl groups. The structure of the crystalline complex of niflumic acid with ethanolamine indicates that they are perhaps retained even when the fenamates interact with other molecules. It appears to be reasonable to assume that these invariant features are a requirement for their pharmacological action.

4. Conclusion

The approach involving crystalline complexes, which has been recognised to be of considerable utility in elucidating biologically and evolutionarily significant non-covalent interactions involving amino acids and peptides (Vijayan 1980; Sudhakar *et al* 1980; Salunke and Vijayan 1981; Vijayan 1983; Suresh and Vijayan 1983a, b) has been found to be useful in studying the structure and interactions of drug molecules as well. Using this approach, it has been possible to elucidate the molecular geometry of several pyrazole derivatives and fenamates with aspirin-like activity, in the free state as well as in states of association with other molecules. This approach has also provided valuable insights into the nature of the non-covalent interactions these drug molecules are likely to be involved in, and the geometric and the electronic consequences of such interactions. These insights are valuable in elucidating the molecular mechanism of action of aspirin-like drugs which are believed to exert their pharmacological effects through the inhibition of prostaglandin biosynthesis.

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