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Assessing the Rates of Ring-Opening of Aziridinium and Azetidinium Ions: A Dramatic Ring Size Effect

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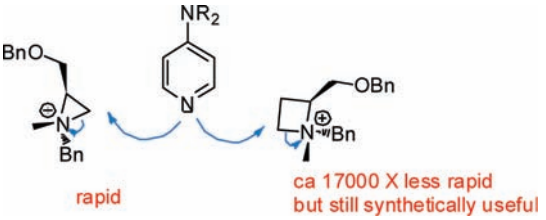
ABSTRACT



Rates for the ring-opening of aziridinium and azetidinium ions by DMAP were measured. The four-membered ring appears to be ca. 17 000 times less reactive compared to the three-membered ring but is still highly relevant from a synthetic viewpoint. The electrophilicity of these strained ammonium ions is measured for the first time.

The strain associated with small rings and its release during a reaction are powerful driving forces for achieving otherwise difficult transformations.[1] In this field, aziridines have become valuable substrates for the synthesis of nitrogen-containing molecules, but their intracyclic nitrogen atom has to be activated in order to support the negative charge created by the ring scission during nucleophilic opening. Thus, *N*-acyl, *N*-carbamoyl, or *N*-tosyl aziridines, in which the anionic charge on the nitrogen atom is stabilized, have emerged as substrates of choice for this purpose.[2] Another way to activate strained aza-heterocycles involved in nucleophilic opening lies in the formation of an ammonium ion, which can be achieved by simple protonation or alkylation. However, the first option is precluded when basic nucleophiles are considered, while the second one gives rise to extremely electrophilic entities, which can only be isolated and fully characterized in certain cases.[3] Therefore, *N*-alkyl aziridinium ions **1** are usually produced in situ, most frequently through intramolecular substitution from *β*-*N*,*N*-dialkylamino halides or sulfonates, and their subsequent nucleophilic opening is the key step in numerous syntheses of biologically relevant molecules.[4] Furthermore, aziridinium ions are known to be the active electrophilic species produced by nitrogen mustards. Due to the pharmacological relevance of this important class of antitumoral molecules, their reaction in physiological mediums and their targeted nucleophilic sites involved in DNA alkylation have been investigated in detail.[5] Despite this, to the best of our

(1) Hesse, M. *Ring Enlargements in Organic Chemistry*; VCH: Weinheim, New-York, Basel, Cambridge, 1991.

(2) For some recent reviews on aziridines, see: (a) Olsen, C. A.; Franzyk, H.; Jaroszewsky, J. W. *Eur. J. Org. Chem.* **2007**, 1717. (b) Bisol, T. B.; Sa, M. M. *Quim. Nova* **2007**, *30*, 106. (c) Watson, I. D. G.; Yu, L. L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *60*, 27. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (e) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichimica Acta* **2003**, *36*, 39. (e) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (f) Mc Coull, W.; Davis, F. A. *Synthesis-Stuttgart* **2000**, *10*, 1347.

(3) (a) Olah, G. A.; Szilagyi, J. *J. Am. Chem. Soc.* **1969**, *91*, 2949. (b) Leonard, N. J.; Jann, K. *J. Am. Chem. Soc.* **1960**, *82*, 6418. (c) Leonard, N. J.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1964**, *86*, 821. (d) Kim, Y.; Ha, H.-J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363. (e) Piotrowska, D. G.; Wroblewski, A. E. *Tetrahedron* **2009**, *65*, 4310.

(4) (a) Oxenfor, S. J.; Moore, S. P.; Carbone, G.; Barker, G.; O'Brien, P.; Shipton, M. R.; Gilday, J.; Campos, K. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1563. (b) Metro, T. X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556. (c) Frizzle, M. J.; Caille, S.; Marshall, T. L.; McRae, K.; Nadeau, K.; Guo, G.; Wu, S.; Martinelli, M. J.; Moniz, G. A. *Org. Process Res. Dev.* **2007**, *11*, 215. (d) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183. (e) Revesz, L.; Blum, E.; Wicky, R. *Tetrahedron Lett.* **2005**, *46*, 5577. (f) Gala, D.; Danahukar, V. H.; Eckert, J. M.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A.; Buholzer, P.; Kubisch, P.; Mergelsberg, I.; Sherer, D. Z. *Org. Process Res. Dev.* **2004**, *8*, 754. (g) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304. (h) Chang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555.

(5) For recent theoretical data, see: (a) Mann, D. J. *J. Phys. Chem. A* **2010**, *114*, 4486. (b) Vasilescu, D.; Adrian-Scotto, M.; Fadiel, A.; Hamza, A. *J. Biomol. Struct. Dyn.* **2010**, *27*, 465. (c) Shukla, P. K.; Mishra, P. C.; Suhai, S. *Chem. Phys. Lett.* **2007**, *449*, 323. (d) Bhattacharyya, P. K.; Mehdi, C. *Indian J. Chem., Sect. B* **2005**, *44*, 1319.

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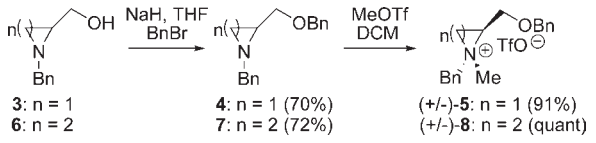
knowledge, *direct* measurement of the second-order rate constant associated with the nucleophilic opening of an aziridinium ion has not yet been reported.[6] On the other hand, our involvement in the chemistry of strained azetidinium **2**,[7] i.e. the higher homologues of aziridinium ions, has led us to note that these species are much less electrophilic than **1**, which can be at first explained by a lower ring strain in the four-membered ring (Figure 1). Here again, no direct rate measurement of the nucleophilic opening of azetidinium ions has so far been published. Aiming at a better understanding of the electrophilic character of these highly relevant building blocks for the synthesis of nitrogen-containing molecules, we report herein the kinetics measurements of their opening with neutral nucleophiles. This allows for the first time a direct comparison of the reactivity of these strained heterocycles and an estimation of their electrophilicity.

Figure 1. Aziridinium **1** and azetidinium **2** ions.

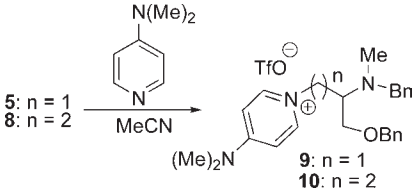
Aziridinium and azetidinium trifluoromethane sulfonates **5** and **8** were prepared as depicted in Scheme 1. These salts could be conveniently isolated after reaction of the corresponding amines **4** and **7** with methyltrifluoromethanesulfonate and were stable enough to be stored without appreciable degradation for weeks.

Scheme 1. Synthesis of Azetidinium and Aziridinium Triflates



In both cases, they were produced as single diastereoisomers, which is due to the preferred disposition of the reacting lone pair, for steric reasons.[8] Considering that alkyl substituted aziridinium and azetidinium ions are known to react regioselectively at the unsubstituted carbon atom,[3d,7e] these salts are perfect candidates for comparative nucleophilic openings, since their only difference lies in the size of the heterocycle. However, in order to compare the kinetics for both substrates, we had to find the proper nucleophile fulfilling the following requirements: (i) measurable rates for both substrates (i.e., not too fast for the aziridinium substrate); (ii) the nucleophile or product should display a specific UV−vis absorption in order to be able to accurately follow the reaction; and (iii) the nucleophile should react irreversibly. We initially studied the nucleophilic opening with anionic nucleophiles, such as thiophenoxides, phenoxides, and benzoates, but in the case of **5** reaction rates were too fast and could not be accurately measured by stopped-flow techniques. We therefore shifted to neutral nucleophiles and found that 4-dimethylaminopyridine (DMAP) reacted with both substrates at measurable rates in acetonitrile[9] to produce pyridinium trifluoromethanesulfonates **9** and **10** (Scheme 2).

Scheme 2. Nucleophilic Opening of **5** and **8** with DMAP



Furthermore, presence of a specific UV absorption band in these compounds allowed accurate measurement of their concentration. These pyridinium salts were isolated in good yields, and no detectable byproducts were formed, except in the case of aziridinium **5**, for which the crude reaction mixture showed a small amount ($<5\%$) of a regioisomer. Since pyridinium ion is a potential nucleofuge, we heated both subtrates in refluxing acetonitrile for a week, but without a significant change or detectable production of the more substituted regioisomer. This is a good indication for the irreversibility of the reaction, because a similar experiment conducted with a chloride atom as a leaving group led to complete isomerization through thermodynamic control in the case of azetidinium ions.[10] The kinetics of nucleophilic opening with aziridinium **5** was followed by UV spectrophotometry: equal amounts of DMAP and **5** in acetonitrile were mixed in the quartz cell, and the increase of absorbance of the produced pyridinium **9** was followed against time at a given temperature. Figure 2 shows an example of such data. After integration of the kinetics rate law, a plot of $(1/C_0 - x) - (1/C_0)$, where C_0 denotes the initial concentration of DMAP

(6) Numerous kinetics data on the reaction rates of nitrogen mustards, precursor of the electrophilic aziridinium with different nucleophiles, have been published. See inter alia: (a) Yang, H. *Bull. Soc. Chim. Belg.* **1996**, *105*, 23. (b) Cullis, P. M.; Green, R. E.; Malone, M. E. *J. Chem. Soc., Perkin Trans. 2* **1995**, *7*, 1503. (c) Kundu, G. C.; Shullek, J. R.; Wilson, I. B. *Pharmacol., Biochem. Behav.* **1994**, *49*, 621. (d) Hovinen, J.; Petterson-Fernholm, T.; Lahti, M.; Vilpo, J. *Chem. Res. Toxicol.* **1998**, *11*, 1377.

(7) (a) Couty, F.; Kletskii, M. *J. Mol. Struct.* **2009**, *908*, 3368. (b) Drouillat, B.; Couty, F.; David, O.; Evano, G.; Marrot, J. *Synlett* **2008**, *9*, 1345. (c) Couty, F.; David, O.; Drouillat, B. *Tetrahedron Lett.* **2007**, *48*, 9180. (d) Couty, F.; David, O.; Durrat, F. *Tetrahedron Lett.* **2007**, *48*, 1027. (e) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, *3*, 479.

(8) (a) For azetidiniums: Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, 4214. (b) For aziridiniums: Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941.

(9) Initial experiments were conducted in DCM, but reaction of the solvent with DMAP led to erratic results; see: Rudine, A. B.; Walter, M. G.; Wamser, C. C. *J. Org. Chem.* **2010**, *75*, 4292.

(10) Sivaprakasham, M.; Couty, F.; Evano, G.; Srinivas, B.; Sridhar, R.; Rama Rao, K. *Arkivoc* **2007**, *(x)*, 71.

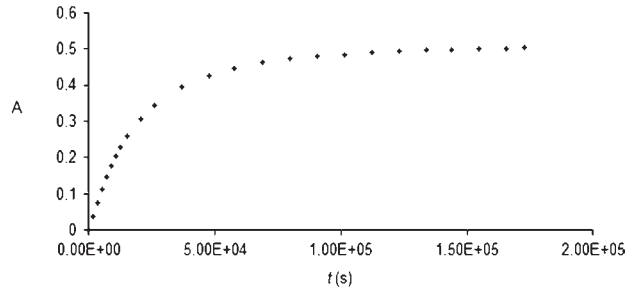


Figure 2. Example of monitoring absorbance A by UV−vis spectrometry at λ_{max} = 291 nm as a function of time of the reaction between aziridinium salt **5** and DMAP at 15 °C in CH_3CN.

and x the concentration of **9**, gave straight lines with the rate constant as the slope (Figure 3). Each experiment was conducted in duplicate or triplicate at different temperatures (see Supporting Information). It should be noted that the observed rate constants include the production of the minor regioisomer, but this can be neglected due to the high regioselectivity.

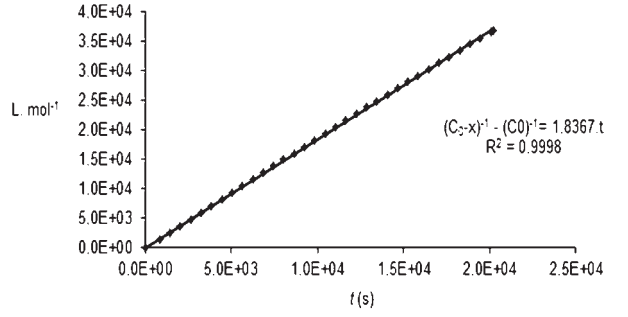


Figure 3. Example of determination of second-order rate constants for the reaction of aziridinium salts **5** with DMAP in CH_3CN (15 °C, λ_{max} = 291 nm). $[DMAP]_0 = [\mathbf{5}]_0 = 3.60 \times 10^{-5}$ mol·L^{-1}. k = 1.84 L·mol^{-1}·s^{-1}.

Being much slower, the kinetics of the ring-opening of azetidinium ion **8** was followed by NMR at 293 K. Integration of the decreasing signals at 6.58 ppm (H-2 in DMAP) and growing signal at 7.84 ppm (same proton in pyridinium) allowed accurate determination of the relative concentrations versus time and thus determination of the rate constant (Figure 4). These experiments afforded a ratio of 1.65×10^4 for the rates of the nucleophilic opening of **5** versus **8** at 293 K. These experiments were also conducted with more nucleophilic[11] 4-pyrrolidinopyridine (PPY) at 25 °C (see Supporting Information) and gave a similar ratio of 1.75×10^4 for the rate constants.

In order to gain further insights on the activation parameters of this S_N2 reaction, the nucleophilic opening of **5**

(11) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem.—Eur. J.* **2007**, *13*, 336.

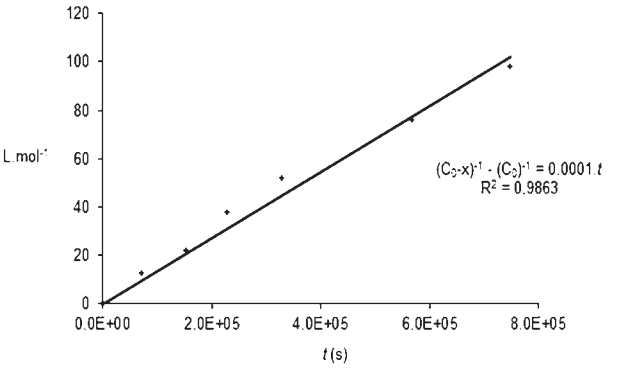


Figure 4. Example of determination of second-order rate constants for the reaction of azetidinium salts **8** with 4-DMAP in CD_3CN (20 °C) by NMR. $[DMAP]_0 = [\mathbf{8}]_0 = 1.60 \times 10^{-3}$ mol·L^{-1}. $k = 1.4 \times 10^{-4}$ L·mol^{-1}·s^{-1}.

was followed at different temperatures, and the Arrhenius plot (Figure 5) gave values of $\Delta H^{\#}$ +46.5 kJ·mol^{-1} and $\Delta S^{\#}$ +165.4 J·mol^{-1}·K^{-1} for this reaction. The strong positive value for $\Delta S^{\#}$ is in accordance with a S_N2 reaction involving a charge neutralization[12] because the positive charge of the produced pyridinium is delocalized. This value is quite high and might be due to strong desolvatation in the transition state. This strong positive value can account for a dissymmetrical transition state in which the positive charge of the intracyclic nitrogen is neutralized to a large extent.

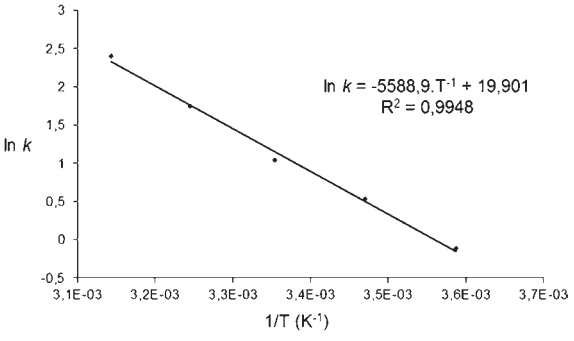


Figure 5. Arrhenius plot for the reaction of **5** with DMAP.

DMAP is a highly studied nucleophile, and its N parameter, which measures the strength of a nucleophile, and s parameter, which characterizes the sensitivity of the nucleophile on variation of the electrophile, following the three parameter eq 1,[13] have been determined in acetonitrile when reacting with benzhydrilium cations.[11]

$$\log k_{20\,°C} = s(N + E) \qquad (1)$$

(12) (a) Earley, J. E.; O'Rourke, C. E.; Clapp, L. B.; Edwards, J. O. *J. Am. Chem. Soc.* **1958**, *80*, 3458. (b) Burns, J. T.; Leffek, K. T. *Can. J. Chem.* **1969**, *47*, 3725.

Assuming that the *s* parameter does not change to a large extent when switching to different electrophiles, it is then possible to estimate the *E* parameter values from eq 1 for aziridinium **5** and azetidinium **9**, which are respectively −14.4 and −20.7. The *E* parameter varies in Mayr's scale from −20.5 (less electrophilic benzylidene malonate) to 6.0 (more electrophilic unstabilized benzylic cation). Therefore, azetidinium ions rank low on the electrophilicity scale, with an *E* parameter similar to the case for benzylidene malonate, while aziridinium ions falls into the range of the stabilized benzhydrilium cation.

The huge difference in the rates of nucleophilic opening between **5** and **9** corresponds to a $\Delta\Delta G^{\#}$ of 5.6 kcal·mol^{-1} at 293 K, which is in agreement with recently calculated values of 6.8 kcal mol^{-1} for the opening of aziridine and azetidine with ammonia in the gas phase.[14] It is clear, however, that this important difference in the rates is not a simple reflection of the lowered ring strain in azetidines versus aziridines, which is estimated[14] to be around 2.1 kcal·mol^{-1}: other subtle parameters govern the boost in electrophilicity when switching from azetidinium to aziridinium ions. In conclusion, we have determined and compared for the first time the direct rates for the irreversible nucleophilic opening of an aziridinium and azetidinium ion: the latter was found to be 1.7×10^4 times less reactive. From a practical viewpoint, the lowered reactivity of azetidinium compared to aziridinium ions makes them an easy to handle yet sufficiently reactive species. Additionally, they remain underscored building blocks for synthetizing nitrogen containing molecules. This work provides a new tool for the determination of the parameters influencing the electrophilicity of these species which will be the subject of future report.

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Supporting Information Available. Synthesis and characterization data for all new compounds. Data for the kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) General reviews: (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (b) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938. (c) Mayr, H.; Patz, M.; Gotta, M. F.; Ofial, A. R. *Pure Appl. Chem.* **1998**, *70*, 1993. (d) Mayr, H.; Ofial, A. R. In *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; Wiley: Hoboken, NJ, 2004; Chapter 13, pp 331−358. (e) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807. (f) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 91. (g) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6176. Nucleophilicities of arenes: (h) Mayr, H.; Bartl, J.; Hagen, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1613. (i) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, *63*, 9769. (j) Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, *3*, 1629. (k) Herrlich, M.; Mayr, H.; Faust, R. *Org. Lett.* **2001**, *3*, 1633.

(14) Banks, H. D. *J. Org. Chem.* **2006**, *71*, 8089.