Reactivity of Activated versus Nonactivated 2-(Bromomethyl)aziridines with respect to Sodium Methoxide: A Combined Computational and Experimental Study

Hannelore Goossens,[†] Karel Vervisch,[‡] Saron Catak,*,[†] Sonja Stanković,[‡] Matthias D'hooghe,[‡] Frank De Proft,[§] Paul Geerlings,[§] Norbert De Kimpe,*,[‡] Michel Waroquier,[†] and Veronique Van Speybroeck*,[†]

[†]Center for Molecular Modeling, Ghent University, Member of QCMM-Alliance Ghent-Brussels, Technologiepark 903, B-9052 Zwijnaarde, Belgium

[‡]Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

[§]Eenheid Algemene Chemie (ALGC), Vrije Universiteit Brussel (VUB), Member of QCMM-Alliance Ghent-Brussels, Pleinlaan 2, 1050 Brussels, Belgium

S *Supporting Information*

ABSTRACT: The difference in reactivity between the activated 2-bromomethyl-1-tosylaziridine and the nonactivated 1-benzyl-2-(bromomethyl)aziridine with respect to sodium methoxide was analyzed by means of DFT calculations within the supermolecule approach, taking into account explicit solvent molecules. In addition, the reactivity of epibromohydrin with regard to sodium methoxide was assessed as well. The barriers for direct displacement of bromide by methoxide in methanol are comparable for all three heterocyclic species under study. However, ring opening was found to be only feasible for the epoxide and the activated aziridine, and not for the nonactivated aziridine. According to these computational analyses, the synthesis of chiral 2-substituted 1-tosylaziridines can take place with inversion (through ring opening/ring closure) or retention (through direct bromide displacement) of configuration upon treatment of the corresponding 2-(bromomethyl)aziridines with 1 equiv of a nucleophile, whereas chiral 2-substituted 1-benzylaziridines are selectively obtained with retention of configuration (via direct bromide displacement). Furthermore, the computational results showed that explicit accounting for solvent molecules is required to describe the free energy profile correctly. To verify the computational findings experimentally, chiral 1-benzyl-2-(bromomethyl)aziridines and 2-bromomethyl-1-tosylaziridines were treated with sodium methoxide in methanol. The presented work concerning the reactivity of 2-bromomethyl-1-tosylaziridine stands in contrast to the behavior of the corresponding 1-tosyl-2-(tosyloxymethyl)aziridine with respect to nucleophiles, which undergoes a clean ring-opening/ring-closure process with inversion of configuration at the asymmetric aziridine carbon atom.
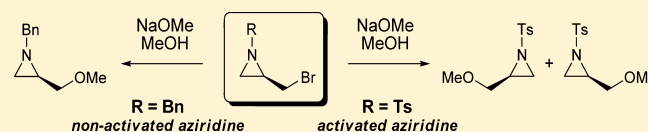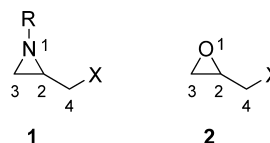
INTRODUCTION

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry due to the uncommon combination of reactivity, synthetic flexibility and atom economy.[1−9] Indeed, ring strain renders aziridines susceptible to ring-opening reactions that dominate their chemistry and makes them useful synthetic intermediates in the arsenal of the organic chemist.[10]

Among 2-(halomethyl)aziridines **1**, 2-(bromomethyl)-aziridines (X = Br) in particular comprise a peculiar class of aziridines and constrained β-halo amines with high synthetic potential.[11−13] Although structurally related to their oxygen analogues epihalohydrins **2**,[14,15] aziridines **1** have been studied to a far lesser extent in the chemical literature. In both systems, the electrophilic reactivity of the constrained heterocycle can be assessed relative to the haloalkyl moiety, meaning that nucleophiles can discriminate between three different electro-philic carbon atoms C2, C3, and C4 (Scheme 1). The regio- and chemoselectivity of nucleophilic attack is of particular importance in the design of synthetic protocols toward the preparation of valuable target compounds starting from aziridines **1** and epoxides **2**, which underlines the need for a

Scheme 1. 2-(Halomethyl)aziridines 1 and Epihalohydrins 2 (X = Halogen)

thorough investigation and rationalization of the reaction outcome.

The reactivity of epoxides **2** with respect to hydroxide and water has previously been evaluated theoretically by means of ab initio calculations, both in the gas phase and in continuum solvent, pointing to the conclusion that epoxides **2** are preferentially attacked at the unhindered carbon atom C3.[16,17] When compared to epoxides, the chemistry of aziridines is further complicated by the presence of an additional valency on the heteroatom, and since the mid-1960s, aziridines have been classified as "activated" or "nonactivated'" according to whether or not quaternization toward an aziridinium intermediate is required for nucleophilic ring-opening reactions.[18] This classification is intimately related to the nature of the N-substituent, i.e., its electron-withdrawing or electron-donating properties. From experimental data, it is clear that the nature of the N-substituent has a profound influence on the reactivity of 2-(bromomethyl)aziridines upon treatment with different nucleophiles. However, up to now, no detailed theoretical and experimental evaluation of the reactivity of aziridines **1** with respect to nucleophiles in terms of the underlying mechanistic pathways has been performed.

One of the most striking features of 2-(bromomethyl)-aziridines **3** is their general reactivity toward nucleophiles. Independent of the nature of the N-substituent, the corresponding 2-substituted aziridines **4** are isolated upon treatment of aziridines **3** with 1 equiv of a large variety of different nucleophiles (Scheme 2). Heteroatom-centered as

Scheme 2. Treatment of 2-(Bromomethyl)aziridines 3 with Nucleophiles

Nu = C-, O-, N-, S-, P-nucleophiles
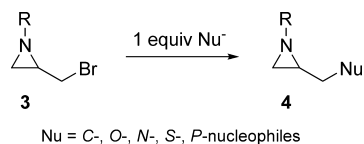
well as carbon-centered nucleophiles can be applied successfully in this reaction, enabling the synthesis of a wide range of aziridines **4** as interesting synthons for further elaboration.[19,20]

Although the net reaction comprises displacement of bromide by a nucleophile, the underlying mechanism of this transformation requires a more detailed investigation. As depicted in Scheme 3, chiral (2S)-2-(bromomethyl)aziridines

Scheme 3. Nucleophilic Substitution of (2S)-2-(Bromomethyl)aziridines 5 via Direct Substitution (Pathway a) and Ring Opening/Ring Closure at the Unhindered Aziridine Carbon Atom (Pathway b)
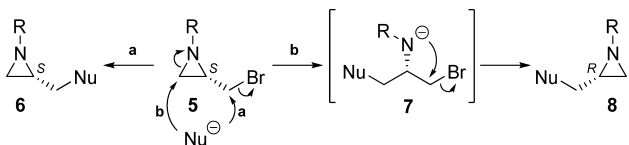
5 can undergo a direct S_N2 nucleophilic substitution at the halogenated carbon atom toward (2S)-aziridines **6** (pathway **a** retention of configuration) or, alternatively, the nucleophile can attack the unsubstituted aziridine carbon atom resulting in a ring-opened intermediate **7**, which is prone to undergo ring closure toward the substituted (2R)-aziridines **8** (pathway **b** inversion of configuration).

If both pathways are competitive, a mixture of both enantiomers will be obtained. It is clear that a deeper understanding of this mechanism is of high importance whenever the synthesis of chiral targets starting from chiral aziridines **5** is contemplated.

Sound experimental evidence has been provided in the literature with respect to the use of the similar 2-(tosyloxymethyl)aziridines in reaction with nucleophiles. It was demonstrated that the activated 1-tosyl-2-(tosyloxymethyl)aziridine undergoes selective ring opening at the less hindered carbon atom of the aziridine moiety upon treatment with organocuprates, immediately followed by ring closure with simultaneous displacement of the tosylate (pathway **b**, Scheme 3).[21] Furthermore, for N,O-bis-(diphenylphosphinyl)-2-(hydroxymethyl)aziridine, an aziridine with a different electron-withdrawing substituent at nitrogen, similar results have been published.[22] On the other hand, it has been proven that the substitution of nonactivated 1-(α-methylbenzyl)-2-(tosyloxymethyl)aziridine with sodium methoxide can proceed via direct S_N2 substitution with retention of configuration, leaving the aziridine moiety untouched (pathway **a**, Scheme 3) or that it can yield two different isomers, coming from both pathways **a** and **b** in Scheme 3, depending on the orientation of the tosyloxymethyl group with respect to the N-substituent.[23,24] Therefore, the stereochemical outcome of substitution reactions of chiral 2-(bromomethyl)aziridines is influenced by many factors, such as the identity and strength of the nucleophile, the leaving group capacity, the electron-withdrawing or electron-donating character of the N-substituent, and even the stereochemistry of the aziridine.

In the present paper, the reactivity of the activated 2-bromomethyl-1-tosylaziridine **9** and the nonactivated 1-benzyl-2-(bromomethyl)aziridine **10** (Scheme 4) with respect to the nucleophile sodium methoxide in methanol will be investigated for the first time from a theoretical point of view. Furthermore, their reactivity will be compared to the reactivity of their oxygen analogue epibromohydrin **11**. For all three species under study, the propensity of methoxide for nucleophilic attack at the three different electrophilic carbon atoms will be assessed. Next, the reactivity of the activated aziridine **9** and the nonactivated 1-(α-methylbenzyl)-2-(bromomethyl)aziridine **12** with regard to sodium methoxide in methanol is evaluated experimentally, particularly focusing on the competition between direct nucleophilic displacement of bromide (pathway **a**, Scheme 3) and a ring-opening/ring-closure process (pathway **b**, Scheme 3), to verify the theoretical findings. Furthermore, the reactivity of the activated 1-tosyl-2-(tosyloxymethyl)-aziridine **13** with regard to sodium methoxide in methanol is investigated experimentally in order to compare its reactive behavior with that of its brominated counterpart **9**.

■ RESULTS AND DISCUSSION

1. Theoretical Results. In this section, the reactivity of activated aziridine **9**, nonactivated aziridine **10**, and epoxide **11** (Scheme 4) with respect to sodium methoxide will be investigated theoretically. In order to discriminate between the three electrophilic carbon atoms in these three-membered rings, the nucleophilic attack of methoxide at all electrophilic centers (pathways **a**, **b** and **c**, Scheme 5) is investigated by means of density functional theory (DFT) calculations within the supermolecule approach (vide infra).

Attack of methoxide at the brominated carbon atom of aziridines **3** affords the corresponding 2-(methoxymethyl)-

Scheme 4. 2-Bromomethyl-1-tosylaziridine 9, 1-Benzyl-2-(bromomethyl)aziridine 10, Epibromohydrin 11, 1-(α-Methylbenzyl)-2-(bromomethyl)aziridine 12, and 1-Tosyl-2-(tosyloxymethyl)aziridine 13
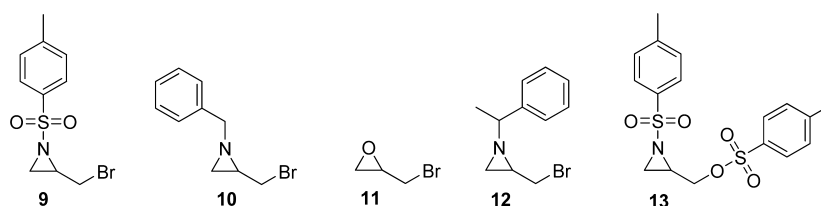
Scheme 5. Nucleophilic Attack of Methoxide at All Electrophilic Centers of Aziridines 3 and Epoxide 11
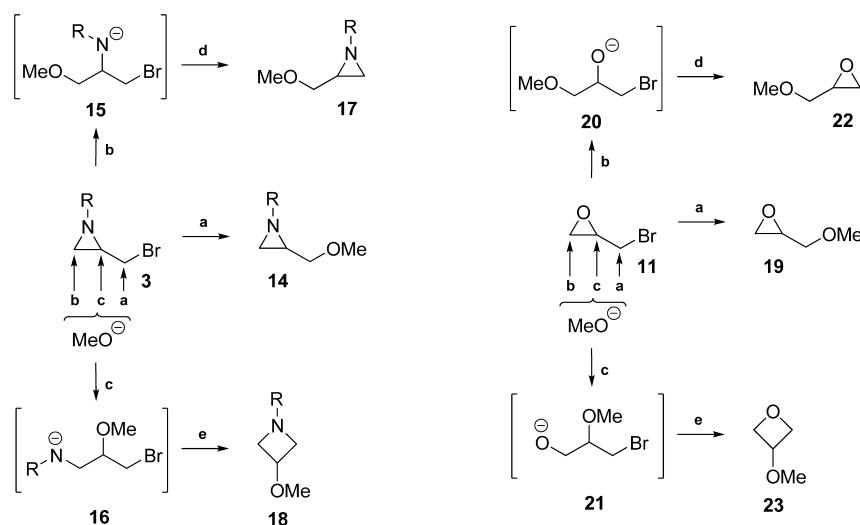
aziridines **14** through direct nucleophilic displacement (pathway **a**), whereas attack at the less hindered aziridine carbon atom results in intermediate β-halo amines **15** via ring opening (pathway **b**), which are readily converted into 2-(methoxymethyl)aziridines **17** via ring closure (pathway **d**). Alternatively, ring opening at the substituted aziridine carbon atom would afford intermediate γ-halo amines **16** (pathway **c**), which might be converted to 3-methoxyazetidines **18** via ring closure (pathway **e**), although this behavior has not been observed in experimental studies so far. On the other hand, the rearrangement of aziridines **3** (R = Ts) to 3-aminoazetidines is known in the literature, albeit based on a different mechanistic pathway.[25] The same pathways can be considered for epoxide **11**, resulting in 2-(methoxymethyl)epoxides **19** or **22** via pathways **a** and **b**, respectively, and 3-methoxyoxetane **23** via pathway **c**.

Computational Methodology. The B3LYP/6-31++G(d,p) level of theory was used for geometry optimizations.[26,27] Stationary points were characterized as minima (ground states) or first-order saddle points (transition states) via frequency calculations. IRC (intrinsic reaction coordinate) calculations[28−30] followed by full geometry optimizations were used to verify the corresponding reactant and product complexes. The B3LYP functional has been proven to produce good geometries but is less accurate for energy calculations.[31] Therefore energies were refined with the following methods: MPW1B95,[32] which has been shown to be efficient for aziridines,[33−37] and BMK[38] and MPW1K,[39,40] which are known for their good performance for describing kinetics of reactions in general. Previous studies have demonstrated the differences between theory and experiment for sulfur systems and concluded that the addition of *d* and *f* polarization

functions on the sulfur basis set gives reliable energies.[41−43] The MPW1B95, BMK, and MPW1K functionals were used with a combined basis set consisting of the 6-311+G(3df,2p) basis set for sulfur and the 6-31++G(d,p) basis set for all other atoms, since this method was shown to be adequate for calculations on sulfur-containing systems.[44] All thermal free energy corrections reported were taken from B3LYP/6-31++G(d,p) optimizations at 1 atm and 298 K. All computations were performed with the Gaussian 03 and Gaussian 09 program packages.[45,46]

Since the reactions under study take place in methanol, which has the potential to form hydrogen bonds with the reactive substrate, it is essential to investigate the influence of the solvent molecular environment on the reactions. The simplest method consists of using a continuum model,[47−50] where the solvent is modeled as a continuous medium characterized by a dielectric constant. However, in this case where explicit hydrogen bonds are possible, this methology is not preferred and a discrete solvent model (also called supermolecule approach or microsolvation),[34−37,44,51] in which discrete solvent molecules are placed around the chemically active species are expected to be more reliable. Ideally, the reactive species could be simulated by means of molecular dynamics calculations in a solvent box;[52,53] however, this approach is computationally very expensive and cannot be routinely applied. Furthermore, to account for potential long-range interactions, this "supermolecule" can be placed in a dielectric continuum, leading to a mixed implicit/explicit model.[54−56] Previous studies have shown that explicit solvation alone can give reliable results provided that it is used with sufficient care.[36] First of all, the number and orientation of the solvent molecules needs to be correctly chosen. For the
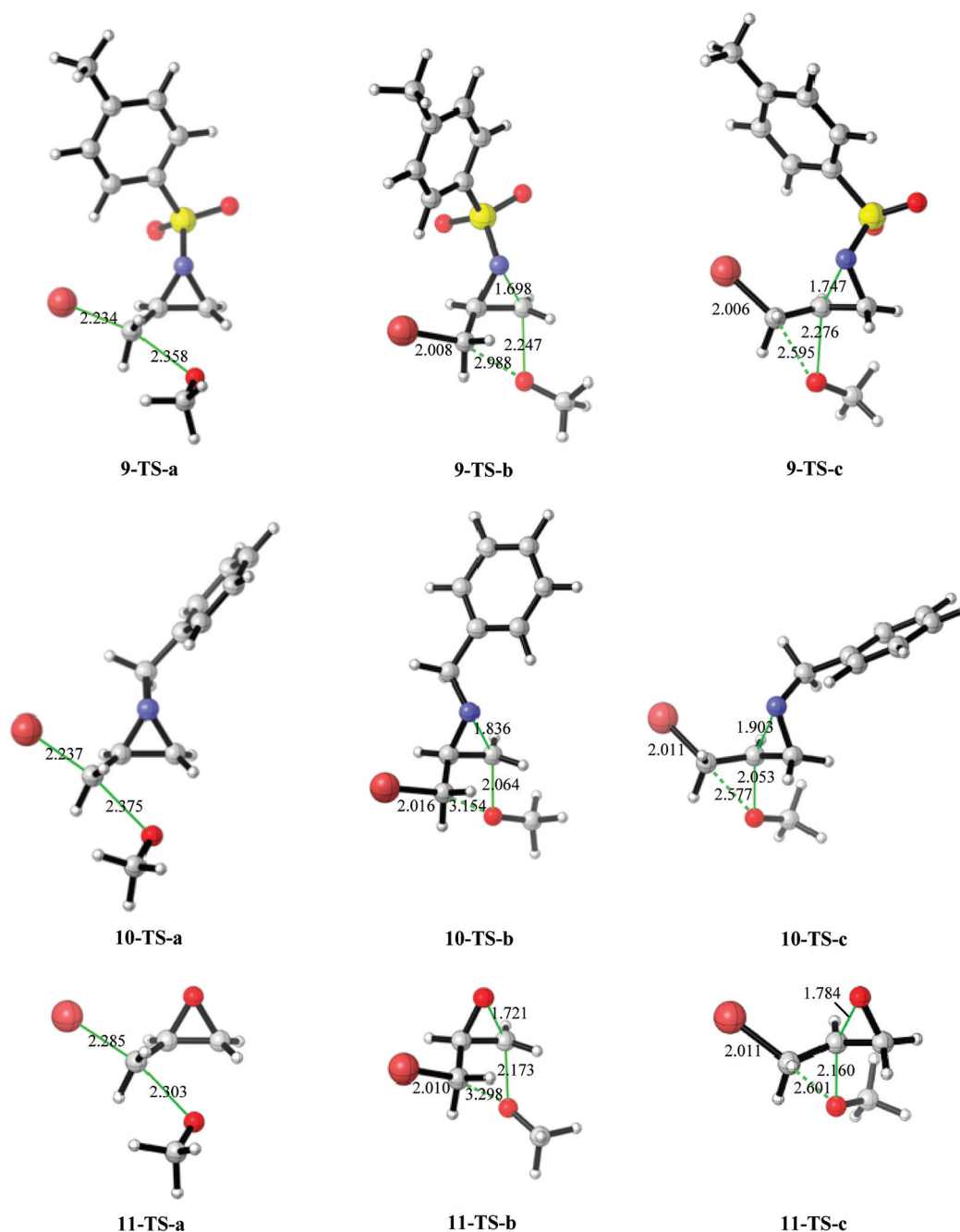
Figure 1. Transition state geometries for nucleophilic attack of methoxide at the electrophilic centers of **9–11**, without explicit solvent molecules. B3LYP/6-31++G(d,p) optimized structures. Some critical distances are given in Å. **TS** denotes Transition State. **a**, **b**, **c** denote pathways shown in Scheme 5.

reactions under study, where a protic solvent is used, the mobility of the solvent molecules is already restricted by H-bonds, but still a variety of orientations is possible. We will explicitly address the influence of the number and orientation of the methanol molecules on the reactive pathways in the Theoretical Results section. Another point of controversy is related to the choice of the reference state for the reactants. One could take either the separate reactants or the reactant complexes. Since the energy of the reactant complexes is usually considerably lower than the total energy of separate reactants, due to favorable complexation, activation barriers were calculated from the reactant complexes and not from the separate reactants. Although, we will show that for the present

study, the particular choice of the reference state does not alter the relative difference in activation barriers for the competitive pathways of nucleophilic attack. As we started from the reactant complexes, it was not necessary to take into account BSSE (basis set superposition error) corrections.[57]

Nucleophilic Attack of Methoxide at the Electrophilic Centers of 3-Membered Heterocycles. Analysis without Explicit Solvent Molecules. A thorough conformational analysis was performed on the three species under study to identify the most plausible conformers, which were then used to model the methoxide attack at the electrophilic centers. Furthermore, nitrogen inversion barriers were calculated for aziridines **9** and **10**. The barriers ($\Delta G^{\ddagger}$ = 45.8 and 66.3 kJ/mol

(MPW1B95) for **9** and **10**, respectively) are too low to allow isolation of the individual invertomers and rapid inversion is expected, leading to thermodynamic equilibrium in favor of the more stable *trans* invertomers. The conformational results and the investigation of the inversion barriers are given on pages S11−S14 and S15−S17 of the Supporting Information, respectively.

Transition state geometries and free energy profiles for attack of methoxide at the three electrophilic centers (Scheme 5) of **9**, **10**, and **11** without explicit solvent molecules are shown in Figures 1−4. In Figures 2 and 4, the subsequent ring-closing
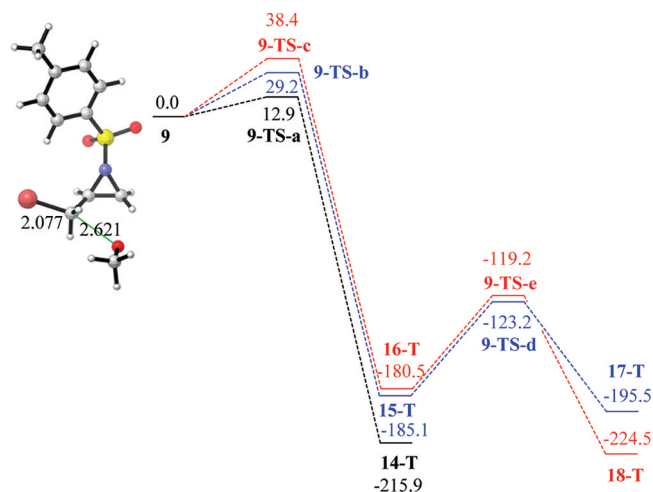

Figure 2. Gibbs free energy profiles (MPW1K/6-31++G(d,p)// B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of aziridine **9**, without explicit solvent molecules. 6-311+G(3df,2p) basis set on the sulfur atom. **T** denotes *N*-substituent = tosyl. **a−e** denote pathways shown in Scheme 5. Some critical distances are given in Å. Free energies in kJ/mol at 298 K and 1 atm.

Figure 3. Gibbs free energy profiles (MPW1K/6-31++G(d,p)// B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of aziridine **10**, without explicit solvent molecules. **B** denotes *N*-substituent = benzyl. **a−e** denote pathways shown in Scheme 5. Some critical distances are given in Å. Free energies in kJ/mol at 298 K and 1 atm.
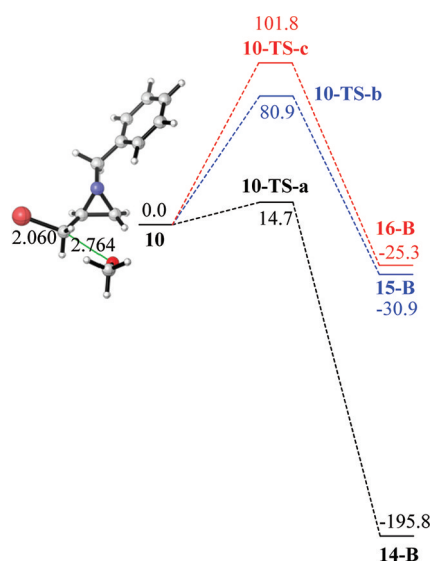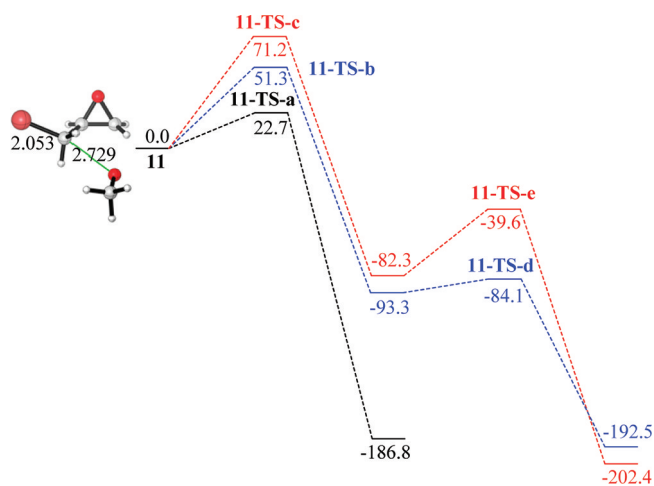

Figure 4. Gibbs free energy profiles (MPW1K/6-31++G(d,p)// B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of epoxide **11**, without explicit solvent molecules. **a−e** denote pathways shown in Scheme 5. Some critical distances are given in Å. Free energies in kJ/mol at 298 K and 1 atm.

reactions for the corresponding intermediates **15**, **16** and **20**, **21** derived from activated aziridine **9** and epoxide **11**, respectively, are also taken up for completeness (pathways **d** and **e**, Scheme 5). As will be shown below, these ring-closing reactions are less important for nonactivated aziridine **10**, since free energies of activation for ring opening are too high.

Energy refinements with the MPW1B95, BMK, and MPW1K functionals give the same trends in terms of the selectivity of methoxide attack at the electrophilic centers of the three-membered rings under study (see Table S6 of the Supporting Information for energies at all levels of theory). Barriers indicated in the following text are at the MPW1K level of theory. The calculations reveal a clear preference for pathway **a** (direct substitution at the brominated carbon atom by methoxide) for **9**−**11**. The difference in free energy of activation between pathway **a** and pathway **b** (ring opening at the less hindered carbon atom) is much smaller for activated aziridine **9** and epoxide **11** than for nonactivated aziridine **10** ($\Delta\Delta G^{\ddagger}$ = 16.3 and 28.6 versus 66.2 kJ/mol). In addition, the difference in free energy of activation between pathway **b** and pathway **c** (ring opening at the substituted carbon atom) is much smaller for activated aziridine **9** than for nonactivated aziridine **10** and epoxide **11** ($\Delta\Delta G^{\ddagger}$ = 9.2 versus 20.9 and 19.9 kJ/mol). Ont he basis of these gas-phase calculations, pathway **c** cannot be excluded for **9**, although this behavior has never been observed in experimental studies.

Solvent Approach: Explicit Solvent Molecules. Nucleophilic substitution reactions are known to be influenced by the solvent environment.[47,58] Therefore, the gas-phase results are extended toward a discrete solvent approach, as explained in the Computational Methodology section. The number of solvent molecules needed to accurately describe the chemical problem at hand was determined by studying the convergence behavior of the energy of solvation in terms of a systematically increasing number of solvent molecules. The number of methanol molecules on the methoxide oxygen atom, the bromine atom, and the ring heteroatoms were varied. A supermolecule model with five explicit methanol molecules, as shown in Figure 5 for the prereactive complex of aziridine **10**, was deduced (see pages S19−S22 of the Supporting
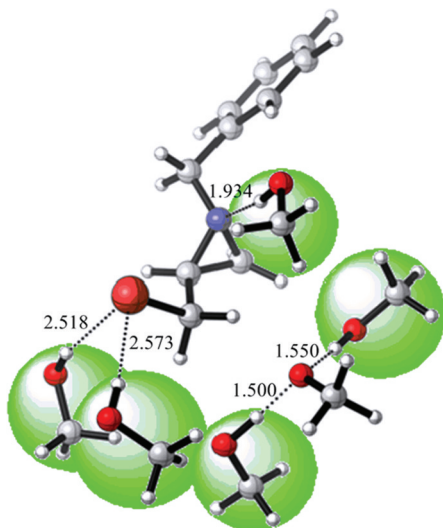
Figure 5. Prereactive complex of aziridine **10** with methoxide, solvated by five explicit methanol molecules. B3LYP/6-31++G(d,p) optimized structure. Some critical distances are given in angstroms.

Information for the complete investigation with figures). The bromine atoms and the methoxide anion are solvated with two methanol molecules, whereas the aziridine nitrogen or epoxide oxygen is solvated with one methanol molecule.

In parallel with this preliminary investigation on the number of solvating molecules, the selected supermolecule was further investigated by studying the Gibbs free energies of activation for nucleophilic attack of methoxide at the various electrophilic centers of aziridine **9** with a different number of explicit methanol molecules. The results of these calculations are shown in Figure 6 and give further evidence for the previously
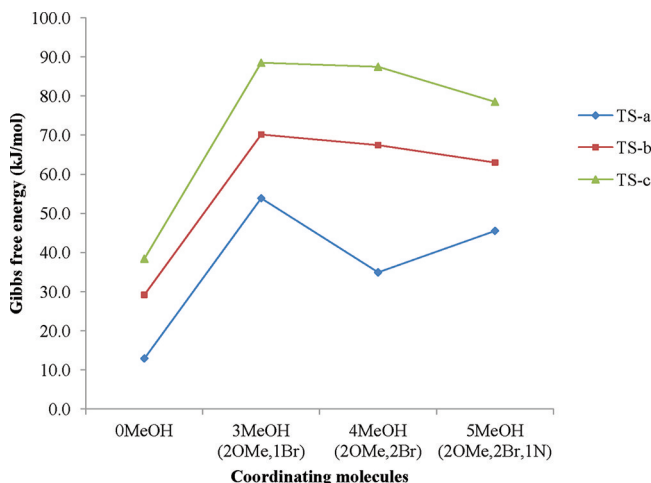

Figure 6. Relative Gibbs free energies of activation ($\Delta G^{\ddagger}$) for nucleophilic attack of methoxide at the electrophilic centers of aziridine **9**, with diffent amounts of explicit methanol molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31++G(d,p) energies with 6-311+G(3df,2p) basis set on the sulfur atom. Free energies at 298 K and 1 atm.

proposed supermolecule. The Gibbs free energies of activation nicely converge by adding an extra methanol molecule on the bromine atom and the nitrogen atom to the supermolecule with three methanol molecules (three on the methoxide oxygen and one on the bromine atom).

One concern regarding this approach is whether one selected minimum on the free energy surface is capable of accurately describing the behavior of the substrate in its true molecular environment. We investigated this by scanning the free energy surface for other minima of the supermolecule having a fixed number of coordinating methanol molecules. For the protic solvent under study, explicit hydrogen bonds are formed with the substrate and thus their mobility with respect to the substrate is a priori limited. The free energy results of the alternative conformers are added in Table S7 of the Supporting Information. The results show that energy variations among various conformers are small (a maximum of 10 kJ/mol) compared to the free energies of activation investigated in this study and more importantly, compared to the difference in energies of activation for nucleophilic attack of the methoxide on the various electrophilic centers (a minimum of 20 kJ/mol).

Transition state geometries and free energy profiles for attack of methoxide at the three electrophilic centers of **9–11** with five explicit methanol molecules are shown in Figures 7–10. Typical methoxide O···HOMe, Br···HOMe, epoxide O···HOMe, and aziridine N···HOMe distances are around 1.6, 2.5, 1.8, and 1.8 Å, respectively. Transition state and reactant critical distances (Å) and bond elongation percentages for nucleophilic attack of methoxide at the electrophilic centers of **9–11**, with and without explicit solvent molecules, are shown in Table 1. Critical distances are different for the transition states with explicit solvent molecules compared to the gas-phase results for all three species under study and for all three different nucleophilic attack trajectories. Solvated transition states are more "product-like", which can be seen by the extent of displacement of bromide (d(C4−Br) in **TS-a**) and ring opening (d(C3−N) in **TS-b** and d(C2−N) in **TS-c**). Bond elongation percentages were calculated with respect to reactants **9–11** in the gas phase and are higher by approximately 5% for transition states with explicit solvent molecules versus transition states from gas-phase calculations.

Solvation has significantly changed the landscape of the energy profiles (Figures 8–10 versus Figures 2–4). All activation energies have increased in the solvated systems. This is due to the stabilization of methoxide. The selectivity for attack at the various electrophilic centers is qualitatively the same at different electronic levels of theory; for completeness, these results are given in Table S8 of the Supporting Information. Barriers indicated in the following text are at the MPW1K level of theory. Pathway **a** (direct substitution at the brominated carbon atom by methoxide) is favored for all three species under study ($\Delta G^{\ddagger}$ = 45.5, 38.1, and 53.9 kJ/mol for **9**, **10** and **11**, respectively). Furthermore, the difference in free energy of activation between pathway **a** and pathway **b** (ring opening at the less hindered aziridine carbon atom) is much smaller for activated aziridine **9** and epoxide **11** than for nonactivated aziridine **10** ($\Delta\Delta G^{\ddagger}$ = 17.5 and 26.1 versus 78.8 kJ/mol), making pathway **b** feasible for **9** and **11**, and not for **10**. Furthermore, activation energies for the subsequent ring-closing reactions (pathways **d** and **e**) make these reactions feasible ($\Delta G^{\ddagger}$ = 44.2 and 33.9 kJ/mol for **9** and **11**, respectively). Calculations with explicit solvent molecules reveal a significant difference in free energy of activation between pathway **b** and pathway **c** (ring opening at the substituted aziridine carbon atom) for both activated aziridine **9** and epoxide **11** ($\Delta\Delta G^{\ddagger}$ = 15.6 and 18.9 kJ/mol, respectively). This fact indisputably shows the necessity of taking into account explicit solvation to obtain the correct reaction profiles.
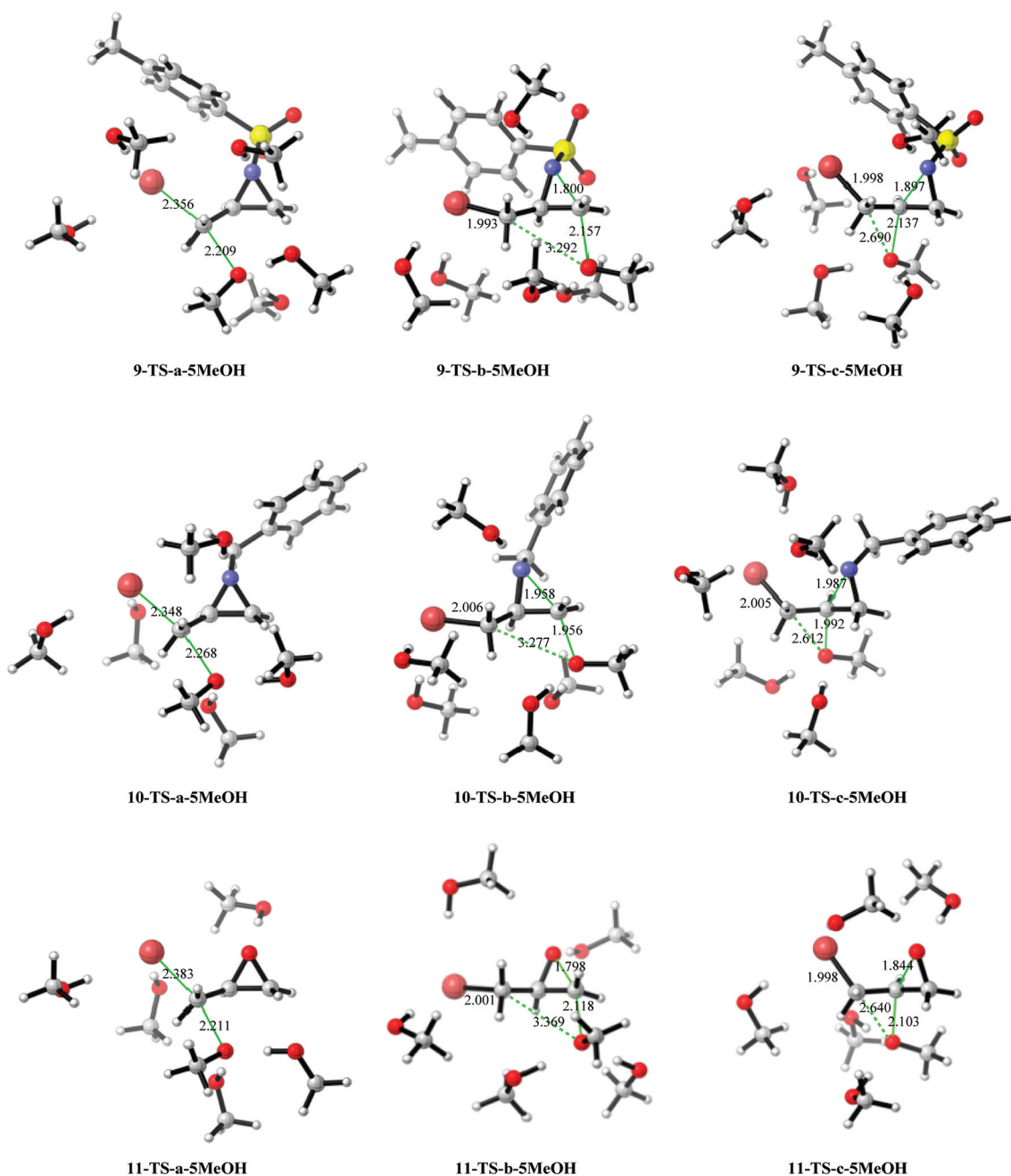
Figure 7. Transition state geometries for nucleophilic attack of methoxide at the electrophilic centers of **9–11**, with five explicit methanol molecules. B3LYP/6-31++G(d,p)-optimized structures. Some critical distances are given in angstroms. **TS** denotes transition state. **a–c** denote pathways shown in Scheme 5. **5MeOH** denotes five explicit methanol molecules.

For transparency, relative Gibbs free energies of activation ($\Delta G^{\ddagger}$) and differences in relative Gibbs free energies of activation ($\Delta\Delta G^{\ddagger}$) for nucleophilic attack of methoxide at the electrophilic centers of **9–11** with and without explicit solvent molecules are summarized in Table 2. In addition, Table S9 of the Supporting Information shows the individual contributions of the enthalpy and entropy to the Gibbs free energies. These results demonstrate that the major contribution to the activation barriers originates from enthalpy, entropy contributions are merely the same. This is to be expected as the selected supermolecule is very similar in all reactive pathways. In the present study, the particular choice of the reference state does not alter the difference in activation barriers for the competitive pathways of nucleophilic attack. Furthermore, Table S10 of the

Supporting Information shows a comparison between the separate reactants and the reactant complexes as the reference state for the reactants. For the present study the particular choice does not alter the results on the competitive pathways for nucleophilic attack and since the energy of the reactant complexes is usually considerably lower than the total energy of separate reactants due to favorable complexation, activation barriers were calculated from the reactant complexes and not from the separate reactants.

Both gas-phase calculations and calculations with explicit solvent molecules reveal a clear preference for direct substitution at the brominated carbon atom (pathway **a**) for all species under study. This is in contrast with the expectations for activated aziridine **9**, since experiments have shown that the

Figure 8. Gibbs free energy profiles (MPW1K/6-31++G(d,p)//B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of aziridine **9**, with five explicit methanol molecules. 6-311+G(3df,2p) basis set on the sulfur atom. T denotes *N*-substituent = tosyl. **a−e** denote pathways shown in Scheme 5. **5MeOH** denotes five explicit methanol molecules. Some critical distances are given in angstroms. Free energies in kJ/mol at 298 K and 1 atm.
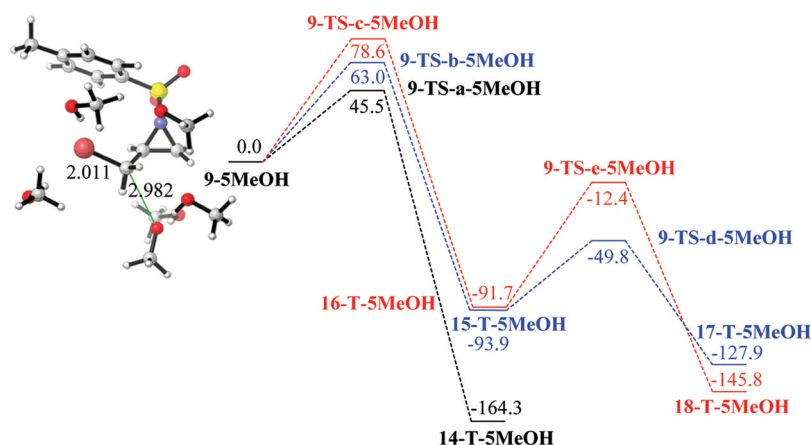

Figure 9. Gibbs free energy profiles (MPW1K/6-31++G(d,p)//B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of aziridine **10** with five explicit methanol molecules. B denotes *N*-substituent = benzyl. **a−e** denote pathways shown in Scheme 5. **5MeOH** denotes five explicit methanol molecules. Some critical distances are given in angstroms. Free energies in kJ/mol at 298 K and 1 atm.
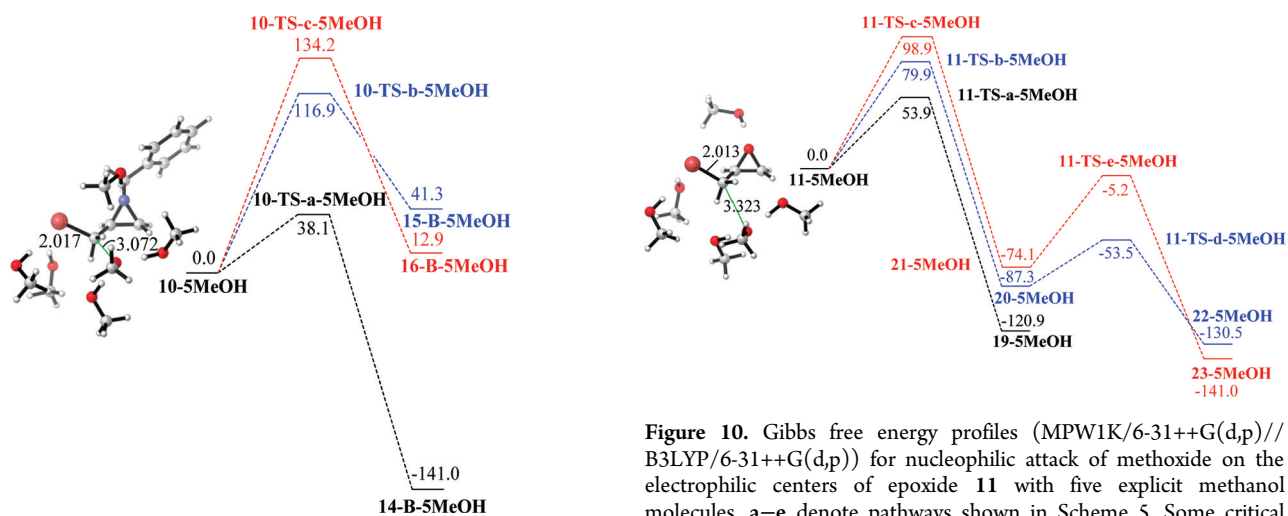

Figure 10. Gibbs free energy profiles (MPW1K/6-31++G(d,p)//B3LYP/6-31++G(d,p)) for nucleophilic attack of methoxide on the electrophilic centers of epoxide **11** with five explicit methanol molecules. **a−e** denote pathways shown in Scheme 5. Some critical distances are given in angstroms. **5MeOH** denotes five explicit methanol molecules. Free energies in kJ/mol at 298 K and 1 atm.

closely related activated 1-tosyl-2-(tosyloxymethyl)aziridine undergoes a selective ring-opening/ring-closure process upon treatment with cuprates (pathway **b**).[21] Although former ab initio calculations of the reactivity of epihalohydrins with respect to hydroxide and water pointed to the conclusion that epichlorohydrins are preferentially opened at the unhindered epoxide carbon atom (pathway **b**),[16,17] epoxide **11** is known to behave differently in that respect. All energies of activation have increased in the solvated systems because of stabilization of the reactive methoxide. On the basis of the calculations with explicit solvent molecules, ring-opening reactions are feasible for activated aziridine **9** and epoxide **11**, although ring opening at the substituted aziridine carbon (pathway **c**) of **9** and at both epoxide carbon atoms of **11** are less probable since they are quite high in energy. Ring-opening reactions are not feasible for nonactivated aziridine **10**, as initially expected.
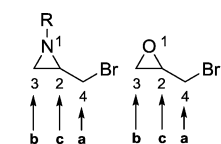
2. Experimental Results.
In addition to computational studies, the reactivity of activated and nonactivated 2-(bromomethyl)aziridines with respect to sodium methoxide in methanol was evaluated experimentally, particularly focusing on the competition between ring opening/ring closure and direct nucleophilic displacement of bromide, in order to confirm theoretical predictions discussed earlier.

At first, racemic 2-bromomethyl-1-tosylaziridine *rac*-**9** was prepared from allylamine **24** according to a literature protocol (involving consecutive treatment with HBr, Br₂, and TsCl in water)[19] and transformed into the corresponding racemic 2-(methoxymethyl)aziridine *rac*-**25** upon treatment with sodium methoxide in methanol (Scheme 6).[19] Both *rac*-**9** and *rac*-**25** were then used to study the discrimination between both enantiomeric pairs by means of ^{1}H NMR analysis (CDCl₃), for which the use of 5 equiv of the chiral shift reagent Pirkle alcohol resulted in the observation of distinct diastereotopic proton signals pertaining to one of the enantiotopic aziridine protons [(H_{trans}CH)N].

Second, the enantiomerically pure 2(*S*)-(bromomethyl)-aziridine 2(*S*)-**9** was prepared through conversion of 2(*R*)-(tosyloxymethyl)aziridine 2(*R*)-**13**, which was synthesized by
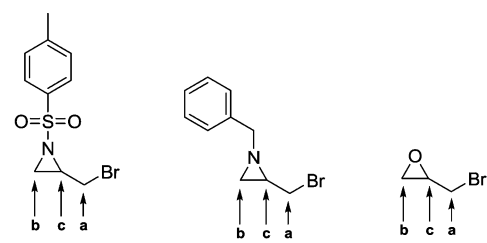
Table 1. Transition State and Reactant Critical Distances (Å) and Bond Elongation Percentages for Nucleophilic Attack of Methoxide at the Electrophilic Centers of 9−11, with and without Explicit Solvent Molecules[a]

	pathway a		pathway b		pathway c	
	Gas phase	*Solvated*	*Gas phase*	*Solvated*	*Gas phase*	*Solvated*
	d(C4-Br)	d(C4-Br)	d(C3-N/O)	d(C3-N/O)	d(C2-N/O)	d(C2-N/O)
9	1.975		1.478		1.481	
9-TS	2.237	2.348	1.698	1.8	1.747	1.897
P (%)	**13.3**	**18.9**	**14.9**	**21.8**	**18.0**	**28.1**
10	1.980		1.464		1.464	
10-TS	2.285	2.383	1.836	1.958	1.903	1.987
P (%)	**15.4**	**20.4**	**25.4**	**33.7**	**30.0**	**35.7**
11	1.977		1.442		1.437	
11-TS	2.234	2.356	1.721	1.798	1.784	1.844
P (%)	**13.0**	**19.2**	**19.3**	**24.7**	**24.1**	**28.3**

[a]Bond elongation percentages P (%) = $(d_{TS} - d_{reactant})/(d_{reactant})$ in bold.

Table 2. Summarizing Table: Relative Gibbs Free Energies of Activation ($\Delta G^{\ddagger}$) and Differences in Relative Gibbs Free Energies of Activation ($\Delta\Delta G^{\ddagger}$) for Nucleophilic Attack of Methoxide at the Electrophilic Centers of 9−11, with and without Explicit Solvent Molecules[a−c]

|		9	10	11
Gas phase	$\Delta G^{\ddagger}_{a}$	12.9	14.7	22.7
	$\Delta G^{\ddagger}_{b}$	29.2	80.9	51.3
	$\Delta G^{\ddagger}_{c}$	38.4	101.8	71.2
	$\Delta\Delta G^{\ddagger}_{b-a}$	16.3	66.2	28.6
	$\Delta\Delta G^{\ddagger}_{c-b}$	9.2	20.9	19.9
Solvated	$\Delta G^{\ddagger}_{a}$	45.5	38.1	53.9
	$\Delta G^{\ddagger}_{b}$	63.0	116.9	79.9
	$\Delta G^{\ddagger}_{c}$	78.6	134.2	98.9
	$\Delta\Delta G^{\ddagger}_{b-a}$	17.5	78.8	26.1
	$\Delta\Delta G^{\ddagger}_{c-b}$	15.6	17.3	18.9

[a]MPW1K/6-31++G(d,p)//B3LYP/6-31++G(d,p) energies with 6-311+G(3df,2p) basis set on the sulfur atom. [b]Free energies in kJ/mol at 298 K and 1 atm. [c]$\Delta\Delta G^{\ddagger}_{b-a} = \Delta G^{\ddagger}_{b} - \Delta G^{\ddagger}_{a}$; $\Delta\Delta G^{\ddagger}_{c-b} = \Delta G^{\ddagger}_{c} - \Delta G^{\ddagger}_{b}$.

Scheme 6. Synthesis of *rac*-2-Methoxymethyl-1-tosylaziridine *rac*-25
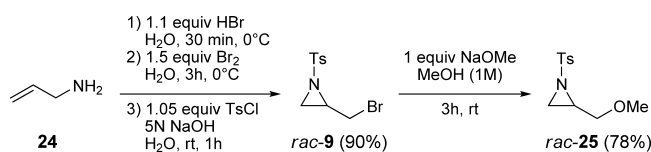
means of a modified literature protocol (Scheme 7).[21] To that end, readily available (S)-serine methyl ester **26** was N-tosylated, followed by protection of the free hydroxyl group with *tert*-butyldimethylsilyl chloride toward α-N-tosylamino ester **27** in 81% yield. Reduction of **27** was performed using

sodium borohydride in the presence of lithium chloride to produce β-amino alcohol **28**.[59] Compound **28** was converted into the corresponding aziridine **29** in 86% yield via a Mitsunobu reaction using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF. Further desilylation of **29** upon treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF followed by tosylation of the alcohol with tosylchloride in CH_2Cl_2 produced aziridine 2(R)-**13** in 63% yield over two steps (Scheme 7). Finally, 2(R)-**13** was treated with tetra-*n*-butylammonium bromide (TBAB) in acetonitrile, affording the desired enantiomerically pure aziridine 2(S)-**9** in excellent yield (96%) (Scheme 7) through a ring-opening/ring-closure protocol based on the reactivity profile of **13** as

Scheme 7. Synthesis of 2(S)-Bromomethyl-1-tosylaziridine 2(S)-9
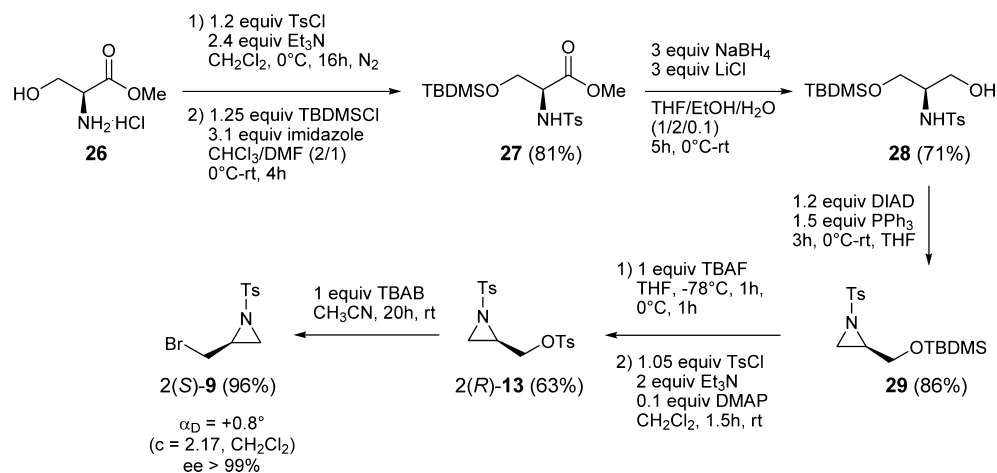
described in the literature[19] and supported by ^{1}H NMR analysis using Pirkle alcohol.

In the next part, the reactivity of 2-(bromomethyl)aziridine 9 toward methoxide was assessed and compared with that of the corresponding 2-(tosyloxymethyl)aziridine 13. First, 2(R)-13 was converted into 2(S)-25 upon treatment with NaOMe in methanol (1 M) (Scheme 8). No racemization of the

Scheme 8. Preparation of 2-Methoxymethyl-1-tosylaziridine 25
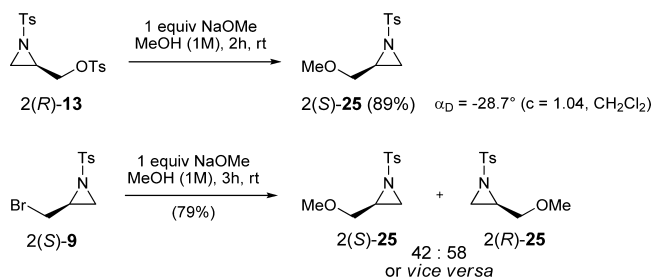
asymmetric aziridine carbon atom was observed upon ^{1}H NMR analysis using Pirkle alcohol, thus supporting the reactivity profile of 13 with regard to nucleophiles (i.e., exclusively via a ring-opening/ring-closure protocol) as described in the literature for organocuprates.[21] Apparently, also the oxygen nucleophile methoxide exhibits the same selectivity. It should be mentioned that the formation 1,3-dimethoxy-N-tosyl-2-propylamine was observed as well due to a second addition of methoxide to the initially formed 2(S)-25.

A similar reaction was performed on 2(S)-9, providing a scalemic mixture of 2(S)-25 and 2(R)-25 (er = 42:58 or vice versa) after treatment with sodium methoxide in methanol (1 M) (Scheme 8), which was evidenced by ^{1}H NMR analysis using Pirkle alcohol. Additionally, 2(S)-9 was treated with sodium methoxide in methanol at room temperature using different concentrations, but no significant changes regarding the enantiomeric ratio were observed (2 M NaOMe in MeOH: er = 43:57; 0.5 M NaOMe in MeOH: er = 44:56). Again, the presence of 1,3-dimethoxy-N-tosyl-2-propylamine was observed in the reaction mixtures, and higher amounts of this side product were formed when a higher concentration of sodium methoxide was used.

The above-described experimental results verified the rather unexpected conclusion from theoretical calculations that competition between ring opening/ring closure and direct nucleophilic displacement of bromide takes place upon treatment of aziridine 9 with nucleophiles, whereas a straightforward ring-opening/ring-closure process with inversion of configuration at the asymmetric center occurs when aziridine 13 is used instead.

In light of these surprising results, efforts were devoted to evaluate the reactivity of nonactivated 2-(bromomethyl)-aziridines with respect to sodium methoxide as well. To discriminate between the two possible routes toward the corresponding 2-(methoxymethyl)aziridine, i.e., direct bromide displacement versus a ring-opening/ring-closure protocol, the reference (1R,2R)-2-methoxymethyl-1-(α-methylbenzyl)-aziridine 31 was synthesized from (1R,2R)-1-(α-methylben-zyl)-2-(hydroxymethyl)aziridine 30 by a Williamson ether synthesis using sodium hydride and iodomethane in THF in 94% yield (Scheme 9, method a).[23] The alternative approach

Scheme 9. Synthesis of (1R,2R)-2-Methoxymethyl-1-(α-methylbenzyl)aziridine 31
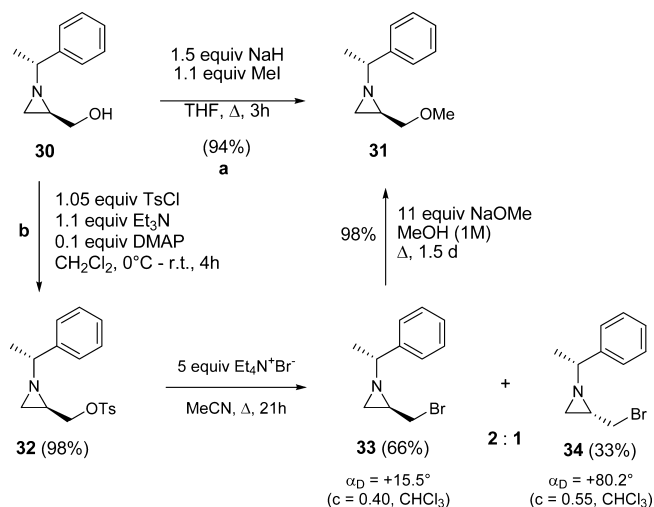
for the synthesis of 31 commenced with tosylation of 30 using tosyl chloride in CH₂Cl₂ in the presence of triethylamine and a catalytic amount of DMAP, furnishing (1R,2R)-1-(α-methyl-benzyl)-2-(tosyloxymethyl)aziridine 32[12] in an excellent yield

(Scheme 9, method **b**). Compound **32** was then subjected to a substitution reaction using tetraethylammonium bromide (TEAB) in CH$_3$CN, resulting in a mixture of (1*R*,2*R*)-1-(*α*-methylbenzyl)-2-(bromomethyl)aziridine **33** and (1*R*,2*S*)-1-(*α*-methylbenzyl)-2-(bromomethyl)aziridine **34** (ratio ~2/1, overall yield 97%). This result showed that aziridine **32** underwent both nucleophilic attack at the exocyclic methylene carbon with displacement of the leaving group and attack at the less hindered carbon atom of the aziridine moiety followed by ring closure, which is in accordance with previous findings described in the literature.[24]

After separation of both diastereomers by silica gel column chromatography (petroleum ether/ethyl acetate 4:1), the major isomer **33** was treated with an excess (11 equiv) of sodium methoxide in methanol (1M) under reflux, resulting in a single reaction product **31**. The comparison of aziridines **31** obtained via two different reaction pathways (**a** and **b** in Scheme 9) by means of various techniques (^{1}H NMR, ^{13}C NMR, IR, and MS) proved these compounds to be identical, showing that the last step of method **b** occurs exclusively *via* direct nucleophilic displacement of bromide by methoxide furnishing 2(*R*)-**31** with retention of configuration, whereas the epimeric 2(*S*)-**31** would have been formed if ring opening/ring closure had taken place. In contrast to the rather unexpected results in the case of activated aziridine **9**, nonactivated aziridine **33** was shown to exhibit a straightforward reactivity with respect to sodium methoxide as initially expected.

CONCLUSIONS

The reactivity of activated and nonactivated 2-(bromomethyl)-aziridines with regard to sodium methoxide has been evaluated both theoretically and experimentally, pointing to the conclusion that 1-benzyl-2-(bromomethyl)aziridines exclusively undergo direct displacement of bromide, whereas for 2-bromomethyl-1-tosylaziridines, competition between ring opening/ring closure at the less hindered aziridine carbon atom and direct displacement of the bromide was observed. The formation of a mixture of (*R*)- and (*S*)-2-(methoxymethyl)aziridine starting from an enantiopure 2-bromomethyl-1-tosylaziridine stands in contrast to the behavior of the corresponding 1-tosyl-2-(tosyloxymethyl)aziridine, which undergoes a clean ring-opening/ring-closure process with inversion of configuration at the asymmetric aziridine carbon atom. In addition, we have critically evaluated the effect of solvent environment on the computational results. We have found that for the chemical problem at hand where the solvent is able to make explicit hydrogen bonds with the reacting substrate, the supermolecule approach gives a fair representation of the molecular environment. On the other hand, explicit accounting for the methanol environment was found to be essential to acquire an adequate representation of the free energy surface and the competition between the various attack modes of methoxide at the different electrophilic centers.

EXPERIMENTAL SECTION

Synthesis of Chiral 2-Bromomethyl-1-(*α*-methylbenzyl)-aziridines 33 and 34. To a solution of (1*R*,2*R*)-1-(*α*-methylbenzyl)-2-(tosyloxymethyl)aziridine **32**[12] (0.99 g, 3 mmol) in MeCN (10 mL) was added tetraethylammonium bromide (2.30 g, 15 mmol, 5 equiv), and the reaction mixture was heated under reflux for 21 h. Extraction with CH$_2$Cl$_2$ (3 × 15 mL), drying (MgSO$_4$), filtration of the drying agent, and evaporation of the solvent afforded a mixture of (1*R*,2*R*)-2-bromomethyl-1-(*α*-methylbenzyl)aziridine **33** and (1*R*,2*S*)-

2-bromomethyl-1-(*α*-methylbenzyl)aziridine **34** (ratio ~2/1, overall yield 97%), which were separated by silica gel column chromatography (petroleum ether/ethyl acetate 4:1).

(1*R*,2*R*)-2-(Bromomethyl)-1-(*α*-methylbenzyl)aziridine 33: yield 65% (0.47 g); white solid; mp = 45.9−47.8 °C; R_f = 0.31 (petroleum ether/EtOAc 4:1); [*α*]$^{28}_D$ = +15.5 (*c* = 0.40, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.44 (3H, d, *J* = 6.6 Hz), 1.44 (1H, d, *J* = 6.6 Hz), 1.60 (1H, d, *J* = 2.8 Hz), 1.85−1.89 (1H, m), 2.42 (1H, q, *J* = 6.6 Hz), 3.17 and 3.44 (2H, 2 x dd, *J* = 10.5, 8.3, 5 Hz), 7.15−7.30 (5H, m); ^{13}C NMR (75 MHz, ref = CDCl$_3$) δ 23.7 (CH$_3$), 35.3 (CH$_2$), 35.9 (CH), 41.2 (CH$_2$), 69.6 (CH), 126.9 (CH), 127.2 (CH), 128.5 (CH), 144.2 (C); IR (neat, cm^{-1}) ν_{max} = 3034, 2923, 2964, 2838, 1493, 1450, 1422, 1223, 1165, 958, 758, 702, 629; MS *m/z* 240/2 (M$^+$ + 1, 100); HRMS *m/z* (ESI) calcd for C$_{11}$H$_{15}$BrN [MH]$^+$ 240.0388, found 240.0388.

(1*R*,2*S*)-2-(Bromomethyl)-1-(*α*-methylbenzyl)aziridine 34: yield 33% (0.24 g); light yellow oil; R_f = 0.51 (petroleum ether/EtOAc 4:1); [*α*]$^{28}_D$ = +80.2 (*c* = 0.55, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.42 (3H, d, *J* = 6.6 Hz), 1.64 (1H, d, *J* = 6.1 Hz), 1.88 (1H, d, *J* = 3.3 Hz), 1.80−1.90 (1H, m), 2.53 (1H, q, *J* = 6.6 Hz), 3.13 and 3.31 (2H, 2 x dd, *J* = 10.2, 6.9, 5.8 Hz), 7.24−7.37 (5H, m); ^{13}C NMR (75 MHz, ref = CDCl$_3$) δ 23.1 (CH$_3$), 34.8 (CH$_2$), 35.5 (CH), 39.5 (CH$_2$), 69.8 (CH), 127.0 (CH), 127.3 (CH), 128.4 (CH), 144.1 (C); IR (neat, cm^{-1}) ν_{max} = 3026, 2968, 2926, 2837, 1493, 1448, 1352, 1240, 1222, 1069, 971, 755, 698, 640; MS *m/z* 240/2 (M$^+$ + 1, 100).

ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates and energies of the optimized geometries (B3LYP/6-31++G(d,p)) of ground states; Cartesian coordinates, energies, imaginary and low frequencies of the optimized geometries (B3LYP/6-31++G**) of transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: saron.catak@UGent.be; norbert.dekimpe@UGent.be; veronique.vanspeybroeck@UGent.be.

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