A Double Ionic Mechanism for the Chapman-like Rearrangement of Imino-ethers to *N*-Alkylamides, in the Solid State or in the Melt. Theoretical and Experimental Evidence

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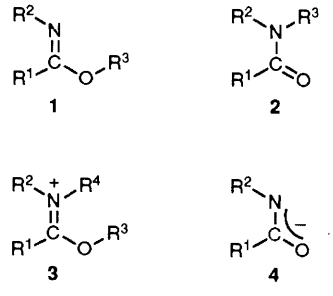
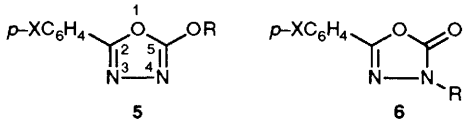
Using 5-methoxy-2-aryl-1,3,4-oxadiazoles as models it was shown that the thermal rearrangement of imino-ethers to *N*-alkylamides proceeds through a double ionic mechanism; kinetics measurements in the solid state and in the melt give apparent activation energies that support *ab initio* calculated activation enthalpies.

The thermal rearrangement of alkyl-imino-ethers **1** into *N*-alkylamides **2**, one of the oldest known in organic chemistry,[1] has been found to be intermolecular[2–5] (though some intramolecular examples have been described[1c]) and not to take place readily (temperatures above 200 °C are normally required). It occurs more easily at 120–200 °C when a second oxygen atom is attached to the carbonyl group (Scheme 1; R^1 = OR).

This Chapman-like rearrangement is catalysed: (*i*) By electrophilic reagents, such as alkyl halides.[4,6,7] It then proceeds *via* the cation **3** (R^4 = R^3) resulting from the alkylation of the nitrogen in **1**. The tetrafluoroborate of this cation was used by Beak and coworkers[6] for equilibration studies between **1** and **2**; (*ii*) By nucleophilic reagents such as amines or quaternary ammonium halides.[8,9] In this case, the intermediate anion **4** results from the dealkylation of the oxygen atom in **1**.



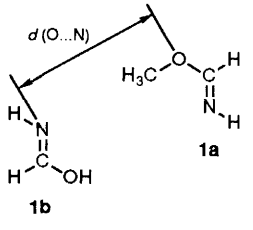
Scheme 1



Scheme 2 **a**: R = CH_3; X = OCH_3. **b**: R = CD_3; X = OCD_3. **c**: R = CH_3; X = H

Only a few studies have been devoted to the thermal, uncatalysed, reaction mechanism. In the case of 2-methoxypyridine, Wiberg and coworkers[2] proposed a radical mechanism, subsequently challenged by a cyclic one.[10] Moreover, the transfer of a methyl cation was proposed in the case of the triple rearrangement of 2,4,6-trimethoxy-1,3,5-triazine.[11]

We found that this rearrangement is unusually fast in the solid state, for some derivatives of 5-methoxy-2-aryl-1,3,4-oxadiazoles **5**[3] (Scheme 2). This unexpectedly fast Chapman-like rearrangement in the solid state can be summarized as the consequence of a very favourable geometry observed in the crystal packing of **5b**:† the three O, C and N atoms involved in the transfer of the methyl group from a given molecule to its

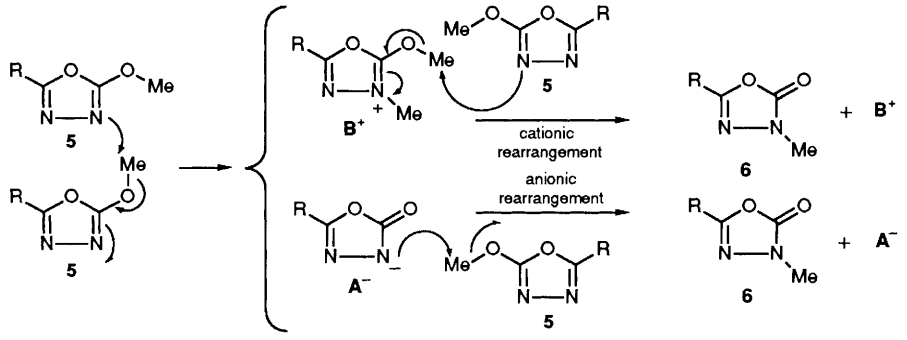


Scheme 3 Geometry for model calculations

† *Crystal data* for **5b**: colourless prisms, $C_{10}H_4D_6N_2O_3$, M = 212.27, D_c = 1.45 g cm^{-3}; orthorhombic; space group $Pna2_1$; a = 7.129(2), b = 20.895(4), c = 6.547(2) Å and Z = 4. Refined to R = 8.9% for 491 independent reflections with $I > 2\sigma(I)$ (unit weights). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Compound **5b** was used for the crystallographic determination since preliminary measurements suggested it would rearrange more slowly than **5a**.

The corresponding N-rearranged product **6b** was also analysed: space group $P2_1/c$, a = 19.187, b = 4.204, c = 12.082 Å, β = 107.9°. **6b** displays a completely different packing. Full details of the X-ray structures will be published elsewhere.



Scheme 4

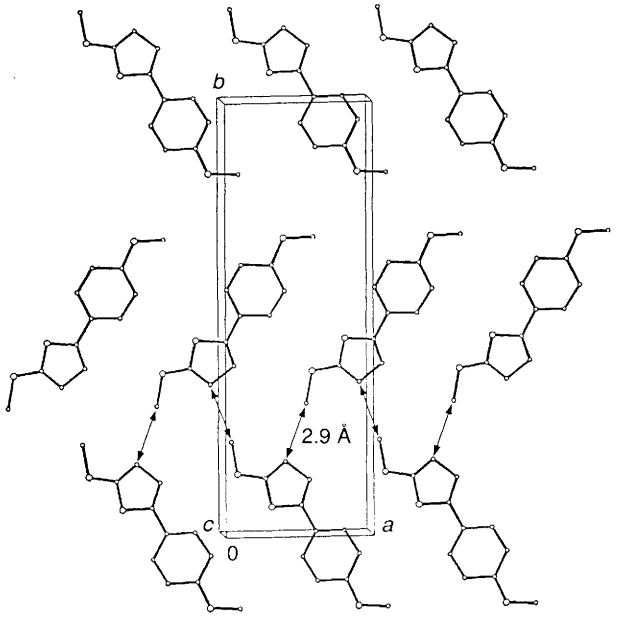


Fig. 1 Crystal structure of **5b** projected down the *c* axis, displaying the molecular packing and the very short intermolecular contact d(N···C) = 2.9 Å, between the OMe group of one molecule and the N(4) atom of a symmetry related molecule (1/2 + x, 1/2 − y, z). The molecules of the packing are interleaved as an infinite sheet arrangement showing the preferential propagation.

neighbour are practically aligned, with a distance between the methyl group and the nitrogen atom equal to 2.9 Å, a value lower than the sum of the corresponding van der Waals radii (3.55 Å) (Fig. 1). In addition, the X-ray structure of **5b** shows a characteristic average intermediate state with a long O(5)–Me distance (1.60 Å).

A theoretical study was undertaken, using molecules **1a** ($R^1 = R^2 = H$; $R^3 = Me$), and the simplified model **1b** ($R^1 = R^2 = R^3 = H$) (when the methyl group is not involved in the reaction) (Scheme 3), and the ions **3** ($R^1 = R^2 = R^4 = H$; $R^3 = Me$) and **4** ($R^1 = R^2 = H$). The two model molecules were positioned as they are in the crystal structure of **5b** with d(O···N) = 4.4955 Å, and the three O, C and N atoms in alignment, as in Scheme 3. All the heavy atoms of the two models were kept coplanar. The transition structure for the methyl exchange was localized with an analytical gradient; all internal coordinates, with the exception of the above constraints, were allowed to relax. The energies were calculated at the restricted Hartree–Fock level with a 3-21G basis set.[12]

The activation energies were obtained for both the cationic and the anionic rearrangements. The transition structures were found to be essentially identical with d(N···C) = 2.173 Å and d(N···C) = 2.170 Å for the two cationic and anionic reactions, respectively. The corresponding activation enthalpies, with respect to the two reactants, optimized in both possibilities, were calculated to be 115.1 and 127.2 kJ mol^{-1}, respectively. At the transition structure, the methyl fragment is found to be planar and bearing a large positive charge which is indicative of a cation moiety transfer in both cases.

Table 1 Activation parameters for the thermal rearrangement of **5**, with or without a catalyst[a]

		Uncatalysed reaction		Catalysed reaction	
				$B^+BF_4^-$	K^+A^-
State	Solid	Melt	Melt	Melt	Melt
Compound	**5a**	**5a**	**5c**	**5c**	**5c**
Temp. range/°C	60–80.5	127–137	99.5–140	60–90	85–120
E_a/kJ mol^{-1}	74.3	122.3	122.7	85.4	97.7
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	−102	−20	−20	−41	−15
$\Delta G^{\ddagger}$/kJ mol^{-1}	111.4	126.7	126.8	98.2	100.5

[a] Catalyst: 2-phenyl-4-methyl-5-methoxy-1,3,4-oxidiazolium tetrafluoroborate ($B^+BF_4^-$), prepared by the method in ref. 13, or the potassium salt of 2-phenyl-1,3,4-oxadiazol-5(4*H*)-one) (K^+A^-). $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ are calculated at 122 °C.

The preceding computations suggest that the mechanism follows that in Scheme 4, the starting point being the initial formation of the anion A^- and the cation B^+ followed by the transfer of a methyl group between these ions and an adjacent molecule in the same plane. This nucleophilic substitution occurs then more easily with the anion A^-, or the cation B^+, than with a neutral molecule **5**. Though the calculated activation enthalpy is lower for the cationic than for the anionic process, the rates remain of the same order, and the transition states have identical geometry. These substitutions are domino-like propagated in chains, along the *a* axis in the crystal (Fig. 1), in two opposite directions, since at each step the same ions are formed, according to Scheme 4.

A kinetic study using NMR measurements of this rearrangement[3] gives support to this mechanism: (*i*) The Arrhenius equation was obeyed well for the solid state as for the melt. The apparent activation energies (Table 1) are in accordance with the calculated activation enthalpies. (*ii*) In the molten state, the reaction is catalysed by the cation B^+ (along with the non-nucleophilic counterion BF_4^-). The reaction can be followed up to 50% completion, owing to the disappearance of this very reactive catalyst. The reaction is also catalysed by the anion A^- (along with the non-electrophilic counterion K^+), and pseudo-first-order kinetics are observed up to 90% completion. The experimental activation energies are almost identical, as is indicated by the free enthalpy of activation (extrapolated at the fusion temperature of **5a**). (*iii*) No direct evidence could be obtained for the presence of A^- or B^+, during the uncatalysed reaction in the melt. However, the observed rate constant indicates that the concentrations of A^- and B^+ should not exceed 10^{-4} mol per mol of **5** (as deduced

from the results of the catalysed reactions) which would not be detectable by NMR.

This rearrangement provides quite a rare example of a reaction proceeding by two different competitive ways, at comparable rates, to give the same final product. Moreover, few examples of intermolecular methyl-transfer reactions in the solid state have been reported and studied.[14a–c] Since the pioneering work of Schmidt on photochemical reactions in the solid state, it is known that the reaction occurs with a minimum amount of atomic or molecular movement,[15a–c] and that the rate is strongly dependent on the relative geometry of the molecules within the crystal. Our system presents an optimal arrangement of the reactants, which results in a higher rate of reaction in the crystal than in the melt,[3] and the geometry of this crystal gives a close picture of the transition state for the Walden inversion on a methyl group (Fig. 1).

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