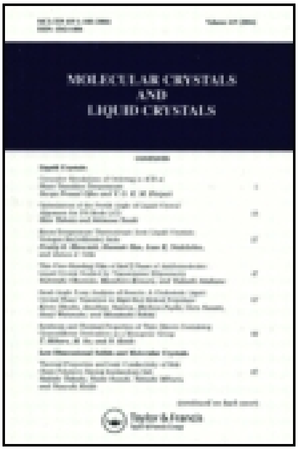

Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl16

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To cite this article: Margaret C. Etter (1983): The Role of Hydrogen Bonds in the Solid State Reactions of Acetyl Anthranilamide, Molecular Crystals and Liquid Crystals, 93:1, 95-100

To link to this article: http://dx.doi.org/10.1080/00268948308073519

Mol. Cryst. Liq. Cryst., 1983, Vol. 93, pp. 95–100
0026-8941/83/9304–0095/$18.50/0

Printed in the United States of America

THE ROLE OF HYDROGEN BONDS IN THE SOLID STATE REACTIONS OF ACETYL ANTHRANILAMIDE

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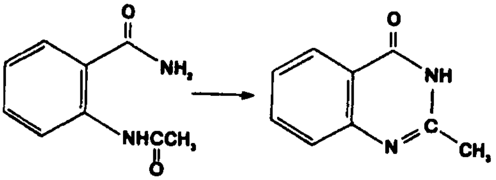
Abstract Acetyl anthranilamide (o-acetamidobenzamide) undergoes thermal cyclodehydration in solution and in the solid state to give a quinazolone structure (2-methylquinazol-4-one). The solid state reaction involves a polymorphic transformation of the starting material, cyclodehydration of the more stable polymorphic form, and dehydration of the polycrystalline solid. Crystal structures of each species in the sequence shows that the hydrogen bonding matrix undergoes a series of changes in which there are preferred H-bond patterns which are maintained while others are broken and reformed in new patterns. The role of the H-bond matrix in controlling reaction pathways is discussed.

INTRODUCTION

The role of hydrogen bonds in determining crystal packing patterns of organic compounds such as carboxylic acids and amides has been the subject of intensive investigations.(1a,b) Certain packing modes occur so frequently for these compounds that they can be used as a guide for predicting the hydrogen bonding patterns of new amides and acids. For example, usually all hydrogens which are available for hydrogen bonding will in fact form such bonds(2) and in addition these bonds will be formed in such a way that the maximum number of acceptor sites will be used.(3a,b) Carboxylic acids and primary amides commonly form hydrogen bonded dimers and, also, intramolecular hydrogen bonds that result in six membered rings. Using these criteria, one can control the structure of a hydrogen bonded matrix by varying the number of hydrogens and the number of acceptor sites available within a chemical series.(3a) The structure of hydrogen bonded matrices can also be altered by solid state reaction in which the number of hydrogen and acceptor sites changes during the course of the reaction. The present study involving a solid state cyclodehyration demonstrates how the structure of H-bonded matrices can influence the course of the reaction.

SOLID STATE REACTIONS

When the crystals or powders of acetyl anthranilamide (I) are heated to about 100°C in the solid state they are converted quantitatively to anhydrous quinazolone (II).(4)



I II

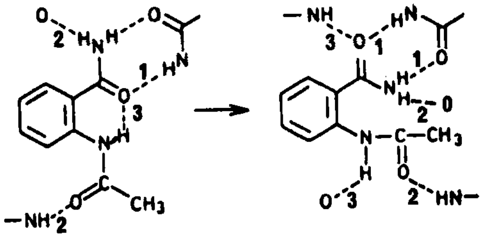
By a combination of infrared, powder pattern, and differential scanning calorimetry techniques it has been shown that the reaction involves three distinct steps.(5) The first step is a polymorphic transformation in which the metastable form of acetyl anthranilamide (Ia) is converted to the high temperature form (Ib). In Ib the amide group is in a favorable conformation for intramolecular cyclization, and further heating leads to an intermediate with a reduced melting point. We have been unable to obtain single crystals of this intermediate but we do know that it contains

I, II and possibly water, and no other chemical species. When the intermdeiate is heated, water is lost from the sample and anhydrous quinazolone is the final product, scheme (1).

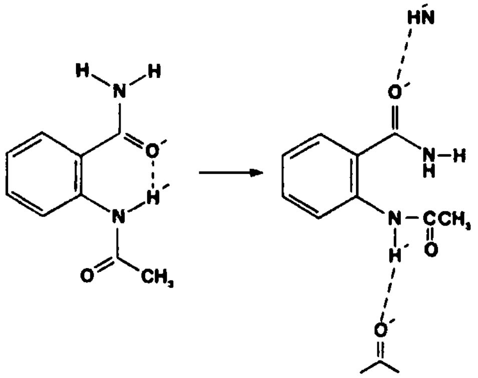
$$\text{Ia} \rightarrow \text{Ib} \rightarrow [\text{intermediate}] \rightarrow \text{II} \qquad (1)$$

ROLE OF THE HYDROGEN BONDING NETWORK

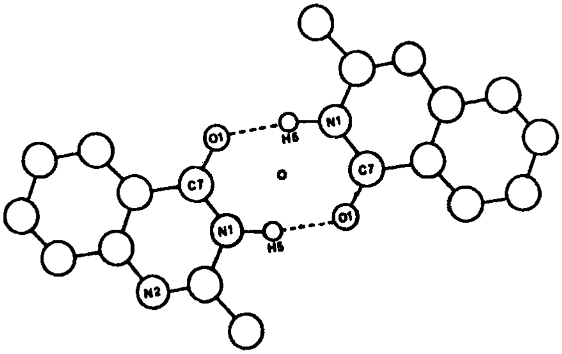
Crystal structures of Ia and Ib show that both structures contain three types of hydrogen bonds: 1) a dimer between inversion related primary amide groups, 2) an intermolecular bond between one of the primary amide hydrogens and the acetyl carbonyl group, and 3) a hydrogen bond between the secondary amide hydrogen and the primary amide carbonyl.(4)



The main difference between the two packing patterns is that in Ia the third type of hydrogen bond is intramolecular, while in Ib this bond is intermolecular. The transformation from Ia to Ib involves a conformational rotation of the primary amide groups which causes the intramolecular bond to break. A "free" hydrogen and a "free" acceptor site are created which subsequently form an intermolecular bond, as shown.

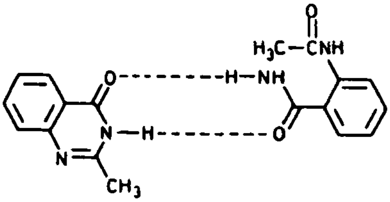


In the crystal structure of quinazolone, the molecules are packed as hydrogen-bonded dimers.(5)



In order to form this structure from Ib, the type 2 and 3 hydrogen bonds of Ib have to break. This process may be assisted by hydrogen bonding to water as it is formed during reaction, but there is no evidence in the reaction sequence for the presence of any crystalline hydrates (even though quinazolone forms a crystalline hydrate from solution). The order in which hydrogen bonds have broken in this reaction sequence is: hydrogen bonds involving water, intramolecular hydrogen bonds, other intermolecular interactions, and then cyclic hydrogen bonded dimers. This is, in effect, a ranking of the relative solid state reactivites of the different hydrogen bonding modes in this system.

The three species which have been identified in the solid state sequence all contain the cyclic dimer interaction. With this in mind, a reasonable structure for the elusive intermediate which occurs when Ib is cyclodehydrated, is that of a mixed dimer of Ib and quinazolône, shown here.



There is precedent in the literature for the formation of mixed hydrogen bonded dimers; e.g. 2-pyridone and 6-chloro-2-hydroxy-pyridine(6). In the case of Ib and quinazolone, the actual solid state intermediate probably is not a distinct species but is a mixture of phases containing varying amounts of Ib, the mixed dimer, and II. As reaction proceeds the concentration of quinazolone increased and water is driven from the lattice, leaving anhydrous quinazolone in quantitative yield.

The fact that quinazolone hydrate (III) was not formed as a reaction intermediate is significant because in its crystal structure there is no H-bonded dimer interaction. Instead water acts as a bridge and forms hydrogen bonds to adjacent quinazolone molecules.(5) Thus, the hydrogen bonding matrix has controlled the pathway of this solid state reaction by precluding an intermediate whose formation would have caused the cyclic dimer pattern to break.

SUMMARY

The solid state cyclodehydration of acetyl anthranilamide occurs in a hydrogen bonded matrix in a three step sequence. The noteworthy features of this reaction are: 1) this is a multistep solid state reaction in which large molecular motions are required both for reaction as well as for reorganization of reaction products into new crystalline lattices, 2) the reactions proceed in a matrix of hydrogen bonds in which the number of hydrogen donor and acceptor sites are changing during reaction yet a maximum number of hydrogen bonds are established at each stage of reaction, and 3) the hydrogen bonded cyclic dimer is the one feature of the H-bond matrix that is retained throughout the reaction sequence, and its retention has precluded the formation of certain possible reaction intermediates.

APPENDIX

Crystal Data:

1a, $P2_1/n$, a=4.952(2), b=14.496(2), c=12.471(3)Å, β=93.99(3)°, Z=4.

1b, $P2_1/c$, a=7.807(2), b=9.039(3), c=12.706(3)Å, β=101.12(2)°, Z=4.

II, Pbca, a=5.081(6), b=14.574(7), c=20.854(3)Å, Z=8.

III, $P\bar{1}$, a=10.000(3), b=12.509(4), c=7.193(3)Å, α=78.26(3), β=79.05(3), γ=89.87(3)°, Z=4.

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