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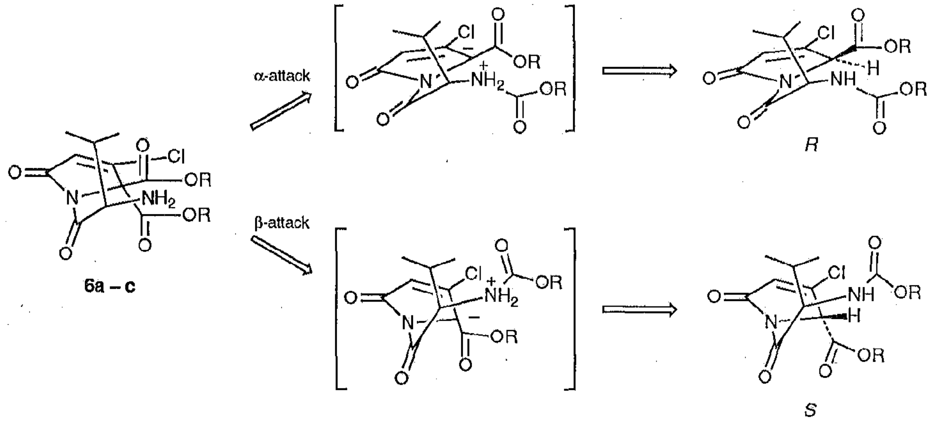

Fig. 2 Reaction pathway for novel oxycarbonyl rearrangement

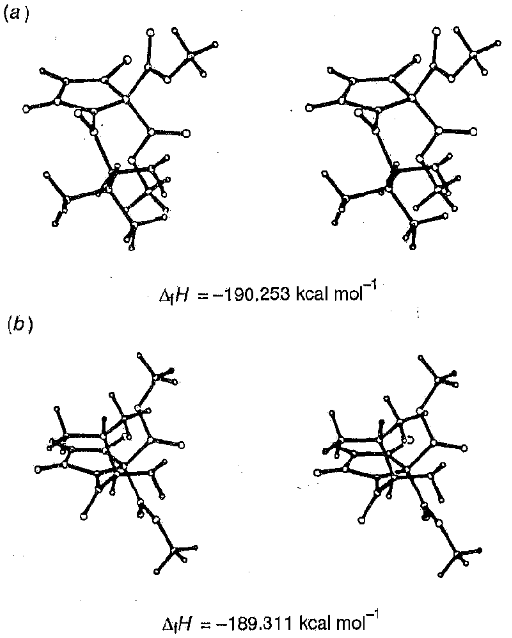

Fig. 3 (*a*) Stereoview of conformer *A*; (*b*) stereoview of conformer *B* (MNDO calculations)

highly stabilized carbanion, which would be immediately protonated from the resultant oxycarbonylammonium species, as shown in Fig. 2. Therefore, the stereochemistry at the newly formed chiral centre would be determined by the orientation of nucleophilic attack of the free nitrogen. In order to determine this orientation, we attempted an MNDO conformational analysis. In the case of attack at the α-carbonyl carbon, a chair-like conformer (*A*), containing the bulky isopropyl moiety (Pr^i) in a pseudoequatorial orientation, is the most favoured conformation and leads to the *R*-ester. In the case of attack at the β-carbonyl carbon, a chair-like conformer (*B*) containing Pr^i in a pseudoaxial orientation is the preferred one and leads to the *S*-ester. Their MNDO-calculated optimized conformations and heats of formation are shown in Fig. 3 (*a*) and (*b*). As a result, *A* is the most favoured conformation, and the energy difference between *A* and *B* was calculated to be 0.942 kcal mol^{-1} (1 cal = 4.184 J). This energy difference corresponds well with the stereoselectivity (*ca.* 80% at room temp.) in this reaction.

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Hydration in Organic Crystals: Prediction from Molecular Structure

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The proportion of non-ionic, metal free, organic compounds that crystallise as hydrates increases, within the class, with an increase in the number of hydrogen-bond acceptor groups with respect to the donor groups.

The inclusion of water within organic crystals is a matter of both fundamental and practical importance and is quite unlike the inclusion of other solvents of crystallisation. Because of its small size and excellent hydrogen bonding ability, water is almost never an innocuous bystander in an organic crystal structure. With the recent impetus in crystal engineering,[1] there has been much interest in the prediction of crystal packing[2–4] and hydrogen bond patterns[5] using simple molecular descriptors. Such efforts have been greatly facilitated by the existence of machine-readable databases such as the

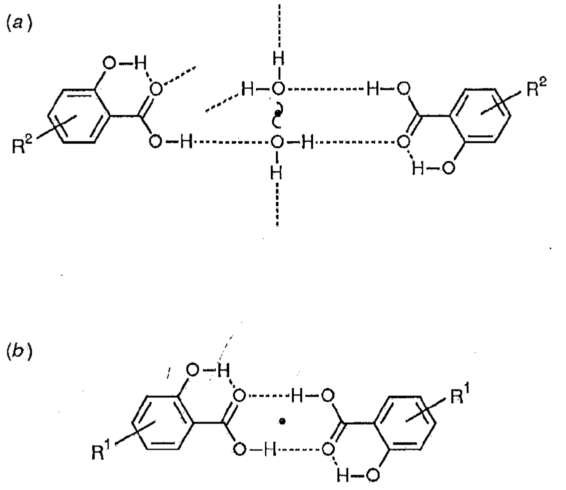

Fig. 1 Hydrogen bonding schemes for hydrated acid **1** (*a*) and anhydrous acids **2**, **3** and **4** (*b*). In acid **1**, the water molecules are also hydrogen bonded to nitro groups which are not shown here.

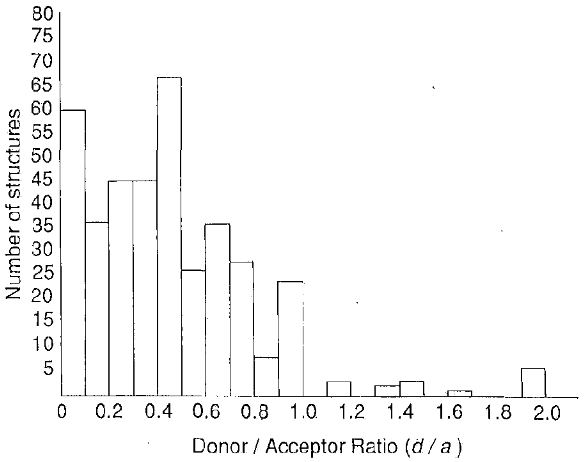

Fig. 2 Histogram of donor/acceptor ratios (*d*/*a*) for 411 hydrated crystal structures. Compounds are metal-free and not salts.

Cambridge Structural Database (CSD).[6] Accordingly, this communication deals with the prediction of the likelihood of an organic molecule to crystallise as a hydrate.

Water is incorporated into organic crystals far more frequently than other common solvents. Of the 69 691 entries in the 1988 (3.1) version of the CSD, 33 886 do not contain any metal atom and of these, 3696 are solvates. It is appropriate to consider only those entries without metal atoms since water enters the coordination sphere of transition metal ions so readily. Even when these 'pure' organics are surveyed, the number of entries having water of crystallisation is far in excess of the number having other solvents. The following statistics were obtained: water (2566); methanol (306); diethyl ether (175); benzene (173); ethanol (168); acetone (108); chloroform (102); others (98). These figures are striking because water is not a particularly good solvent for organic compounds and also because of the possibly comparable frequencies with which any of the above common solvents were used for crystallisation.

This study was prompted by the observation that 3,5-dinitrosalicylic acid **1** crystallises as a monohydrate while the related compounds salicylic acid **2**, 5-nitrosalicylic acid **3** and 3-amino-5-nitrosalicylic acid **4** form anhydrous crystals.[7] In all four structures, the phenolic hydroxy group is intramolecularly hydrogen bonded to the carbonyl oxygen of the carboxy group and does not seem to play any differentiating role. The crystal structure of **1** is unusual in that, unlike **2**, **3** and **4**, the molecules do not form centrosymmetric hydrogen bonded dimers but rather form hydrogen bonds along a catemer in which water molecules connect carbonyl and carboxy oxygen atoms (Fig. 1). These water molecules act in effect as hydrogen bond donors to the former (O · · · O 2.92 Å) and as hydrogen bond acceptors from the latter (O · · · O 2.52 Å). Normally the catemer motif is not accessible to aromatic carboxylic acids for steric reasons.[8] In the structure of **1**, however, water molecules acts as spacers so that the aromatic rings move sufficiently apart to avoid repulsive contacts with the catemer itself. Now, the interesting question is why this unusual structure is adopted at all. A possible rationale is obtained by considering that the number of hydrogen bond donors (two) and acceptors (seven) in acid **1** is quite unbalanced. It has been stated that all good proton donors and acceptors are used in hydrogen bonding.[5] If this is the case, three-centre interactions[9] would appear inevitable in order that the maximum number of acceptors be included in the hydrogen bonding scheme. However, an alternative possibility to redress the donor : acceptor imbalance is by the inclusion of one or more water molecules. In the present case, the 2 : 7 donor : acceptor ratio becomes a 4 : 8 ratio in the monohydrate. This possibility is an attractive one since stronger hydrogen bonds would be formed; this is so because not as many of them need be of the three-centre type.

The next step in the analysis was to extend the argument with the CSD. From the 2566 hydrates mentioned above, salts and cyclodextrins were excluded. It is not surprising that charged species should crystallise as hydrates, while it may be easy for water molecules to enter the large cavities of the cyclodextrins. Since, at this stage, the structures had to be examined manually (and individually) in order that the number of hydrogen bond donors and acceptors in the molecular structure be counted, a smaller group of 411 structures was selected. To avoid any bias the structures were chosen according to journal.†

The following groups were defined as proton donors (*d*): 1° (primary) amine (2 donors); 2° amine (1); 1° amide (2); 2° amide (1); imine (1); alcohol, phenol, carboxylic acid, sulphonic acid (1). The following were defined as proton acceptors (*a*): N in amine, amide, imine (1); O in hydroxy and carboxy (1); sp^3 O in ethers and esters (1); sp^2 O in carbonyl compounds (1); O in nitro (2); N in nitrile and isonitrile (1); F in a C–F bond was not included as a proton acceptor.

Barring a single structure,[10] all the selected hydrates contain groups capable of participating in hydrogen bonding. Fig. 2 is a histogram of the number of structures as a function of the donor : acceptor ratio (*d*/*a*). There are hardly any structures where *d*/*a* is greater than unity but this is not surprising; from the definitions of donor and acceptor used here, only a few types of compounds such as 1° amines and some of their derivatives would be expected to have $d > a$. The vast majority of hydrogen bonded compounds (hydrated or otherwise) would probably have *d*/*a* ratios in the range 0.5–1.0. What is significant, however, is that 65% of the hydrated structures have $d/a < 0.5$ with 16% of them having $d/a < 0.1$. In many of these hydrates therefore, the number of hydrogen bond donor groups is far less than the number of acceptors. There are a number of reasons why such a correlation should be indistinct: the existence of three-centre bonds; the possibility of water hydrogen bonding to itself rather than to the organic compound and water performing a space-filling role within the lattice of an awkwardly-shaped molecule. Indeed all these situations were encountered among the 400-odd structures

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† Structures were selected if they appeared in any of the following journals: *J. Chem. Soc.* (all sections); *Acta Chem. Scand.*; *Acta Crystallogr.* (prior to bifurcation); *Angew. Chem.*; *Bull. Chem. Soc. Jpn.*; *J. Chem. Phys.*; *J. Am. Chem. Soc.*; *J. Org. Chem.*; *Tetrahedron*; *Tetrahedron Lett.*

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