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Methyl Rearrangement of Methoxy-Triazines in the Solid- and Liquid-State

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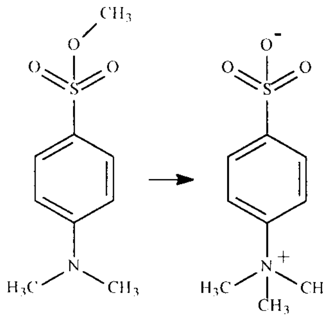
Abstract—2,4,6-Trimethoxy-1,3,5-triazine **11**, and 6-methoxy-3,5-dimethyl-tetrahydrotriazine-2,4-dione **13** undergo intermolecular O→N methyl rearrangement in the liquid-state to 1,3,5-trimethyl 2,4,6-trioxohexahydro-*s*-triazine **14**. 4,6-Dimethoxy-3-methyl-dihydro-triazine-2-one **12** was found to exhibit a different thermal behavior, and the methyl rearrangement takes place in the solid-state. The thermal behavior of each was investigated by calorimetry and high-temperature X-ray diffraction. It was found that **11** undergo phase transition to **11′**, and the methyl rearrangement takes place in the melt. The solid-state methyl rearrangement of **12** is topochemically controlled. Two courses of methyl migration in the solid-state of **12** are proposed. A quantitative analysis of samples of **12** heated to different temperatures proves the existence of the two courses. A computer simulation was used to rationalize the reaction routes in **12** and **13**. © 2000 Elsevier Science Ltd. All rights reserved.

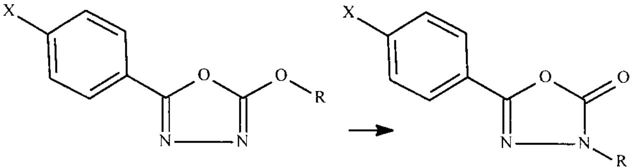
Introduction

Over 120 years ago, Hoffman and Olshausen[1] and later Klason[2] gathered evidence to prove that methyl esters of cyanuric acid and their thio derivatives undergo alkyl migration. From the end of the 1960s[3] to the mid-1980s,[4] the methyl rearrangement in methyl esters of cyanurates and thiocyanurates was investigated.

Twenty years of intensive investigation revealed an enormous amount of information regarding all feasible methyl migrations and their products. It was pointed out that the methyl rearrangement can take place in the solid-state but firm conclusions were not made. There are several other known examples of solid-state methyl rearrangements, such as the conversion of methyl *p*-dimethylaminobenzenesulfonate **1** into the zwitterionic product *p*-trimethylammoniobenzene-sulfonate **2**, first discovered by Kuhn and Ruelius,[5] and later investigated by a few other groups.[6a–g] It was shown[6a] that the reaction is intermolecular and proceeds much faster in the solid-state than either in the melt or in solution. A second example of a methyl transfer in the solid-state is the Chapman-like rearrangement of imino-ethers to *N*-alkylamides. Dessolin and Golfier[7] found that in some derivatives of 5-methyoxy-2-aryl-1,3,4-oxadiazoles **3**, the rearrangement to the derivatives of 4-methyl-1,3,4-oxadiazole-5(4*H*)-ones **4** is unusually fast in the solid-state. It was shown that **3** undergo intermolecular rearrangement in the solid-state faster than it does in the liquid-state. For example, for **3b**, $t_{1/2}$ is 7.85 min in the solid-state and 1.8 min in the melt, however, for **3d**, it is 0.8 min in the solid-state and 307 min in the melt.



1 **2**



3 **4**

a: R=Me X=H
b: R=Me X=Cl
c: R=Me X=OMe
d: R=Me X=NO$_2$
e: R=CD$_3$ X=OCD$_3$

The mechanism of the solid-state reaction was the subject of two interesting publications.[6b,7b] From the extended Hückel theory calculation, a two-step mechanism involving a

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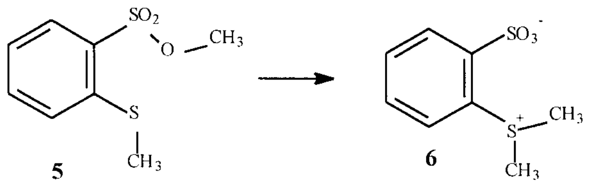
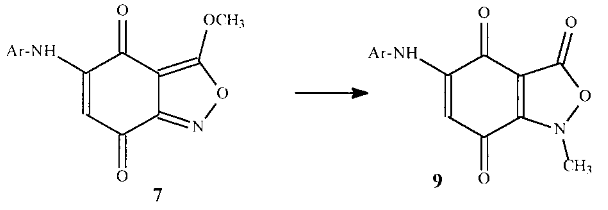
molecular ion-pair intermediate was proposed[6b] for the conversion of **1** into **2**. A model system was used for studying the conversion of **3** into **4**. The transition state structure for the methyl exchange was localized with an analytical gradient, and the energies were calculated at the restricted Hartree–Fock level with a 3-21G-basis set. These computations[7b] suggest that the starting point of the conversion is the formation of an anion and a cation, followed by the transfer of the methyl group between these ions and an adjacent molecule in the same plane. These substitutions are domino-like, propagating in chains.

Three other examples of solid-state methyl migration are known[8a,d] When tri- or tetraglycine methyl ester was heated at 400°C in the solid-state, a mixture of products was obtained and it was shown[8a,b] to include the methyl rearranged product, but no further work has been carried out on these systems. A thermally induced non-topochemical solid-state methyl rearrangement of methyl 2-(methylthio) benzenesulfonate **5** to the zwitterionic 2-(dimethylsulfonium)benzenesulfonate **6** was observed.[8c] This rearrangement is known to proceed in solution by intermolecular methyl transfer. The crystal structure of **5** shows that the molecular packing is not conducive to intermolecular methyl transfer.

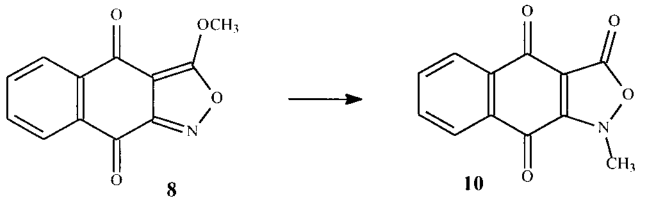


5 **6**

By fast-atom-bombardment mass spectroscopy on reaction products of mixed crystals composed of **5** and its deuteriomethylated species, and from the results obtained from reaction rate study, it was concluded that the reaction proceeds not topochemically but rather at defects. A recent example[8d] is the thermal rearrangement of benzisoxazole **7** and naphthisoxazolequinones **8** to **9** and **10**, respectively.



7 **9**

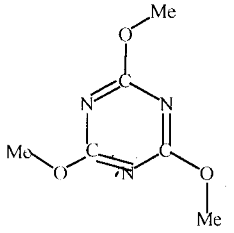


8 **10**

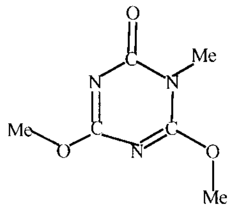
In all the above-mentioned examples, the rearrangement involved the migration of a single methyl group of one molecule. 2,4,6-Trimethoxy-1,3,5-triazine **11** is the only chemical system composed of three methyl groups that may rearrange, therefore this compound should show a more complicated and interesting rearrangement. Isotope labeling by ^{18}O and deuterium led to the conclusions[4] that the conversion of 2,4,6-trimethoxy-1,3,5-triazine **11** into 1,3,5-trimethyl-2,4,6-trioxohexahydro-*s*-triazine **14** in the melt is intermolecular and irreversible, and no intermediates could be isolated at temperatures above 473 K. Kinetic measurements using IR spectra showed that this is a second-order reaction having an activation energy of 118.3 kJ/mol. A mechanism was proposed whereby a methyl cation is the active species. We were interested in the geometric factors controlling the solid-state reaction, and in determining the conditions and state of matter at which the rearrangement takes place.

Results and Discussion

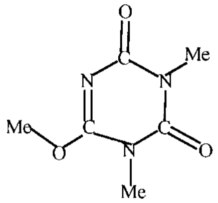
It is known[3,4] that **11** undergo methyl rearrangement to **14** in the melt, and it was speculated that the same reaction might be executed in the solid-state. In the liquid-state, molecules should collide to enable intermolecular methyl transfer.



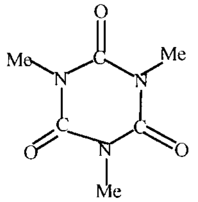
11



12



13



14

However, a transfer of three methyl groups cannot take place in a single collision. Therefore, the complete rearrangement of **11** to **14** must involve several stages of methyl migration. Two intermediates **12** and **13** are expected. Understanding the mechanism of the rearrangement will be complete only when the thermal behavior of each of the different steps is known. Therefore, the thermal behavior of each of the four compounds were investigated using differential scanning calorimeter (DSC), high-temperature X-ray diffraction (HTXRD), single crystal structure determination, nuclear magnetic resonance (NMR), and hot stage microscopy. Each of the four compounds was synthesized according to known procedures.[9] Preliminary results have been published.[10a–d]

The packing arrangement and the thermal behavior of 11

The crystal structure of **11**[10a] is made up of layers consisting of planar molecules. A typical layer is shown in Fig. 1. The coplanar molecules within a layer form an infinite net of hexagonal closed packing with close contacts between the methyl groups of one molecule and a nitrogen atom of a neighbor molecule.

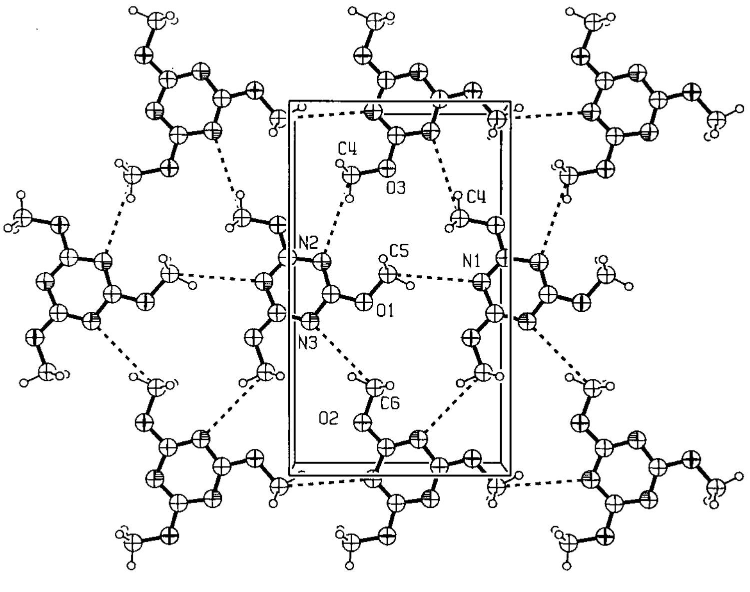


Figure 1. A layer structure of **11** showing an infinite net of hexagonal closed molecules.

The distances between the methyl carbon atoms to the nearest nitrogen atoms are 3.574, 3.668, and 3.681 Å, and the O–C···N angles are 120.2, 125.4, and 117.0°. The ideal geometry, assuming a S_N2 type reaction, is that the O–C···N angle is 180°. For comparison, the corresponding distances and angles observed in the crystal structure of **1** are 3.469 Å, 150.9° at 193 K, 3.492 Å, 150.4° at 255 K, and 3.54 Å, 147° at 298 K. An almost ideal geometry for methyl transfer was found in the crystal structure of **3d**. The N···CO distance is 2.922 Å (more than 0.5 Å shorter than the sum of van der Waals radii), the D_3C–O bond length is 1.602 Å, which is longer by 0.187 Å than the normal C–O covalent bond in methoxy groups,[11] and the O–C···N angle is 164°. This geometry was found for the molecule frozen at an incipient stage of the rearrangement. The thermal behavior of **11** was studied by HTXRD (not shown here), and by DSC (shown in Fig. 2).

The DSC thermograph in the 25–250°C temperature range shows two endothermic peaks followed by an exothermic peak. The first endothermic peak (at 67°C with an enthalpy of 3.9 kJ/mol) was assigned to a phase transition of **11**. This assignment was based on the facts that while HTXRD shows change of the powder diffraction pattern of **11** above 70°C, the NMR spectra show that no chemical change took place. Attempts to grow single crystals of the high-temperature phase **11′** recently succeeded and its crystal structure is shown in Fig. 3. The second endothermic peak (at 122°C, and enthalpy of 18.1 kJ/mol) was assigned to the melting of the new phase (**11′**). The exothermic peak starting at 173°C (measured enthalpy of −194.1 kJ/mol) was assigned to the consecutive migration of the three methyl groups. The nature of the interrupted exothermic peak at 180°C is not clear. The formation of the final product, **14**, following the melting of **11′** was proven by NMR spectra of the cooled sample. The conclusion drawn from the experimental results is that the methyl migration takes place in the melt and not in the solid.

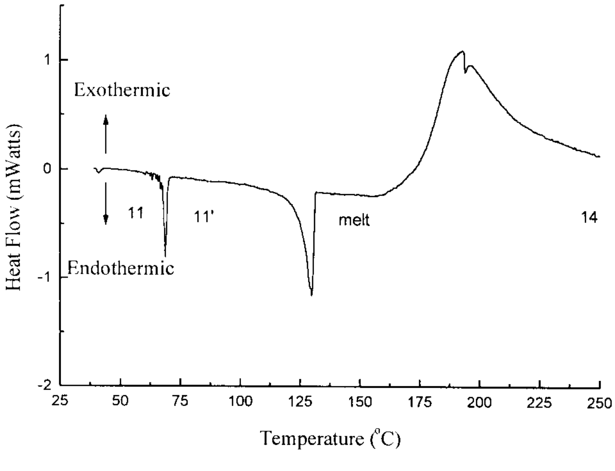


Figure 2. DSC curve for **11** at a heating rate of 1°/min.

This is in contradiction with the expectation based on the crystal structure of **11** that has the 'correct' intermolecular geometry. The phase transition of **11** to **11′** involved the variation of the molecular packing mode, from stacking to herringbone. The latter does not have a layer structure, and the ideal geometry for topochemically assisted methyl transfer is lost. Therefore, melting takes place before the methyl groups are transferred. An alternative reasoning was given[4] by the 'Rule for Isomerisation.' This rule states that whenever a methoxy group is bonded to a carbon atom situated between two identical nitrogen atoms, much more energy is needed for the methyl migration to proceed and therefore the methyl migration will take place in the melt.

The packing arrangement and thermal behavior of 12

The packing arrangement of **12** (shown in Fig. 4) is very similar to that of **11**. Although there are two crystallographically independent molecules in the asymmetric unit (marked as A and B), they are coplanar and arranged in ribbons forming a layer structure. The ribbon exhibits intermolecular contacts similar to those found in **11**. The

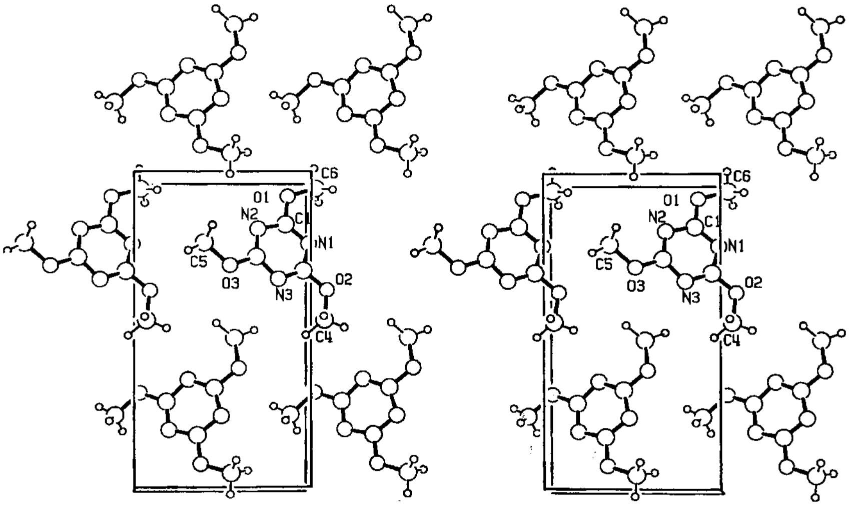


Figure 3. Stereo view of the crystal structure of **11′**.

distances between the methyl carbon atoms and the nearest nitrogen atoms are 3.615, 3.574, 3.580, and 3.574 Å, and the O–C···N angles are 133.7, 143.0, 129.0, and 143.1°. The thermal behavior was studied by HTXRD (not shown here), and by DSC (shown in Fig. 5). By heating the material to melt and holding the temperature constant[4] for 10 min, a mixture of **12**, **13**, and **14** was obtained. The thermal behavior of **12** is strongly dependent on the heating rate and on pretreatment of the powder sample. The result of pretreatment of the powder sample, by heating to 95°C followed by cooling to room temperature, is shown in Fig. 5.

Three distinct peaks composed of three exothermic peaks (with a total enthalpy of −133.7 kJ/mol) are observed, followed by the endothermic peak assigned to the melting of **14**. The first two peaks suggest that there are two consecutive stages of methyl migration, followed by a sharp exothermic peak of the solidification of **14**. An alternative assignment is that each of the first two exothermic peaks is a result of a specific course of methyl migration (see below). Powder diffraction of cooled samples of the product indicates that there are two different polymorphs of **14**. One of the polymorphs is identical to **14** obtained by crystallization from solution or from the melt. The second polymorph (**14′**) could not be isolated. The condition at which this polymorph can be obtained is not known.

It is possible to envisage two courses of methyl migration (see Schemes 1 and 2):

1. Homo Chain Mechanism (HCM)—the methyl migrates within one chain of molecules of the same type ((A) or (B)). This course will lead to the formation of **13**. There are two chemically different methyl groups that can migrate. Only one of them is expected to be transferred by the HCM route. It is noteworthy that this is in consistence with the results obtained by the above-mentioned labeling experiment.[4]
2. Hetero Ribbon Mechanism (HRM)—the methyl groups are transferred within the ribbon's triangular

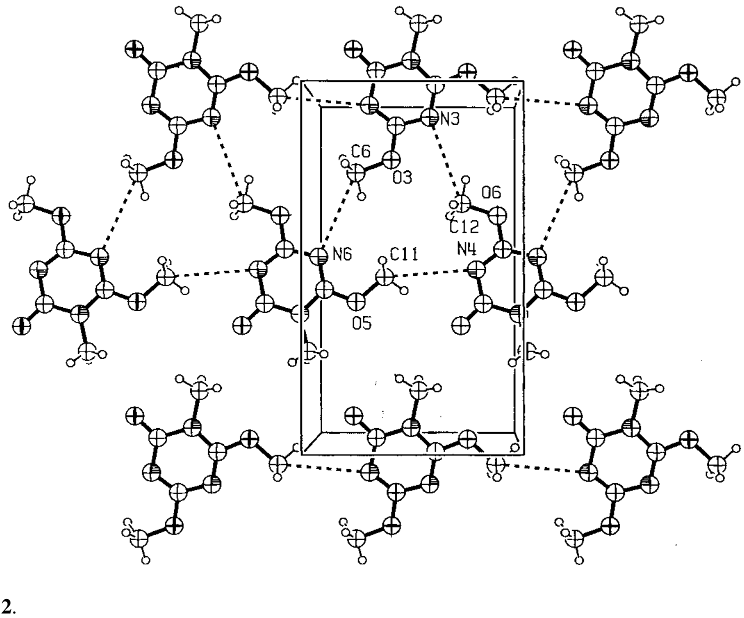


Figure 4. The layer structure of **12**.

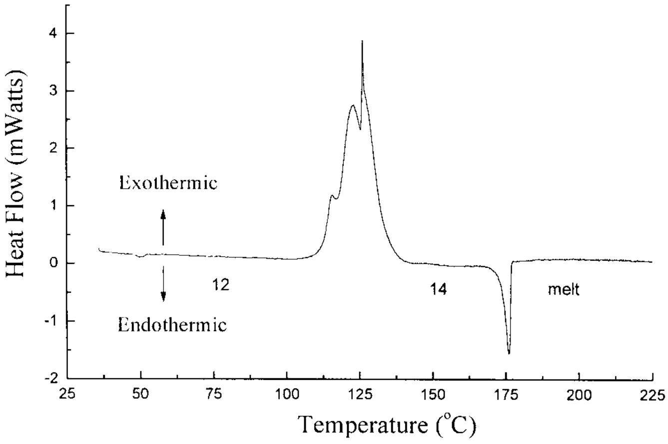


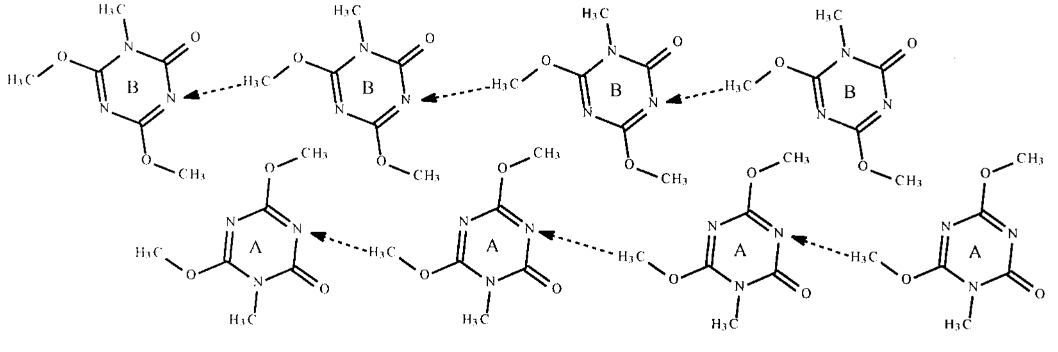
Figure 5. DSC curve of **1** at a heating rate of 1°/min.

arrangement. This course will lead to the formation of **14**. The distinction between the two possible courses and further work on the methyl migration in **12** are described later in a separate paragraph.

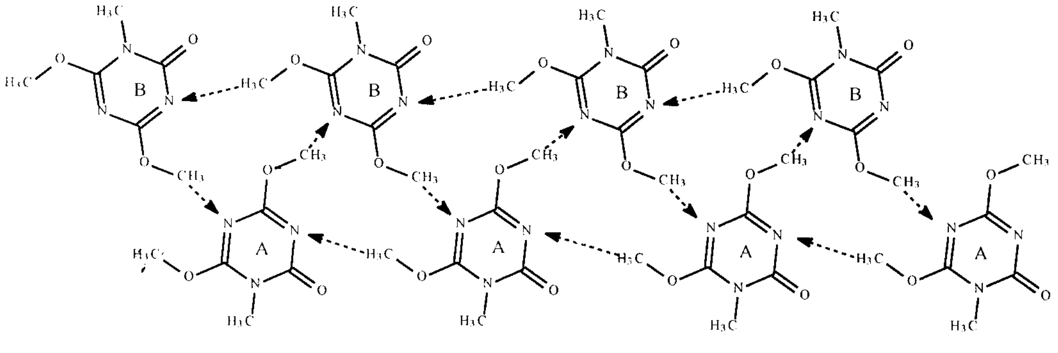
The packing arrangement and the thermal behavior of 13

The packing arrangement of molecules of **13** in the unit cell is shown in Fig. 6. Although the molecules of **13** are planar, the packing is different from that found for **11** and **12**. It is made up of two infinite ribbons related by a glide plane.

Each ribbon consists of molecules related by inversion centers arranged in dimers, analogous to the hydrogen bonding patterns found in crystal structures of carboxylic acids and amides.[12] The geometry at the site of the potential rearrangement center seems to be ideal, namely, the distance between the methylcarbon atom to the nearest nitrogen atom is only 3.383 Å (shorter than the sum of the van der Waals radii, 3.50 Å), and the O–C···N angle is 154.8°. It is therefore expected that the methyl migration will occur in the solid-state. The thermal behavior shown by the DSC thermograph is given in Fig. 7. The DSC thermograph consists of two endothermic peaks and two exothermic peaks. The first shallow endothermic peak (starting at 90°C, with an enthalpy of 12.7 kJ/mol) is assigned to the melting of **13**; the next exothermic peak (at 119°C, with an enthalpy of −15.0 kJ/mol) is assigned to the methyl migration forming **14**, which crystallizes at 133°C (seen by the sharp exothermic peak) and then melts.



Scheme 1. Homo Chain mechanism.



Scheme 2. Hetero Ribbon mechanism.

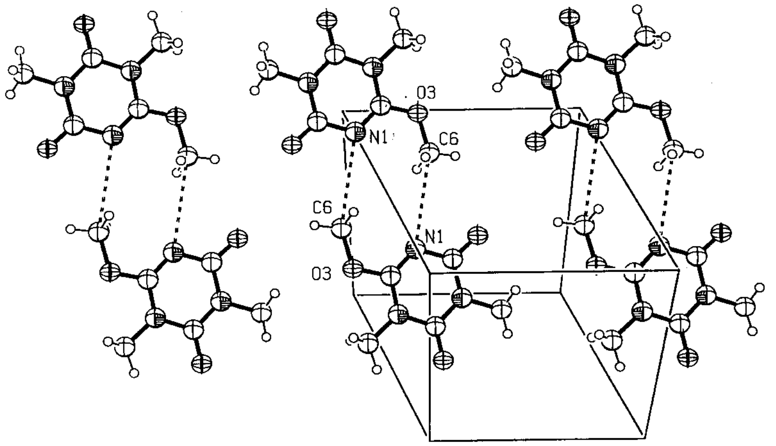


Figure 6. Packing of molecules of **13** in the unit cell, showing the arrangement of dimers.

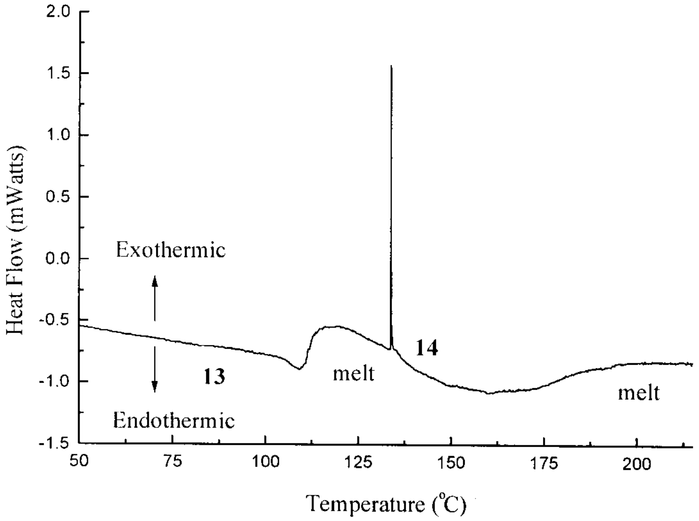


Figure 7. DSC curve of **13** at a heating rate of 1°/min.

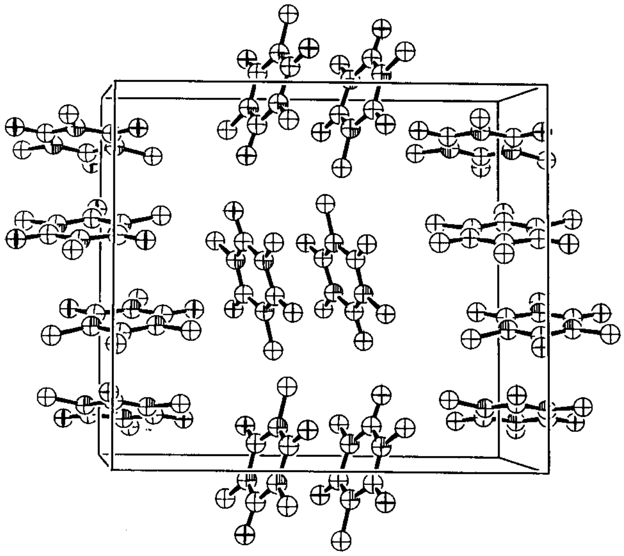


Figure 8. Molecular packing of **14** in the unit cell.

It is therefore believed that the methyl migration in **13** does not proceed in the solid-state but in the melt. The rationalization of this conclusion is discussed below.

The packing arrangement and the thermal behavior of 14

The packing arrangement of molecules of **14** in the unit cell is shown in Fig. 8. There are two crystallographically independent planar molecules in the asymmetric unit. They are not packed in a layer structure similar to **11** or **12**. The DSC thermograph (shown in Fig. 9) consists of an endothermic peak (at 175°C) assigned to its melting.

Computer simulation

Computer simulations have been used to estimate intermolecular distances resulting during the methyl migration in **12** and **13**. The simulation is based on the assumption that the reaction is topochemically controlled, meaning that the change within the structure will be a result of a minimal movement of atoms. The expected outcome of such a

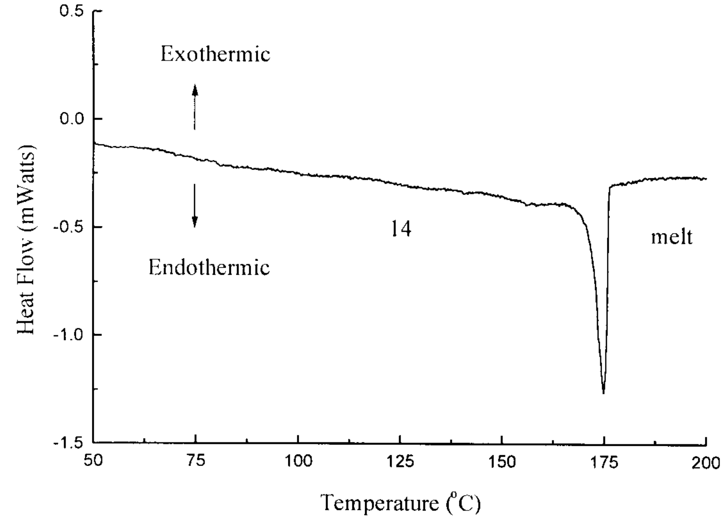
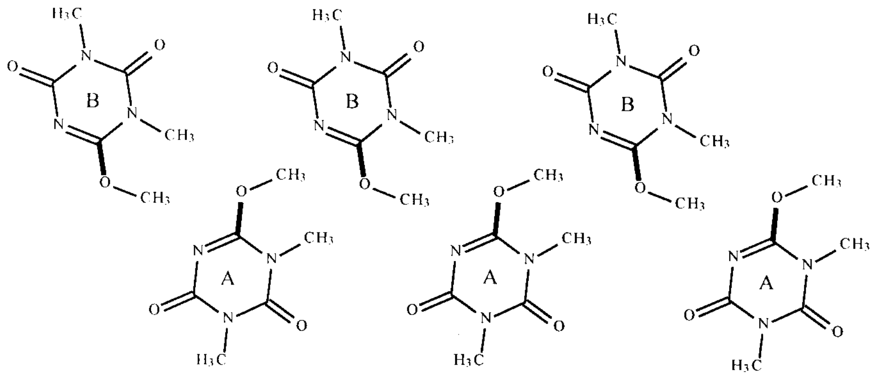


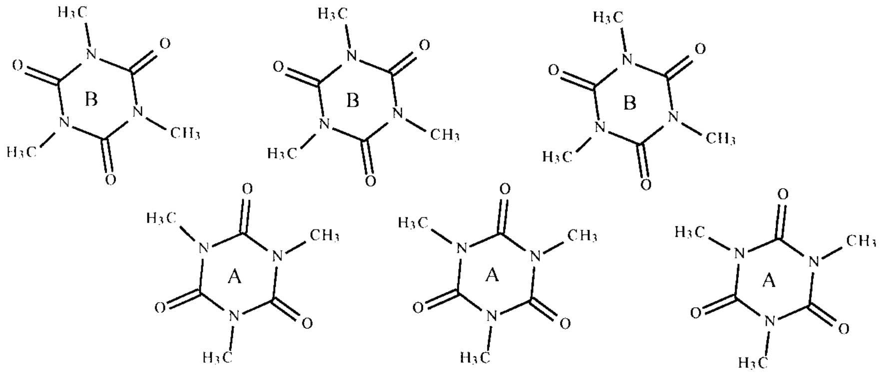
Figure 9. DSC curve of **14** at a heating rate of 1°/min.



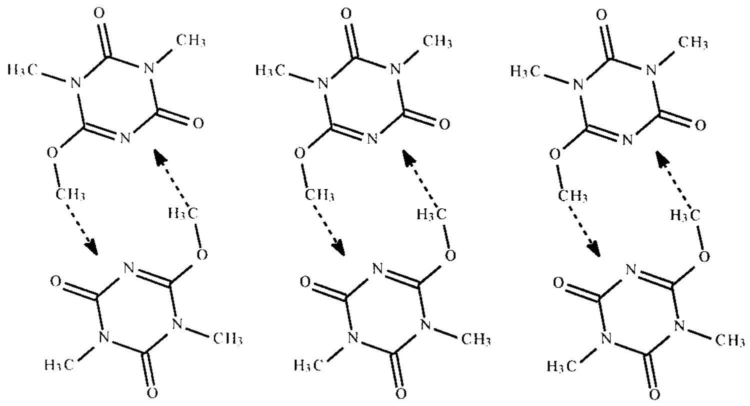
Scheme 3.

simulation is the distinction between the proposed two possible courses of the solid-state reaction of **12** (HCM and HRM), and a rationalization of the experimental results whereby **13** undergoes methyl migration in the liquid-state and not in the solid-state.

The computer simulation is performed by breaking the O–Me bond, forming a new N–Me bond, and allowing geometrical optimization.[14] During this procedure, the intermolecular distances are monitored. In the HCM (see Scheme 1) the methyl groups are transferred from one molecule to the adjacent molecule in the same chain. The resulting structure is shown in Scheme 3. It may be seen that the product molecule **13** adopts a different conformation than that observed in the crystal structure of **13**. Since the methoxy group is on the same side of the methylamine group, steric repulsion exists, and the conformation is therefore expected to be less favorable. The Molecular



Scheme 4.



Scheme 5.

Mechanics calculation[15] shows that the molecular conformation found in the crystal structure of **13** is energetically more stable by 103.7 kJ/mol than the one obtained by the simulation described above. The stable conformation could be achieved if, following the methyl transfer, the remaining methoxy group rotates about the bond marked in bold in Scheme 3. No potential barrier to such a rotation exists in the gaseous state, however, in the solid-state, neighboring molecules can interfere. Therefore, HCM is expected to occur primarily where free space is available, namely at defects such as micro-cavities, surfaces, and other irregularities in the ordered crystal arrangement.

The Hetero Ribbon mechanism is described by a cooperative transfer of two methyl groups within the layer, as shown in Scheme 1. The structure resulted from the computer simulation is shown in Scheme 4. The main characteristics of the structure are that no short intermolecular distances have been detected during the optimization process, and that a layer structure was formed. This structure is different than **14** that was crystallized from solution or from the melt. We have reason to believe that this is the structure of **14′** (the second polymorph of **14** mentioned above).

The lack of appropriate crystals prevents structure analyses. It was recently shown[13] that the crystal structure of a complex between **14** and 1,3,5-trinitrobenzene consists of alternating flat layers of the constituents. The structure of the layer made up of **14** is essentially identical to that obtained by the computer simulation, therefore, we are confident that the structure of **14′** obtained from the computer simulation is correct. The conclusion that may be drawn from the computer simulation of the two possible courses is that the HRM is favored.

Molecules of **13** are packed as dimers in the crystal, and the rearrangement may be described by interchanging methyl groups between two molecules, as shown in Scheme 5. Computer simulation of the methyl transfer in **13** indicates that the proximity of the two methyl groups will be 1–2 Å in this rearrangement, and is therefore not likely that it will take place in the solid. A small shearing movement of parallel chains related by inversion centers in opposite directions could provide the space necessary for the methyl migration. It is possible that such a motion of molecules does not completely destroy the structure to produce a melt. It is noteworthy that in an earlier study,[4] it was found that the reaction observed in **13** started in the solid-state and accelerated at the beginning of the melting process. A solid-state reaction was not detected, but the solid-state reaction may

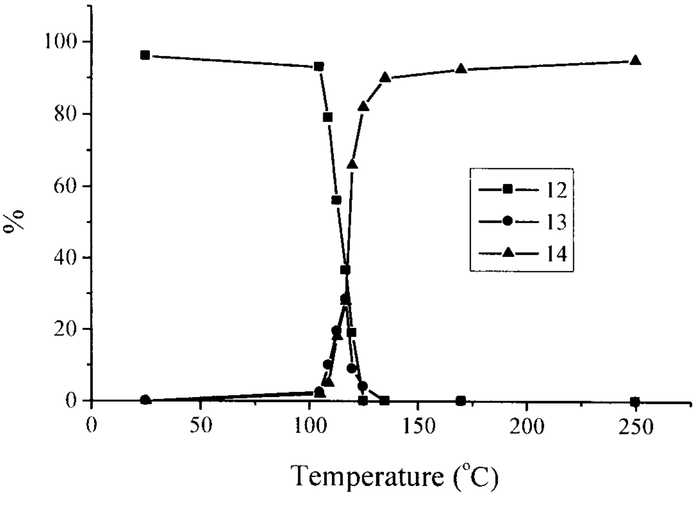


Figure 10. Compositions of samples of **12** heated to different temperatures.

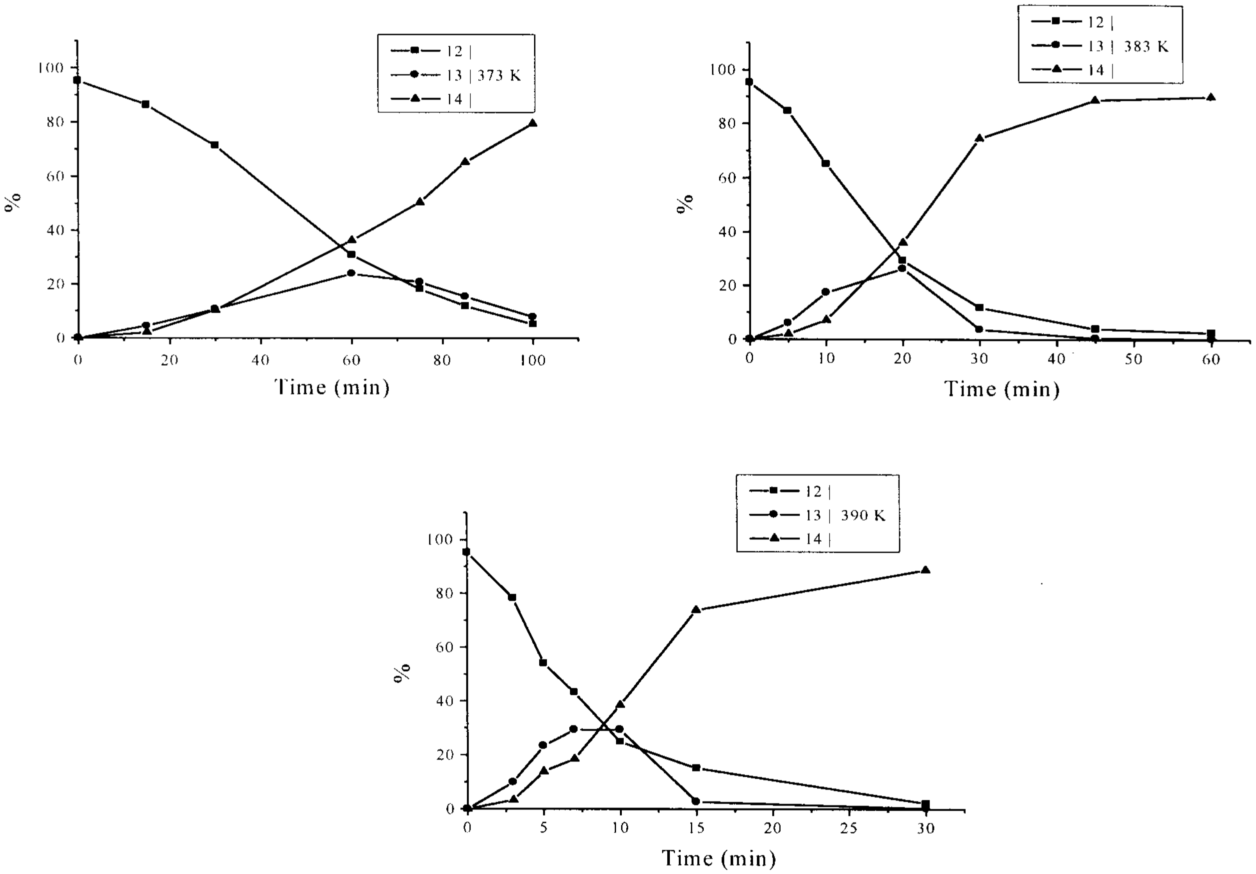


Figure 11. Time dependent composition of samples of **12** at three temperatures: (a) at 373 K; (b) at 383 K; and (c) at 390 K.

occur at dislocation sites. The acceleration of the migration upon melting agrees with our assumption that shearing motion (described above) will enable the methyl group exchange between two adjacent molecules without steric interference.

Quantitative analysis of the methyl migration in 12

The experiments described so far do not provide sufficient data to conclude which of the two routes, HCM or HRM, take place when solid **12** is heated. Quantitative analyses of the composition of samples of **12** that were heated to various temperatures may be used to distinguish between the two routes of methyl transfer. The composition of the products was calculated from the NMR spectra. Fig. 10 shows the composition of the reaction mixture at various temperatures (impurities of up to 5% have been omitted). At lower temperatures, the two products are formed in almost equal amounts. At approximately 117°C, the production of **13** reaches a maximum and then decreases at higher temperatures. At 117°C, the newly formed **13** melts (as shown in Fig. 7), and a second methyl migration takes place to yield **14**.

A different approach would be to analyze the time-dependent composition of samples of **12** that were heated to different temperatures (isotherms). The results obtained for three different temperatures are shown in Fig. 11.

The three isotherms very clearly show that the two possible products **13** and **14** are already formed at the early stage of the rearrangement, and that **13** later undergoes methyl transfer to form **14**. Logarithmic plots of the percentage of **12** versus time at the three different temperatures revealing the reaction rates are shown in Fig. 12. The reaction rates were found to be $4.8(5)\times10^{-4}$, $11.0(7)\times10^{-4}$, and $21.6(6)\times10^{-4}$ s^{-1} at 373, 383, and 390 K, respectively (the values of *R* for the regression lines are 0.971, 0.990, and 0.998, respectively). From the Arrhenius plot shown in Fig. 13, (*R* for the regression line is 0.998), an 'activation energy' of 106.3 kJ/mol is obtained. Surprisingly, the rate constants are of the same order of magnitude as those observed in a kinetic study[3] of the methyl rearrangement

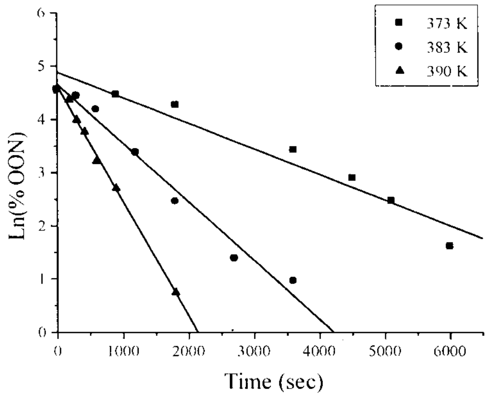


Figure 12. Rate constants of the diminishing of **12**.

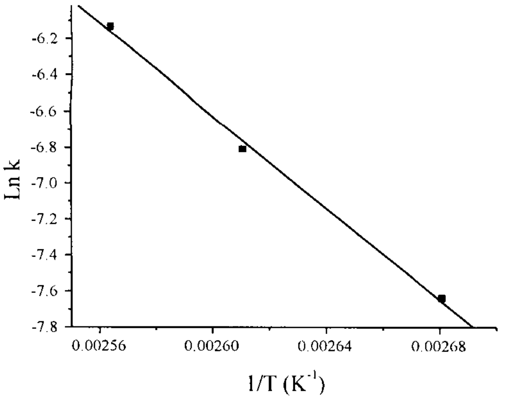


Figure 13. Arrhenius plot of the diminishing of **12**.

of **11** to **14** in the melt. They were determined from the area of the infrared absorption band at 7.35 to be 4.7×10^{-4}, 10.2×10^{-4}, and 21.0×10^{-4} s^{-1}, at 485, 498, and 511 K, respectively, from which the activation energy of 118.3 kJ/mol was calculated. This similarity may suggest that the rate-determining step is identical in both cases, and it is connected with the bond-breaking step rather than the diffusion step.

Summary

Previous investigation[4] of the methyl rearrangement of **11–13** proved that the methyl transfer from oxygen to nitrogen atoms is intermolecular. Calorimetric measurements as well as crystal structure determination of the compounds, carried out in the present research, provides additional insight into the molecular and structural parameters responsible for the thermal behavior of these compounds. Additional information on the methyl rearrangement of similar compounds is under investigation.

Experimental

All compounds were prepared according to procedures mentioned in Ref. 9. The crystal structures are described in Ref. 10d. Thermal behavior was studied using a DSC TA-3000 of Mettler and DSC-PL of Polymer Laboratory. NMR spectra were collected on a Bruker AC200 and AC400. High-temperature X-ray diffraction was carried out using a home-built camera. Computer simulation was carried out using the CHEMX software package of Chemical Design Ltd.[14]

Data collection, structure analysis and refinement

Diffraction intensities for **11′** were collected on a Phillips PW 11000 diffractometer, $\omega/2\theta$ mode, graphite monochromator, MoKα radiation. The crystal structure was solved by direct methods and refined by a full-matrix Least Squares procedure using F^2. All non-hydrogen atoms were refined with anisotropic, and hydrogen atoms with isotropic atomic displacement parameters. Final agreement factors and other refinement details are given below. A list of computer programs used and data sources are provided in Ref. 16.

Crystal data

11′:($C_6H_9N_3O_3$, M=171.16, Monoclinic, a=13.779(3) Å, b=7.488(2) Å, c=3.825(2) Å, β=98.84(3)°, V=390.0(2) Å^3, λ=0.71070 Å^3, space group $P2_1$, Z=2, D_x=1.458 g cm^{-3}. Colorless prismatic crystals of size 0.7×0.2×0.08 mm, μ(MoKα)=0.118 mm^{-1}. 864 reflections measured ($2.5<\theta<25.04°$), 748 used for refinement of 134 parameters. Final agreement factors are: R=0.0626, wR=0.153, for reflections with ($I>2\sigma(I)$), R=0.0746, wR=0.161 for all the data. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. Supplementary data such as tables of bond lengths and angles and structure factors are available. See Notice to Authors, *Tetrahedron* **1984**, *40* (2), ii.

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14. Computer simulation was carried out with the CHEMX software package of Chemical Design Ltd.

15. The conformation analysis was performed with the Cerius^2 software package, using Universal 1.01 force field. Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard-III, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.

16. The following computer program were used for crystal structure analysis: Program used to solve the crystal structures: *SHELXS86* (Sheldrick, 1990). Program used to refine the crystal structures: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEP II* (Johnson, 1976); *TEXSAN* 1.6 MSC.