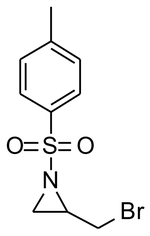
Reactivity of Three-membered Heterocyclic Rings with respect to Sodium Methoxide

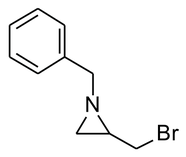
Hannelore Goossens, Saron Catak, Frank De Proft, Paul Geerlings, Michel Waroquier, Veronique Van Speybroeck

Center for Molecular Modeling, Ghent University, Technologiepark 903, 9052 Zwijnaarde (Ghent), Belgium-
Eenheid Algemene Chemie, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium

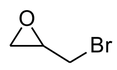
Aziridines and Epoxides



2-bromomethyl-1-tosylaziridine **1**



1-benzyl-2-(bromomethyl)aziridine **2**



epibromohydrin **3**

- Combination of ring strain and electronegative atom → **favorable balance between stability and reactivity**
- Reactivity dominated by ring opening → useful synthetic intermediates

- **Aziridines** further complicated by additional valency:
electron-withdrawing or electron-donating nature of *N*-substituent → quaternization towards aziridinium intermediate required for nucleophilic ring opening or not
  → **classified as activated or non-activated**
  → nature of *N*-substituent has profound influence on reactivity of aziridines towards nucleophiles.

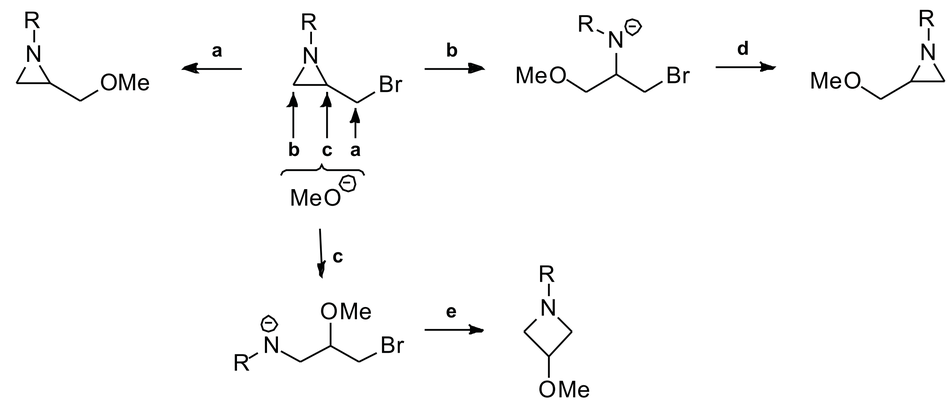
- **2-(Halomethyl)aziridines and epihalohydrins**: 3 different electrophilic carbon atoms
  → high synthetic potential
  → possible to evaluate nucleophilic reactivity of constrained heterocycles relative to alkyl halides.

Goal

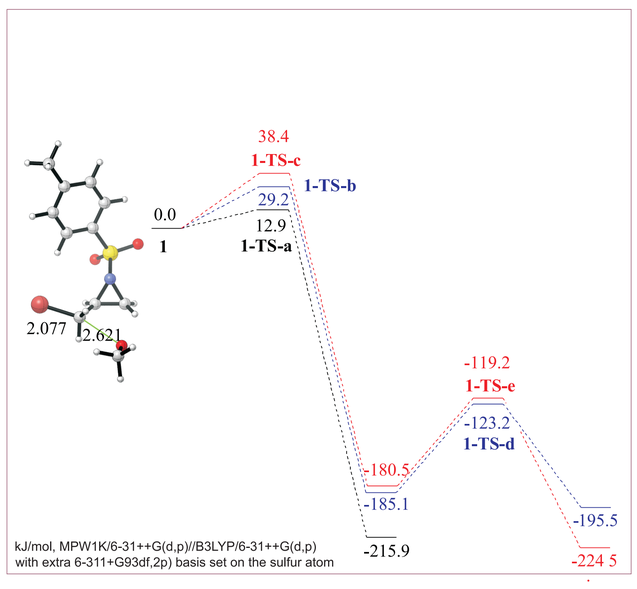
- Wide range of 2-substituted aziridines can be synthesized from 2-(bromomethyl)aziridines, independent of nature of N-substituent
- Replacement of bromine atom by nucleophile:
  → direct nucleophilic substitution (pathway **a**)
  → attack at unsubstituted aziridine carbon (pathway **b**) → ring opened intermediate which is prone to ring closure.
- Chiral substrate: pathway **a** → **retention of configuration**
  pathway **b** → **opposite enantiomer**.
  both pathways competitive → mixture of both enantiomers

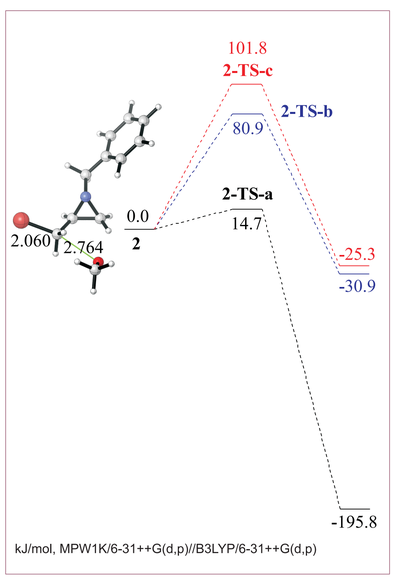
- Better understanding mechanism important for synthesis of **chiral targets**

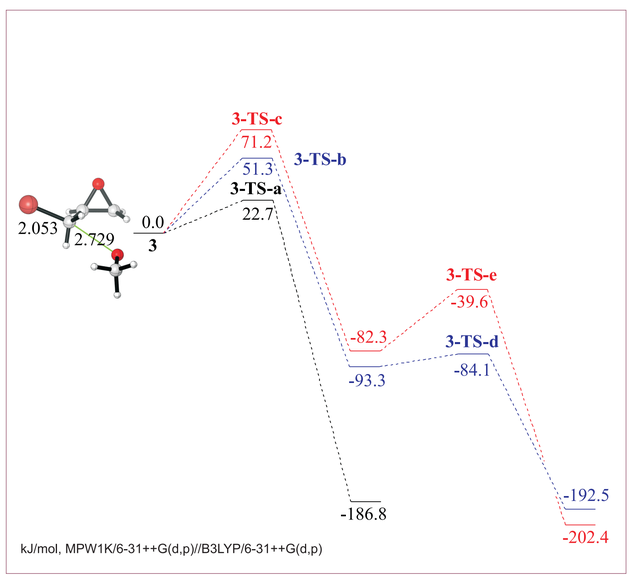
- Difference in reactivity between activated aziridines **1**, non-activated aziridines **2** and epibromohydrins **3** upon treatment with methoxide was comparatively analysed by means of DFT calculations



In Vacuo

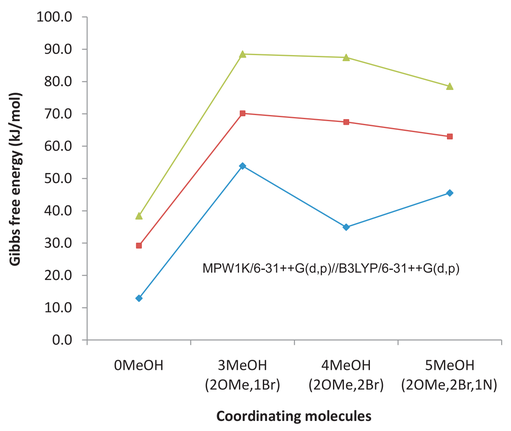


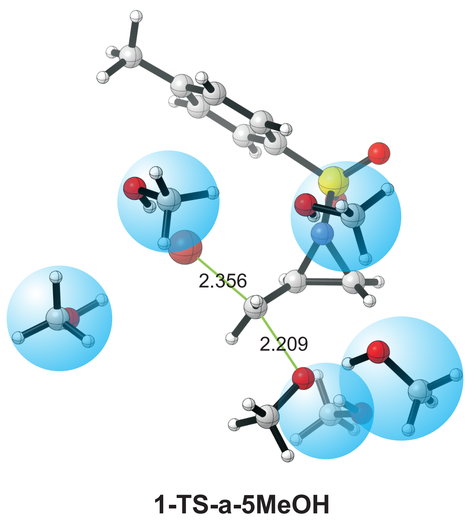


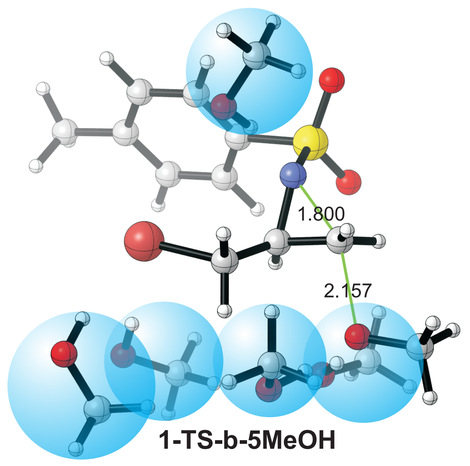


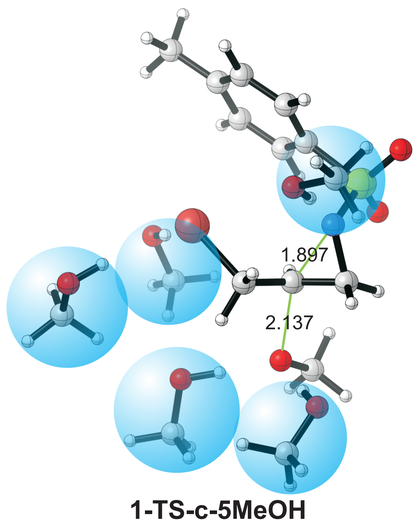
- **Clear preference for direct substitution at brominated carbon atom** by methoxide (pathway **a**)
- Difference between direct substitution at brominated carbon atom (pathway **a**) and ring opening at less hindered carbon atom (pathway **b**) much smaller for activated aziridine **1** and epoxide **3** than for non-activated aziridine **2**
- Difference between ring opening at less hindered carbon atom (pathway **b**) and at substituted carbon atom (pathway **c**) much smaller for activated aziridine **1** than for non-activated aziridine **2** and epoxide **3**
- **Ring opening at substituted aziridine carbon atom (pathway c) cannot be excluded for activated aziridine 1**

Solvent Approach: Microsolvation

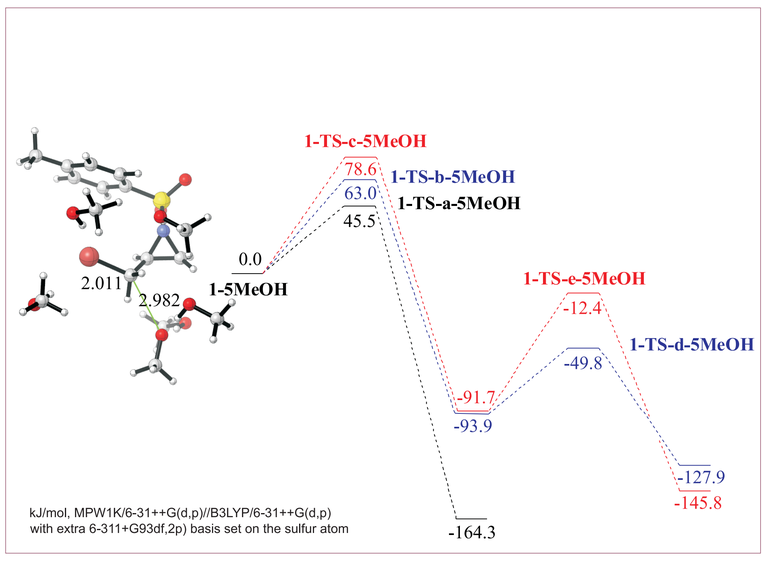


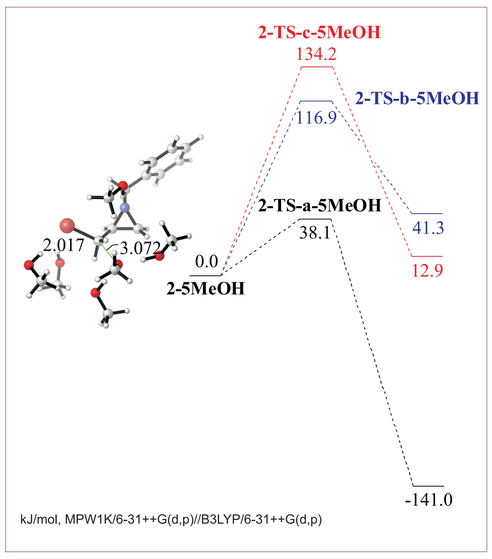


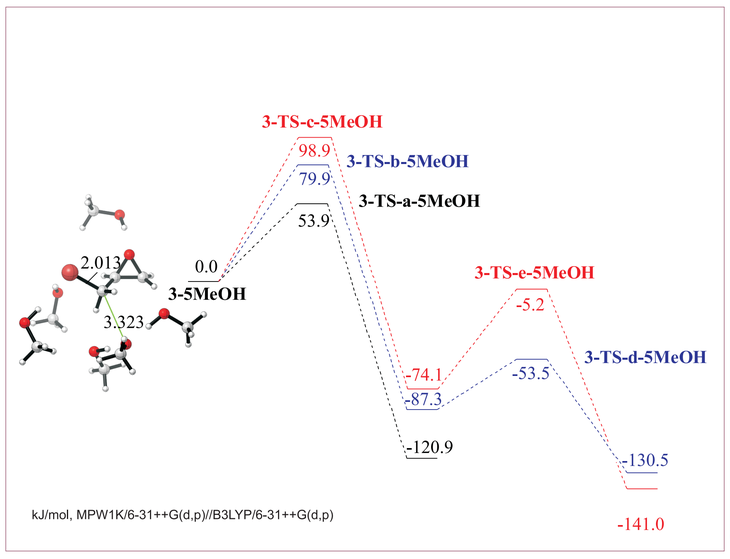




- Solvation has significantly changed landscape of energy profiles
- **Direct substitution at brominated carbon atom by methoxide (pathway a) favored**
- Difference between direct substitution at brominated carbon atom (pathway **a**) and ring opening at less hindered carbon atom (pathway **b**) much smaller for aziridine **1** and epoxide **3** than for aziridine **2** → **ring opening at less hindered carbon atom feasible for activated aziridine 1 and epoxide 3** but not for non-activated aziridine **2**
- Significant difference between ring opening at less hindered (pathway **b**) and at substituted carbon atom (pathway **c**) for both aziridine **1** and epoxide **3**







[1] H. Goossens, K. Vervisch, S. Catak, S. Stanković, M. D'hooghe, F. De Proft, P. Geerlings, N. De Kimpe, M. Waroquier, and V. Van Speybroeck, in revision for JOC
[2] S. Stanković, S. Catak, M. D'hooghe, H. Goossens, K. A. Tehrani, P. Bogaert, M. Waroquier, V. Van Speybroeck and N. De Kimpe, *J. Org. Chem.* **76**, 2157 (2011)