Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 2067–2069

Tetrahedron Letters

# Aziridinium ring opening: a simple ionic reaction pathway with sequential transition states

María A. Silva and Jonathan M. Goodman*

*Unilever Centre for Molecular Science Informatics, Department of Chemistry, Lensfield Road, Cambridge CB2 1EW, UK*

Received 7 January 2005; accepted 25 January 2005

---

**Abstract**—Most organic reactions go from a starting material to an intermediate or a product after crossing one transition state. We report calculations that show a simple ionic reaction, aziridinium ring opening, proceeds through sequential transition states without an intervening intermediate.

---

Most organic reactions are expected to go from a starting material to a product after going through a transition state. More complex reactions may go through a series of intermediates, each separated by a transition state. Recently, it has been shown that reactions may proceed through sequential transition states without intervening ground states.[1] These examples relate to complex pericyclic processes. Reaction paths with sequential transition states are examples of one of the types of phenomena that can occur near a valley-ridge inflection point on a potential energy surface.[2] Here we demonstrate that the same phenomenon can occur in a superficially simple ionic reaction.

The opening of aziridine rings is a useful process in organic synthesis, which has been recently reviewed.[3] Aziridinium ring openings have been widely used.[4] Despite its familiarity, a simple example of this reaction (Fig. 1) has the extraordinary property of sequential transition states. It may be that this phenomenon is not particularly unusual.

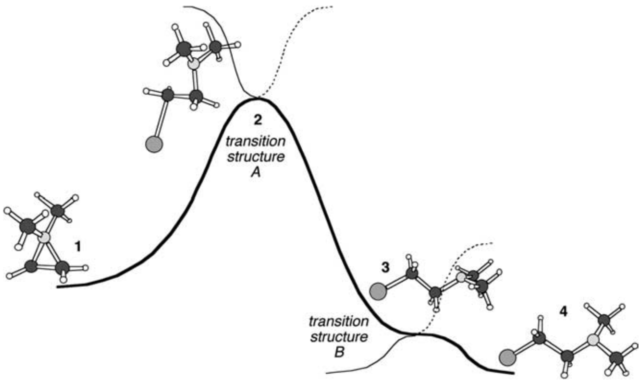


**Figure 1.** Aziridinium ring opening pathway.

For the reaction in Scheme 1, the first transition state (**2**) occurs as the chloride opens the aziridinium ring. The transition state has $C_s$ symmetry (a mirror plane). The reaction continues after the transition state, with the three-membered ring opening up to a structure resembling **3**. This structure still has a mirror plane, as the reaction coordinate has no reason to twist to the left or the right. However, the methyl groups of the amine eclipse their neighbouring hydrogens, and the energy of this structure can be lowered by twisting around the C–N bond to form **4**, which is a ground state. This analysis is consistent with our calculations.

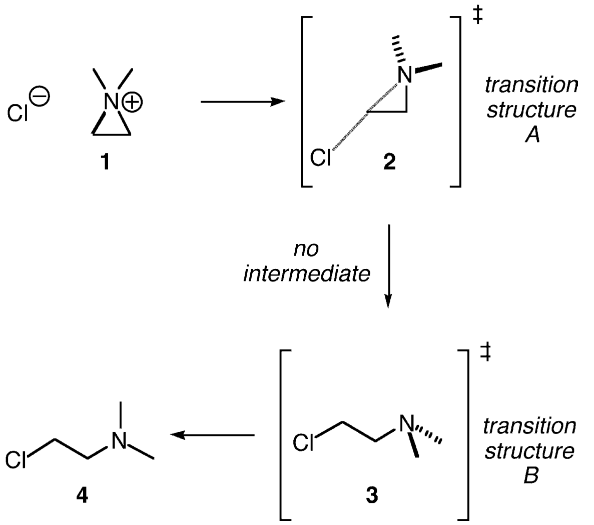
This result highlights the importance of not merely identifying transition states on reaction pathways, but also following the course of the reaction. This is usually done with an IRC calculation,[5] which is reliable but time consuming. We have recently introduced a quicker alternative procedure QRC,[6] which also follows reaction pathways, but with more approximations, making the calculation quicker, but possibly deviating from the IRC pathway. A reaction path that includes sequential transition states is likely to be more difficult to follow than a simple path connecting two ground states by a

---

*Keywords*: Aziridinium; QRC; IRC.

* Corresponding author. Tel.: +44 1223 336434; fax: +44 1223 336362; e-mail: jmg11@cam.ac.uk

doi:10.1016/j.tetlet.2005.01.142



**Scheme 1.** Aziridinium ring opening through two transition states.

single transition state, and so should be a good test of the QRC procedure.

The calculations were done using GAMESS-US[7] and Jaguar[8] at the B3LYP/6-31+G* level with a water solvent model. All the transition structures had a single negative normal mode, which was explored both by IRC and by QRC. The GAMESS and the Jaguar calculations identified the starting materials, the products and the two transition states. The results are summarised in Table 1. The energies calculated by the two programs are not the same because the two programs do the calculations in different ways.[9]

The reaction pathway was followed both by an IRC calculation and by a QRC calculation. The GAMESS results are illustrated in Figure 2, which plots the energy of each IRC/QRC step. The QRC used the default minimisation settings, and so spent some time optimising the final structures. Despite this, the IRC and QRC took about the same length of time. The QRC could be made quicker by a looser convergence criterion, at the expense of a less accurate determination of the stationary point.

The $y$-axis of the graph is the energy in kilojoules per mole. The $x$-axis is the mass weighted root mean square geometric difference between structures, measured in Bohr.amu$^{0.5}$. For an IRC, this step size is constant. The QRC $x$-values are calculated by the QRC program[5] by superimposing the structures found by a minimisation algorithm with the starting structure, and so the step size can vary. The large step sizes at the start of the procedure can make the QRC quicker than the IRC.

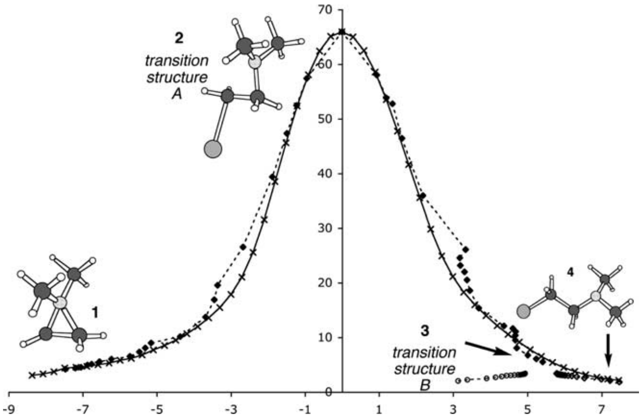


**Figure 2.** GAMESS B3LYP/6-31 + G*/water (kJ mol$^{-1}$) against reaction coordinate (Bohr.amu$^{0.5}$); IRC–solid line; QRC–dotted line.

**Table 1.** Results of GAMESS-US and Jaguar calculations (B3LYP/6-31+G* and water)

| | Jaguar | kJ mol$^{-1}$ | GAMESS | kJ mol$^{-1}$ |
|---|---|---|---|---|
| **1** | −673.420503 | −18.4 | −673.194031 | 2.9 |
| **2** | −673.390657 | 59.9 | −673.170066 | 65.9 |
| **3** | −673.411531 | 5.1 | −673.193713 | 3.8 |
| **4** | −673.413485 | 0.0 | −673.195149 | 0.0 |

There is a major difference between an IRC and the QRC analysis. The IRC goes from the first transition structure (**2**) directly to the product (**4**, or its mirror image **4′**), and gives no indication that a second transition structure may be involved. The QRC, however, stops at the second transition structure (**3**). This part of Figure 2 is enlarged in Figure 3. This is the first time we have seen a qualitative difference between an IRC and a QRC pathway.[6] A second QRC, starting from the second transition structure (**3**), descends to the products (**4** and **4′**). The path to **4′** has been drawn to the left rather than continuing to the right, so it can be seen more clearly.

A reaction trajectory would not come to a halt at the second transition structure. Instead, random fluctuations would push it to one side or the other, and so it would reach the product without passing precisely through the second transition state geometry. It may be argued, therefore, that an IRC is more realistic than the QRC. However, the QRC leads to the identification of the second transition structure, and this may be important in a mechanistic understanding of the reac-

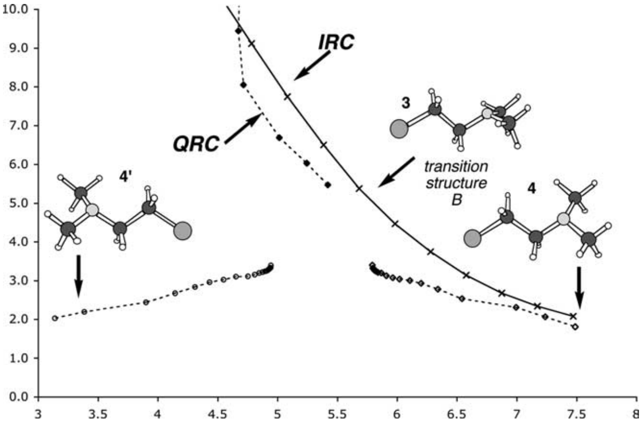


**Figure 3.** This is an enlarged section of Figure 2. The QRC line with circles has been reflected around the point for transition structure B.

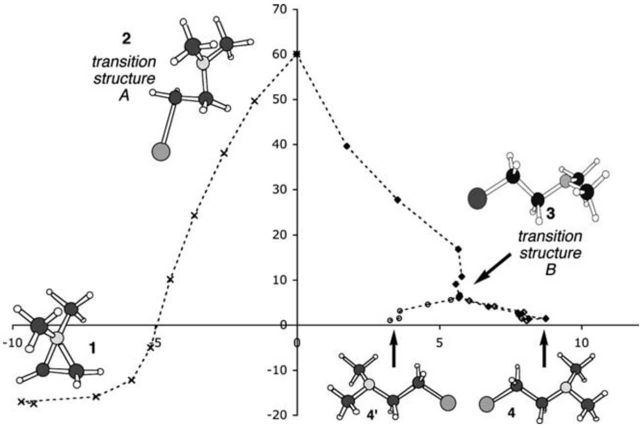


**Figure 4.** Jaguar QRC: B3LYP/6-31+G*/water (kJ mol$^{-1}$) against reaction coordinate (Bohr.amu$^{0.5}$).

tion pathway. It is likely that adjusting the IRC parameters to take smaller steps would lead to it terminating at the first transition state. However, this would slow the calculation down and the shape of the IRC profile does not suggest that this area of the path is particularly interesting.

The same calculation using Jaguar instead of GAMESS gives a slightly different result. IRC calculations are not available in this version of Jaguar (4.2), so only a QRC was performed and this is shown in Figure 4. The left hand side of the graph shows the chloride moving around relative to the aziridinium ring to form a stable complex, after the system has gone back along the reaction coordinate to form the three-membered ring. The right hand side of the reaction coordinate goes directly to the product **4** and does not stop at the second transition state **3**. However, unlike the IRC, the coordinate shows a wobble in the curve as it goes near the second transition state, and this should be interpreted as suggesting that the potential energy surface is flat in this region and may be worth further investigation.

The calculations were also carried out at the B3LYP/6-31G* level with a water solvent model. This gave qualitatively similar results for both GAMESS and Jaguar. The main difference was that the energy of the starting materials, including the chloride ion, was much higher, relative to the rest of the reaction coordinate, without a diffuse orbital to stabilise it.

In conclusion, we have demonstrated that a simple ionic reaction can have sequential transition states without an intervening ground state. The pathway was analysed both by IRC and QRC. With the default settings, the IRC gives more information about the area of the potential energy surface around the transition state, as it is designed to do, and the QRC proved to be better at highlighting points of interest on the reaction pathway, and this may be more useful for the mechanistic analysis of organic reactions.

## Acknowledgments

We thank Unilever for their support. M.A.S. thanks the European Community for a Marie Curie Fellowship.

## References and notes

1. (a) Bartsch, R. A.; Chae, Y. M.; Ham, S.; Birney, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 7479; (b) Zhou, C.; Birney, D. M. *Org. Lett.* **2002**, *4*, 3279; (c) Reyes, M. B.; Lobkovsky, E. B.; Carpenter, B. K. *J. Am. Chem. Soc.* **2002**, *124*, 641; (d) Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *J. Org. Chem.* **2003**, *68*, 6035; (e) Zhou, C.; Birney, D. M. *J. Org. Chem.* **2004**, *69*, 86.
2. Taketsugu, T.; Tajima, N.; Hirao, K. *J. Chem. Phys.* **1996**, *105*, 1933.
3. Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
4. For example: (a) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555; (b) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304; (c) McKay, C.; Wilson, R. J.; Rayner, C. M. *Chem. Commun.* **2004**, 1080.
5. (a) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161; (b) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.
6. Goodman, J. M.; Silva, M. A. *Tetrahedron Lett.* **2003**, *44*, 8233, Download: http://www.ch.cam.ac.uk/MMRG/software/QRC/.
7. GAMESS version 20: Iowa State University: Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. I.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.
8. Jaguar version 4.2: Schrodinger, Inc., Portland, Oregon, 2000.
9. Jaguar uses a pseudospectral method[10] for converging the SCF, and this can lead to small energy discrepancies. The main cause of the difference, however, is likely to be the different methods for calculating solvent effects. Jaguar uses a self-consistent reaction field method with its own Poisson–Boltzmann solver,[11] whilst GAMESS uses a polarisable continuum model.[12]
10. Ringnalda, M. N.; Won, Y.; Friesner, R. A. *J. Chem. Phys.* **1990**, *92*, 1163.
11. Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.
12. Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.