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Opposite Regiospecific Ring Opening of 2-(Cyanomethyl)aziridines by Hydrogen Bromide and Benzyl Bromide: Experimental Study and Theoretical Rationalization

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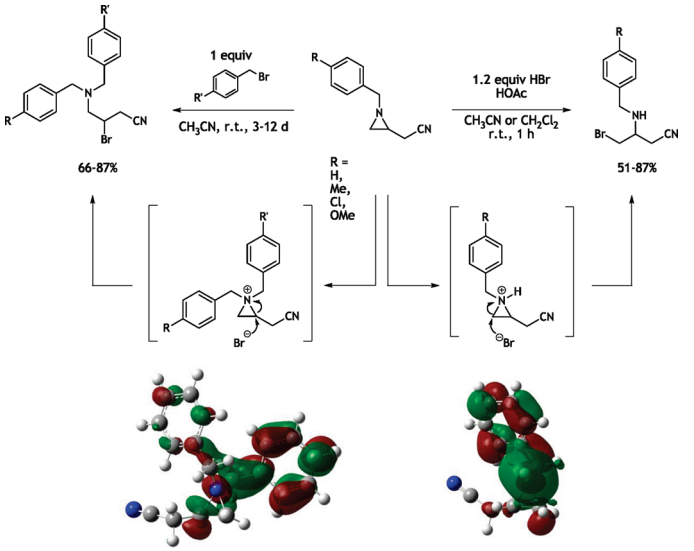

Ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines with HBr afforded 3-(arylmethyl)amino-4-bromobutyronitriles via regiospecific ring opening at the unsubstituted aziridine carbon. Previous experimental and theoretical reports show treatment of the same compounds with benzyl bromide to furnish 4-amino-3-bromobutanenitriles through ring opening at the substituted aziridine carbon. To gain insights into the regioselective preference with HBr, reaction paths have been analyzed with computational methods. The effect of solvation was taken into account by the use of explicit solvent molecules. Geometries were determined at the B3LYP/6-31++G(d,p) level of theory, and a Grimme-type correction term was included for long-range dispersion interactions; relative energies were refined with the meta-hybrid MPW1B95 functional. Activation barriers confirm preference for ring opening at the unsubstituted ring carbon for HBr. HBr versus benzyl bromide ring opening was analyzed through comparison of the electronic structure of corresponding aziridinium intermediates. Although the electrostatic picture fails to explain the opposite regiospecific nature of the reaction, frontier molecular orbital analysis of LUMOs and nucleophilic Fukui functions show a clear preference of attack for the substituted aziridine carbon in the benzyl bromide case and for the unsubstituted aziridine carbon in the HBr case, successfully rationalizing the experimentally observed regioselectivity.

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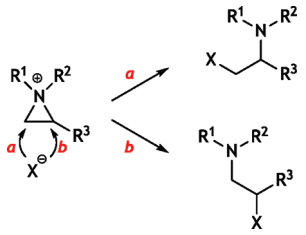
Introduction

The aziridine moiety represents one of the most valuable three-membered ring systems in synthetic organic chemistry,[1−11] and regio-controlled ring-opening reactions of C-substituted aziridines constitute useful tools in organic synthesis for the preparation of a large variety of functionalized nitrogen-containing target compounds.

Ring opening of activated aziridines, i.e., aziridines bearing an electron-withdrawing group on the nitrogen, has been studied intensively in the literature.[4] Nonactivated aziridines, however, have to be activated prior to ring opening because of the presence of an electron-donating substituent on the nitrogen and have been evaluated to a limited extent up to now. Nevertheless, the reactivity and applications of nonactivated aziridines are different and often complementary as compared to activated aziridines and epoxides, providing interesting opportunities for the selective synthesis of a variety of valuable amines. The most common approach for the activation of nonactivated aziridines involves the formation of highly electrophilic aziridinium intermediates through N-alkylation or complexation with a Lewis acid, which then can easily be opened by different types of nucleophiles. In that respect, the ring opening of aziridinium salts by halides constitutes a convenient approach toward β-halo amines, which are useful building blocks in organic chemistry.[12−15] If 2-substituted aziridines are used for the synthesis of the corresponding β-halo amines, the issue of regioselectivity in the ring opening of the intermediate aziridinium salts becomes important. As depicted in Scheme 1, ring opening can occur at the unhindered (path a) or the hindered aziridine carbon atom (path b), leading either to primary halides (path a) or to secondary halides (path b).

In this respect, the ring opening of 2-acyl[16,17] and 2-arylaziridinium salts,[18] obtained through reaction of the starting aziridines with acid chlorides, has been studied in the literature, pointing to a preferential ring opening at the substituted aziridine carbon atom. This effect can be explained considering the high electrophilicity of the substituted aziridine carbon atom in 2-acyl- and 2-arylaziridines. A less pronounced yet similar regioselectivity was observed in the ring opening of

SCHEME 1. Ring Opening of Aziridinium Salts



2-(cyanomethyl)aziridines with acid chlorides, affording mainly *N*-(2-chloro-3-cyanopropyl)amides through ring opening at the substituted position.[19] However, also the opposite regioselectivity has been described sporadically, e.g., upon reaction of a methyl aziridine-2-carboxylate with acetyl chloride.[20] Furthermore, the reaction of alkyl aziridine-2-carboxylates with hydrogen halide (hydrogen chloride[21] or hydrogen bromide[22]) has been evaluated, resulting in ring opening at the more hindered carbon atom. If 2-(trifluoromethyl)aziridines are used instead, *N*-(1-halomethyl-2,2,2-trifluoroethyl)amines are obtained via ring opening at the unsubstituted aziridine carbon atom.[23,24] A different class of substrates, i.e., 2-(bromomethyl)-,[25] 2-(aryloxymethyl)-,[26] 2-(alkanoyloxymethyl)-,[27] 2-(cyanomethyl)-,[28] and 2-(cyanoethyl)aziridines,[29,30] has been used extensively in ring-opening reactions with arylmethyl bromides in acetonitrile. In all cases, the intermediate aziridinium salts were opened regiospecifically at the substituted carbon atom, and these experimental results have been rationalized on the basis of DFT-based calculations.[28,31−33] In analogy, the ring opening of 2-alkyl-substituted aziridinium salts by chloride at the more hindered position has been reported recently, thus affording the thermodynamic products.[34] Alternative regiochemistry in the ring opening of aziridines with HBr, which was later rectified by the present authors,[35] have appeared in literature.

The use of aziridinium ions for regio- and stereoselective ring-opening reactions remains a challenging topic in

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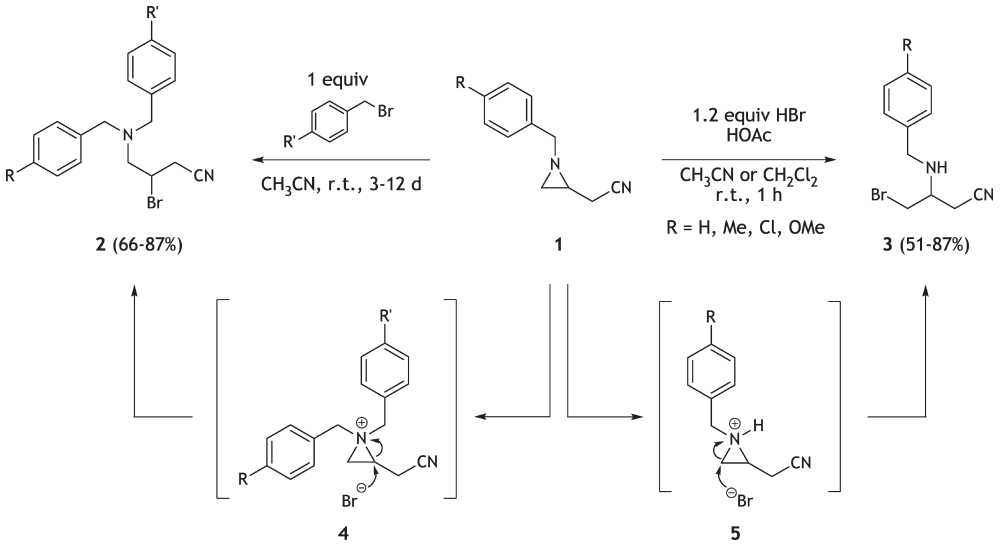
SCHEME 2. Ring Opening of 1-Arylmethyl-2-(cyanomethyl)aziridines by HBr and Benzyl Bromide



organic chemistry, and a thorough insight into the role of the different factors can result in a common and general use of aziridinium salts as versatile substrates in organic synthesis. In recent years, many efforts have been devoted to the development of new methods for the biocatalytic conversion of aminonitriles into the corresponding amino acids,[36−40] and as a consequence, the search for novel types of functionalized aminonitrile derivatives has gained much interest and has become an important challenge in organic synthesis.[41,42] In that respect, the use of 2-(cyanomethyl)aziridines has been studied to a limited extent and might provide a convenient entry into a variety of novel aminonitrile derivatives.

In the present paper, the ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines with HBr in acetonitrile or dichloromethane is described, affording 3-(arylmethyl)amino-4-bromobutyronitriles via regiospecific ring opening at the unsubstituted carbon atom. It is clear that the regioselectivity associated with the ring opening of C-substituted aziridinium salts is a complex issue, in which the nature of the substrate, the nucleophile, and the solvent can be of importance. Theoretical methods used in this study are ideally suited to discriminate between the various effects mentioned, and when combined with experimental data, this approach can lead to an in-depth understanding of the factors determining the reaction outcome. Moreover, understanding the underlying factors for the regioselective preference is of high interest, since this knowledge may eventually be useful in the selective synthesis of relevant nitrogen-containing target compounds.

Results and Discussion

Experimental Results. 1-Arylmethyl-2-(cyanomethyl)aziridines **1** can be prepared easily and in high yields from 1-arylmethyl-2-(bromomethyl)aziridines[43−46] upon treatment with 1 equiv of potassium cyanide in DMSO and heating at 60−70 °C for 3 h.[47] The search for new pathways toward aminonitriles as precursors of the corresponding amino acids is an important challenge in organic synthesis. The combination of an aziridine moiety and a cyano group in aziridines **1** enables the preparation of a variety of functionalized aminonitriles through ring-opening reactions of the constrained ring.

As reported before, treatment of 1-arylmethyl-2-(cyanomethyl)aziridines **1** with benzyl bromide in acetonitrile afforded 4-amino-3-bromobutanenitriles **2** through a regiospecific ring opening of the intermediate 2-(cyanomethyl)aziridinium salts **4** by bromide at the more hindered aziridine carbon atom (Scheme 2), which was further validated by means of DFT calculations.[28,31] Long reaction times at room temperature were required in order to avoid subsequent dehydrohalogenation at elevated temperatures. This method offers a convenient approach toward β-substituted γ-aminonitriles upon nucleophilic displacement of the bromo atom in β-bromonitriles **2**.

Surprisingly, treatment of the same substrates **1** with 1.2 equiv of hydrogen bromide (as a 33% solution in acetic acid) in acetonitrile or dichloromethane as a solvent for one hour at room temperature resulted exclusively in 3-*N*-(arylmethyl)-amino-4-bromobutanenitriles **3** in good yields (Scheme 2). Due to the high intrinsic reactivity of β-bromoamines **3**, these compounds are not suited for long time preservation, and should therefore be used for further elaboration shortly after preparation. These observations can be explained through the formation of intermediate aziridinium ions **5** upon N-protonation of the aziridine ring, followed by regiospecific ring

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opening by bromide at the unsubstituted aziridine carbon atom (Scheme 2). Obviously, the structural difference between 1,1-dialkylaziridinium salts **4** and 1-protio-1-alkylaziridinium salts **5** has a profound influence on the reactivity toward bromide. It is likely that the presence of a single benzyl substituent on the aziridinium nitrogen in intermediates **5** changes the charge distribution and the electrostatic potential in the aziridine ring compared to the 1,1-dialkylaziridinium ions **4**; however, it is also likely that there is a significant difference in the frontier orbital picture; these effects will be further investigated with computational techniques.

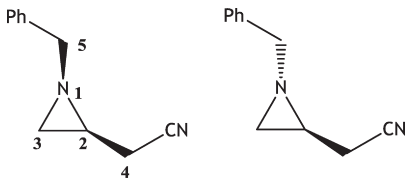
In summary, 1-arylmethyl-2-(cyanomethyl)aziridines **1** can be easily transformed into γ-amino-β-bromobutanenitriles **2** or β-amino-γ-bromobutanenitriles **3**, depending on the reagent used. The complementarities of both approaches, i.e., treatment with benzyl bromide in CH_3CN or hydrogen bromide in CH_3CN or CH_2Cl_2, consolidates the versatility of 2-(cyanomethyl)aziridines **1** toward the synthesis of different types of aminonitriles.

Computational Results. The current study aims to elucidate the regiospecific preference in the ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines **1** by HBr and comparatively analyze the opposite regioselectivity observed with benzyl bromide. It is difficult to directly compare these two reaction mechanisms, since solvation is different; however, the nature of the aziridinium intermediates will be studied in detail in terms of electronic structure.

The initial step of the reaction is proposed to be the formation of aziridinium ion **5**, which then undergoes attack by the bromide ion at the unsubstituted (less hindered) aziridine carbon (Scheme 2), resulting in 3-*N*-(arylmethyl)-amino-4-bromobutanenitriles **3**, exclusively. This is in contrast with results attained from ring opening by benzyl bromide, which yields 4-amino-3-bromobutanenitriles **2**,[28,31] suggesting bromide attack at the substituted (more hindered) aziridine carbon. The latter case has been previously theoretically investigated[31] and will serve as a basis in the effort to understand the difference in regioselectivity observed in these two reactions.

Computational Methodology. An in-depth level of theory study on the ring opening of aziridines with benzyl bromide was recently performed.[33] It was shown that the MPW1B95[48] level of theory successfully reproduced SCS-MP2[49] results and adequately described the reaction barriers and product stabilities, provided solvation effects were taken into account via effectively solvating the bromide with explicit solvent molecules. The same approach is adopted in the present study.

SCHEME 3. Atom Labeling and Schematic Representation of 1-*trans* and 1-*cis*



1-*cis* **1-*trans***

All DFT calculations were carried out with the Gaussian 03 program package.[50] Stationary points were fully optimized with the B3LYP/6-31++G(d,p) level of theory,[51,52] which is known to produce reliable geometries for aziridine compounds, and characterized as minima or first-order saddle points via frequency calculations. Intrinsic reaction coordinate (IRC)[53] calculations followed by full geometry optimizations were used to verify reactant complexes (ion-dipole complexes) and products reached by each transition state. Free energies of activation ($\Delta G^{\ddagger}$) were calculated as the difference of free energies between transition states and reactive conformers. Relative energies were further refined using the meta-hybrid GGA MPW1B95.[48] Furthermore, a computationally feasible method, which consists of adding an empirical $-C_6R^{-6}$ correction on DFT energies to account for dispersive interactions was adopted. The so-called DFT-D approach, shown to provide high accuracy in a variety of simulations,[54] was implemented utilizing the ORCA 2.6.35 software package.[55]

Invertomers for 1-Arylmethyl-2-(cyanomethyl)aziridines. A conformational search taking into account the most pertinent degrees of freedom was performed on both invertomers, **1-*trans*** and **1-*cis*** (Scheme 3), of 1-arylmethyl-2-(cyanomethyl)aziridines **1** by means of a systematic *relaxed*-potential energy surface (PES) scan at the B3LYP/6-31++G(d,p) level of theory, in order to identify the most stable conformer for each isomer. Simultaneous rotation around dihedrals $CN-C_4-C_2-N$ and C_2-N-C_5-Ph has revealed six significant conformers for the *cis* and nine for the *trans* invertomer.

Relative free energies at different levels of theory (Table 1) show a range of approximately 5 kJ/mol energy difference among conformers for each invertomer at all levels of theory, excluding conformers **1-*trans*-g**, **1-*trans*-h**, and **1-*trans*-i** in which the aromatic group is directed toward the aziridine ring. Calculations show a consistent difference in stability between **1-*trans*** and **1-*cis***, favoring the *trans* invertomer (17.4, 12.7, and 14.7 kJ/mol for B3LYP, B3LYP-D, and MPW1B95, respectively) as seen in the difference between the most stable conformers of each invertomer, namely, **1-*trans*-d** and **1-*cis*-d**.

Pyramidal inversion at the nitrogen center of amines is known to occur at a fast rate, preventing a permanent chiral center on the nitrogen atom and hence not allowing the isolation of invertomers (inversion isomers). However, there are literature studies in which invertomers have been isolated by slowing down the inversion rate through the use of large central atoms (P and As) or by the inclusion of a heteroatom in a small ring, as seen in certain aziridines.[56] Increased angle strain in the aziridine ring is

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TABLE 1. Relative Free Energies (kJ/mol) for Stable Conformers of Aziridine Invertomers 1-*trans* and 1-*cis*[a−c]

	1-*trans*-a	1-*trans*-b	1-*trans*-c	1-*trans*-d	1-*trans*-e	1-*trans*-f	1-*trans*-g	1-*trans*-h	1-*trans*-i
B3LYP/631++G(d,p)	0.5	1.3	5.9	0.0	4.4	5.6	9.7	9.4	15.8
B3LYP-D/631++G(d,p)	1.6	2.0	5.2	0.0	3.5	3.8	4.7	3.8	9.4
MPW1B95/631++G(d,p)	0.7	1.3	4.0	0.0	4.5	3.9	7.5	6.4	11.6

	1-*cis*-a	1-*cis*-b	1-*cis*-c	1-*cis*-d	1-*cis*-e	1-*cis*-f
B3LYP/6-31++G(d,p)	1.0 (18.3)	0.5 (17.9)	3.9 (21.3)	0.0 (17.4)	5.2 (22.6)	4.6 (22.0)
B3LYP-D/6-31++G(d,p)	3.5 (16.2)	2.0 (14.7)	3.2 (15.9)	0.0 (12.7)	5.2 (17.9)	0.7 (13.3)
MPW1B95/631++G(d,p)	2.1 (16.8)	1.4 (16.2)	2.7 (17.4)	0.0 (14.7)	5.4 (20.2)	1.3 (16.0)

[a]Free energies listed in brackets are relative to **1-*trans*-d**. [b]B3LYP/6-31++G(d,p) geometries. [c]Thermal free energy corrections from B3LYP/6-31++G(d,p) calculations at 1 atm and 298 K.

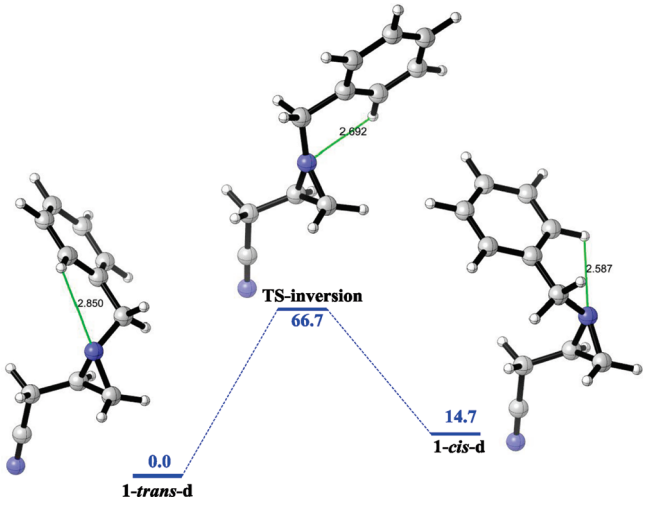

FIGURE 1. Free energy profile (kJ/mol, MPW1B95/6-31++G(d,p)) for nitrogen inversion in 1-arylmethyl-2-(cyanomethyl)aziridines.

known to lead to an increased barrier for nitrogen inversion, in some cases high enough for the isolation of separate invertomers. For this reason, pyramidal inversion at the ring nitrogen of 1-arylmethyl-2-(cyanomethyl)aziridines **1** was computationally investigated, in order to verify the possibility of invertomer resolution (Scheme 3).

The free energy barrier ($\Delta G^{\ddagger}$) for nitrogen inversion at 1-arylmethyl-2-(cyanomethyl)aziridines **1** and the standard free energy change ($\Delta G°$) for isomerization of invertomers **1-*trans*** and **1-*cis*** are shown in Figure 1. The trigonal pyramidal nature of the nitrogen center is depicted in the inversion transition state (**TS-inversion**). The free energy barrier for inversion (MPW1B95) from *trans* to *cis* ($\Delta G^{\ddagger}_{trans\rightarrow cis}$) is shown to be 66.7 kJ/mol, whereas the reverse barrier for inversion from *cis* to *trans* ($\Delta G^{\ddagger}_{cis\rightarrow trans}$) is 52.0 kJ/mol.

TABLE 2. Free Energies of Activation ($\Delta G^{\ddagger}$) for Nitrogen Inversion, Free Energy Change for *cis*−*trans* Isomerization ($\Delta G°$), and Invertomer Ratios[a,b]

	$\Delta G^{\ddagger}_{trans\rightarrow cis}$	$\Delta G^{\ddagger}_{cis\rightarrow trans}$	$\Delta G°_{trans-cis}$	invertomer ratio (*trans*:*cis*)
B3LYP/6-31++G(d,p)	67.8	50.5	17.4	10000:8
B3LYP-D/6-31++G(d,p)	71.5	58.8	12.7	10000:63
MPW1B95/6-31++G(d,p)	66.7	52.0	14.7	10000:27

[a]Thermal free energy corrections from B3LYP/6-31++G(d,p) calculations at 1 atm and 298 K. [b]Energies in kJ/mol.

Calculated barriers are in line with earlier reports on experimental and theoretical aziridine inversion barriers,[57−59] which were shown to range from 50 to 90 kJ/mol (79 kJ/mol for the parent, unsubstituted aziridine) depending on ring substituents, in particular on the identity of the N-substituent, where electron-withdrawing groups were shown to destabilize the transition state by inductive effects and therefore increase the barrier to inversion. It is generally expected that resolution of a single invertomer by slow inversion is possible if the barrier to nitrogen inversion is higher than 100 kJ/mol (at room temperature). However, in the present study, free energy change ($\Delta G°$) for *trans*-*cis* isomerization is significantly high (14.7 kJ/mol). Considering the relatively low barrier, rapid inversion at room temperature is expected to lead to thermodynamic equilibration; it is highly likely that the *trans* invertomer (**1-*trans***) will be overpopulated. This is in line with previous experimental findings, where the *trans* invertomer was shown to be preferred in the crystalline structure.[60] Table 2 shows forward

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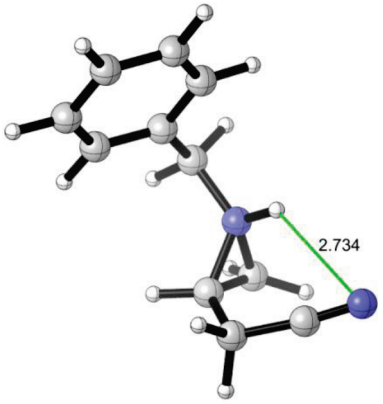

5-*trans*-f

FIGURE 2. Intramolecular H-bonding in aziridinium ion **5-*trans*-f**. (B3LYP/6-31++G(d,p)).

and reverse inversion barriers and invertomer stabilities at different levels of theory. Calculated invertomer ratios show a clear preference for the *trans* invertomer, 10000:27 (*trans*:*cis*) at the MPW1B95/6-31++G(d,p) level of theory, and therefore the *cis* invertomer is not expected to have a significant presence in the reaction mixture.

Nucleophilic Ring Opening of 1-Arylmethyl-2-(cyanomethyl)-aziridines with HBr. Despite aziridine's inherent reactivity due to the ring strain energy (111.7 kJ/mol),[61] non-activated aziridines are generally not prone to nucleophilic ring-opening reactions, without prior activation, which can be achieved by protonation, N-substitution with electron-withdrawing groups, or quaternization. The increased *s* character of the nitrogen center renders aziridines less basic than acyclic aliphatic amines; however, they are still expected to be easily protonated to yield intermediary aziridinium ions and hence become activated in acidic medium. The intermediate aziridinium ions **5** that form upon protonation of the parent aziridines, 1-arylmethyl-2-(cyanomethyl)aziridines **1**, are much less stable and therefore more susceptible to ring opening than their unactivated aziridine counterparts.

Aziridinium conformers **5** corresponding to the parent aziridine **1** were generated for all structures listed in Table 1; *trans* conformers were energetically more favorable at all levels of theory. Henceforth, only the *trans* invertomers will be analyzed in terms of relative stabilities and specific interactions in the corresponding aziridinium ion. Once protonated, the aziridinium moiety is further capable of forming intramolecular H-bonding interactions as depicted in **5-*trans*-f** (Figure 2), causing a strong preference for certain *trans* conformers. In the presence of a polar protic solvent (acetic acid), intramolecular interactions are likely to be less significant, and therefore the extra stabilization observed in conformers with intramolecular H-bonds is most likely an artifact of gas-phase calculations. Intramolecular H-bonds do not occur in the *cis* case.

Similarly, the reactive complex that forms between the aziridinium ion and bromide displays a strong interaction between the bare halide ion and the nitrogen proton. However, in reality the bromide ion will be solvated by solvent molecules, since acetic acid molecules are capable of forming strong hydrogen bonds with charged species; therefore, the bromide ion is not expected to be so tightly bound to the nitrogen proton in solution. In order to get more insight into the effect of solvation, discrete solvent molecules were added to the model as described in the next section.

Effect of Solvation: A Discrete Solvent Model. Nucleophilic substitution reactions are known to be influenced by the solvent environment.[62] Previous theoretical studies on regioselective ring opening of aziridinium ions with bromide have shown that the role of the solvent cannot be underestimated.[28,31,33] Gas-phase calculations, in which a bare halide ion attacks the electrophilic aziridinium ion, are unrealistic and incapable of representing the real system at hand. Accordingly, previous studies on modeling the bromide-induced ring opening of aziridinium ions have effectively made use of explicit solvent molecules.[28,31,33]

Simulations of reactions in organic solvents are considered one of the most challenging tasks in the field of molecular modeling. In many theoretical studies, the solvent is either neglected or simulated by means of continuum solvation models.[63−65] In such a dielectric model, the solvent is modeled as a continuous medium, usually assumed homogeneous and isotropic, characterized solely by a scalar, static dielectric constant. In some cases, these results give the correct reactive behavior, provided there are no essential explicit solvent interactions with the solute. However, in many cases, specific solvent interactions are in play in the first solvation shell. Ideally, the reactive species could be simulated by means of molecular dynamics calculations in a solvent box, and the number of solvent molecules in the first solvation shell can be considered to determine the coordination number at the site of interest. However, this approach is computationally very expensive and is not routinely applied. Another alternative is to include explicit solvent interactions by placing discrete solvent molecules around the chemically active species.[28,31,33,66−70] The number of explicit solvent molecules that should be incorporated in this "discrete solvent model" is often not clear.[71] This number is generally determined by the value at which the coordination solvation energy converges. This methodology was followed by the present authors in a recent study, which successfully pointed to the correct regioselective outcome.[28,33] Additionally, the supermolecule can be placed in a continuum with a fixed dielectric constant to account for bulk solvation; this is referred to as a mixed implicit/explicit solvent model.[71−73] A comparative study of continuum,

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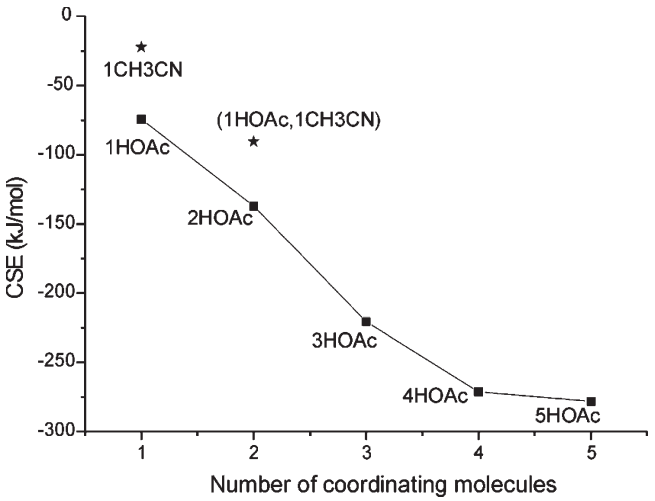

FIGURE 3. Coordination solvation energies (CSE) for the aziridinium−bromide complex (MPW1B95/6-31+G*).

explicit, and mixed solvation models performed by Warshel illustrated that mixed implicit/explicit solvation gave unreliable results with increasing number of explicit solvent molecules and was highly influenced by their orientation/alignment.[74]

The present study involves a solvent mixture composed of acetic acid and acetonitrile, and thus the initial set up for the cluster model is more complicated and the incorporation of explicit solvent molecules is not straightforward. To investigate this issue, the reactive complex between the intermediate aziridinium **5** and bromide was coordinated by an increasing number of explicit acetic acid and acetonitrile molecules, the corresponding coordination solvation energies (CSE) were calculated. At each stage various possibilities were explored, in order to investigate the preference for coordination with acetic acid or acetonitrile, and a thorough conformational search was conducted to locate the most stable points on the PES. As expected the bare bromide ion coordinates very strongly with surrounding solvent molecules. The CSE of acetic acid and acetonitrile, as the first coordinating solvent molecule, were calculated to be −74.0 and −22.0 kJ/mol, respectively. The preference for coordination with the polar protic acetic acid over the polar aprotic acetonitrile is understandable. Figure 3 depicts CSEs with respect to a varying number of solvent molecules. Coordination is favorable up to four acetic acid molecules; from that point on the CSE converges and further addition of explicit solvent molecules does not cause any appreciable stabilization. The first three acetic acid molecules form hydrogen bonds with the bromide anion, whereas the fourth hydrogen bonds to neighboring solvent molecules. The fifth acetic acid does not form any explicit hydrogen bonds. In the present study, a supermolecule model consisting of the substrate, the bromide anion, and three acetic acid molecules was used. This choice is motivated by the fact that only three acetic acid molecules have explicit contacts with the bromide anion. Moreover, free energy of solvation is expected to converge earlier as a result of the entropic penalty of adding more solvent molecules.

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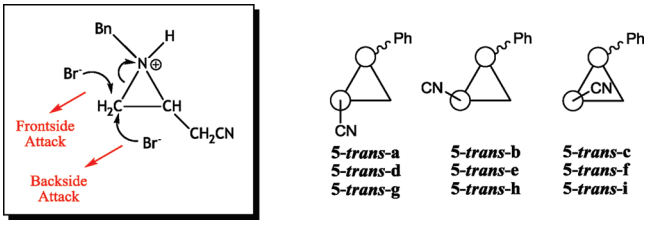
SCHEME 4. Nucleophilic Attack Modes on Aziridinium Ions 5 and Aziridinium Conformers



Bromide Attack on Aziridinium Ions. In light of these results, the nucleophilic ring opening of aziridinium ions **5** with bromide was further investigated with three explicit acetic acid molecules coordinating the halide ion. Bulk solvation was not taken into account since the dielectric constant as well as the solvent radius is difficult to estimate for the solvent mixture at hand. Moreover, the problems reported by Warshel[74] invoke caution when using a combined implicit/explicit solvent model.

Reaction pathways for nucleophilic attack at the unsubstituted (path a) and substituted (path b) aziridine ring carbons were modeled. Scheme 4 depicts modes of nucleophilic attack on aziridinium ion **5**. Needless to say, bromide attack will take place in an S_N2 fashion through a backside attack, where the leaving group is the ring nitrogen. Although **1-*trans*-a** and **1-*trans*-d** were previously shown to be two of the best conformers for the aziridine (Table 1), backside attack of the nucleophile is not favorable in the corresponding aziridinium conformers (**5-*trans*-a** and **5-*trans*-d**), since the cyanide group is in the attack trajectory. These conformers would only be able to accommodate a frontside attack, which would clearly have a higher barrier. Therefore, nucleophilic attacks were modeled using aziridinium ion **5-*trans*-b**, which corresponds to one of the most energetically favorable aziridine conformers, **1-*trans*-b**.

Transition state geometries for the solvent-assisted ring opening are depicted in Figure 4, where the bromide ion is shown to H-bond with three acetic acid molecules. Critical distances indicate "product-like" transition states, where the nitrogen−aziridine carbon distances are quite large (1.875 and 1.909 Å, for **TS-a-3AcOH** and **TS-b-3AcOH**, respectively) compared to the reactant-complexes (~1.5 Å). For comparative purposes, these transition states were also modeled without explicit solvent molecules; critical distances showed drastic differences from the solvated case, where nitrogen−aziridine carbon distances were

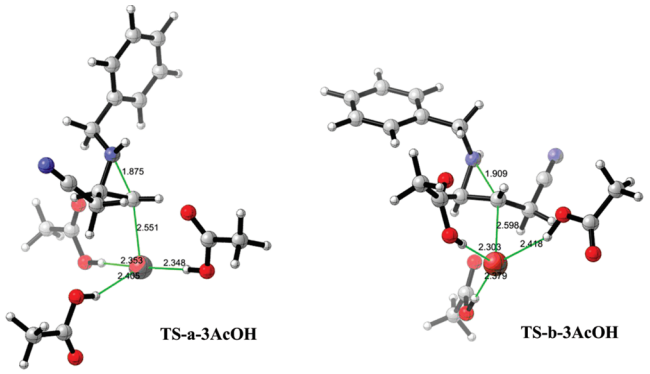


FIGURE 4. Transition state geometries (B3LYP/6-31+G(d,p)) for the solvent-assisted ring opening of aziridinium ions by bromide: unhindered (**TS-a-3AcOH**) and hindered (**TS-b-3AcOH**) pathway. Some critical distances (Å) are given.

TABLE 3. Free Energies of Activation ($\Delta G^{\ddagger}$) and Free Energies of Reaction (ΔG_{rxn}) for the Non-solvated and Solvated Bromide-Induced Ring Opening of 5-*trans*-b[a,b]

		$\Delta G^{\ddagger}$		ΔG_{rxn}	
		path a	path b	path a	path b
nonsolvated	B3LYP/6-31++G(d,p)	11.8	7.5	−142.3	−135.0
	B3LYP-D/6-31++G(d,p)	15.4	9.2	−136.9	−131.2
	MPW1B95/6-31++G(d,p)	15.3	14.1	−135.2	−128.8
solvated	B3LYP/6-31++G(d,p)	20.0	45.8	−33.7	−7.2
	B3LYP-D/6-31++G(d,p)	21.5	43.6	−27.4	−4.1
	MPW1B95/6-31++G(d,p)	33.0	55.3	−28.7	−4.1

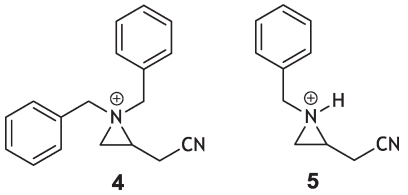
[a]Thermal free energy corrections from B3LYP/6-31++G(d,p) calculations at 1 atm and 298 K. [b]Energies in kJ/mol.

approximately 1.6 Å and bromide−aziridine carbon distances were 2.8 Å. This is a clear indication that in the absence of explicit solvent molecules, the reaction profile is significantly different and transition states are "reactant-like" in nature. The difference in the solvated versus nonsolvated potential energy surfaces is merely an artifact of gas-phase calculations and can be attributed to the extremely reactive nature of the bare bromide ion, whereas in the solvated case the bromide ion is stabilized by solvent molecules and is considerably less reactive. This is also reflected in the corresponding barrier heights (Table 3); nonsolvated barriers are significantly smaller in comparison to the solvated ones. This indicates that the solvated bromide ion is less reactive because of a considerable amount of stabilization, whereas the bare bromide is extremely active as shown in the exceptionally small barriers for both pathways. Additionally, reaction energies show dramatic differences between the solvated and nonsolvated cases; the nonsolvated case is unrealistically exothermic as a result of the stability difference between the bare bromide ion in the reactant and the stabilized bromide in the product.

In the nonsolvated case, the barrier heights are practically indistinguishable. This is most likely because of the considerably long bromide−aziridine carbon distances (approximately 2.8 Å) previously mentioned. At this distance, the bromide ion is not affected by the difference in steric hindrance between the two aziridine carbon atoms and does not discriminate between them. In the solvated case, however, calculations reveal a clear preference for path a (Scheme 1) at all levels of theory, confirming the experimentally observed regioselectivity. The solvated case shows a clear kinetic preference for path a, as barriers for the reverse reaction are less than 60 kJ/mol for each pathway. This would suggest the possibility of thermodynamic equilibration. Incidentally, path a also leads to the thermodynamically more stable product. However, this argument does not hold for the nonsolvated case, which has reverse barrier heights that are more than 150 kJ/mol, preventing any possibility of thermodynamic equilibration. These conclusions clearly indicate the necessity to solvate halide ions in order to get a realistic overview of the PES, in line with results obtained in previous theoretical studies on bromide-induced aziridine ring-opening reactions.[28,31,33]

HBr- versus Benzyl Bromide-Induced Ring Opening of Aziridines. The current study has presented experimental and theoretical evidence suggesting that the ring opening of aziridines (**1**) with HBr proceeds via the unsubstituted aziridine carbon, whereas previous experimental and theoretical reports have shown that treatment of the same compounds with benzyl bromide leads to ring opening at the substituted aziridine carbon.[28,31] The main difference between these two reactions, apart from the difference in solvent, is the nature of the intermediate aziridinium ion (Scheme 5) that undergoes nucleophilic attack

SCHEME 5. Aziridinium Ions 4 and 5



by bromide. In this section, the effect of N-substituents on the aziridinium electronic structure will be investigated. The correlation between regioselective preference in ring-opening reactions and aziridinium N-substituent identity will be explored. For this purpose, the electronic structures of aziridinium ions **4** and **5** have been subjected to a thorough analysis from an electrostatic and a frontier molecular orbital point of view.

Electrostatic Analysis. Population analysis is a conventional tool to gain insight into the electronic structure of molecular systems.[75−80] This technique is appealing to chemists, since it gives a simple depiction of net atomic charges based on the more complex density matrix representation of the electronic many-body system. However, results from a population analysis should be carefully interpreted. There is no unique definition of the atomic charge from the quantum-mechanical viewpoint, i.e., the atom is not a quantum-mechanical observable.[81] Several schemes (mathematical definitions) have been developed over the past decades to derive atomic charges from electronic structure computations. Each scheme has its strengths and weaknesses, which must be carefully taken into account in the interpretation of partial charges.

MPA (Mulliken Population Analysis)[82] charges are regularly reported to be very sensitive to the choice of basis set used; large basis sets are known to reflect unphysical trends.[83−86] CHELPG (CHarges from the ELectrostatic Potential)[87] charges are known to be unnecessarily sensitive to the choice of the grid points, the orientation of the molecule, and conformational changes.[88] The NPA (Natural Population Analysis)[83] scheme is clearly superior to MPA and ESP-fitted charges.[89] Its robustness toward large basis sets has been tested extensively.[85,90] However, a remaining drawback of NPA charges is the poor reproduction of the ESP

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TABLE 4. Mulliken, CHELPG, NPA, and Hirshfeld-I Charges (MPW1B95/6-31++G(d,p)) for Aziridine Carbons C2 and C3 on Conformers of Aziridinium Ions 5-*trans*

	MPA		CHELPG		NPA		Hirshfeld-I	
	C2	C3	C2	C3	C2	C3	C2	C3
5-*trans*-a	−0.297	−0.188	0.137	−0.233	−0.049	−0.230	0.100	−0.196
5-*trans*-b	0.095	−0.245	0.145	−0.247	−0.048	−0.230	0.101	−0.190
5-*trans*-c	0.227	−0.308	0.111	−0.209	−0.050	−0.237	0.101	−0.206
5-*trans*-d	−0.343	−0.177	−0.092	−0.066	−0.045	−0.234	0.107	−0.195
5-*trans*-e	−0.019	−0.202	−0.047	−0.106	−0.043	−0.238	0.109	−0.196
5-*trans*-f	0.079	−0.187	−0.123	−0.034	−0.046	−0.240	0.108	−0.205
5-*trans*-g	−0.403	−0.108	0.080	−0.105	−0.052	−0.234	0.108	−0.192
5-*trans*-h	−0.138	−0.130	0.064	−0.083	−0.051	−0.235	0.109	−0.188
5-*trans*-i	0.122	−0.266	0.032	−0.052	−0.053	−0.241	0.109	−0.203
Mean	−0.054	−0.208	0.025	−0.131	−0.047	−0.235	0.107	−0.197
Std Dev	0.187	0.055	0.104	0.083	0.004	0.003	0.004	0.005

around the molecule compared to ESP-fitted charges.[91,92] Charges obtained with the Hirshfeld-I (Iterative Hirshfeld)[86] method are comparable to NPA charges in terms of robustness with respect to the choice of basis set[86] and do have the additional advantage of reproducing the ESP around the molecule.[91,92] In light of this, Hirshfeld-I charges are considered the most reliable.

Various conformers of the aziridinium ions provide an ideal case study for a comparative investigation of different population analysis schemes. As the aim is to rationalize the opposite preference for nucleophilic attack at the aziridine carbons of aziridinium ions **4** and **5-*trans***, electrostatic properties of these reactive sites have been investigated. Four population analysis schemes mentioned above, namely, MPA, CHELPG, NPA, and Hirshfeld-I, are used for comparison. Although, the first three schemes are regularly used,[75−80] the last method is a recent development, and is not yet extensively tested. Atomic charges for aziridine carbons C2 and C3 are listed for aziridinium conformers of **5-*trans*** and **4** in Tables 4 and 5, respectively. While MPA and CHELPG charges significantly fluctuate from one conformer to the other, NPA and Hirshfeld-I charges are more robust with respect to changes in geometry, as reflected in their respective standard deviations, and will therefore be further used to explain the electrostatic interactions between the aziridinium and bromide ions. The geometry dependence of the MPA charges in Tables 4 and 5 is mainly due to the dependence of the (atom-centered) basis functions on the geometry, which in turn affects MPA charges. These results confirm once again that MPA charges are not reliable.

C3 is shown to bear a slightly larger negative charge (average Hirshfeld-I = −0.260) in aziridinium **4** when compared to its counterpart (average Hirshfeld-I = −0.197) in **5**, whereas C2 charges do not deviate too much among the two aziridinium ions, although C2 in **5** is slightly more positive (average Hirshfeld-I = +0.107). This is in line with the expectation that the positive charge on the quaternary nitrogen is better stabilized through electron donation from two benzyl groups (as in **4**) rather than one (as in **5**). In turn, this causes less electron withdrawal from the ring carbons, resulting in less positive charges on C2 and C3 for aziridinium ion **4**. The identity of the N-substituents is shown to have an effect on the charge distribution in the aziridine ring. Although these results provide insight, the experimentally observed regioselective preference cannot be attributed to the difference in charge distribution in the respective aziridinium ions. The difference in charges on C2 and C3 in aziridinium **4** is on average 0.330, whereas this difference is reduced to 0.304 in aziridinium **5**. There is no significant change in the bond-dipole, and it is clear that the regioselectivity has no electrostatic driving force. Note that considering a single conformer could be misleading when nonrubost population schemes such as MPA or CHELPG are used.

From the overall charge analysis viewpoint, it is tempting to conclude that C2 is always the preferred atom to undergo a nucleophilic attack by the bromide ion. However, it is important to realize that the electrostatic interaction between two molecules can never be ascribed to the net charge of a few atoms in each molecule. Figure 5 depicts the ESPs on the van der Waals surface of conformers **4g** and **5-*trans*-b**. It is clear that the electrostatic potential in the vicinity of C2 and C3 is nearly equal in both cases. The value of the electrostatic potential is not solely based on net charges on C2 and C3 but also on atoms in close proximity. Therefore, conclusions drawn from a population analysis should always be compared and verified by analyzing the ESP.

Frontier Molecular Orbital Analysis. Results drawn from the previous section clearly indicate that experimental regioselectivities cannot be explained on the basis of pure electrostatic considerations. In the attempt to rationalize the observed difference in nucleophilic attack, a secondary approach, analysis of frontier molecular orbitals, is applied. For this purpose, DFT-based reactivity indicators are used.[93−95] In particular, local Fukui functions $f(r)$, which can be used to describe orbital-controlled reactions, were analyzed.[96,97] Although, a recent study on other local descriptors, namely, local softness and hardness, indicates that their interpretation is not always straightforward,[98] reactivity descriptors have been successfully used to elucidate reaction pathways for a variety of reactions.[67,99−101]

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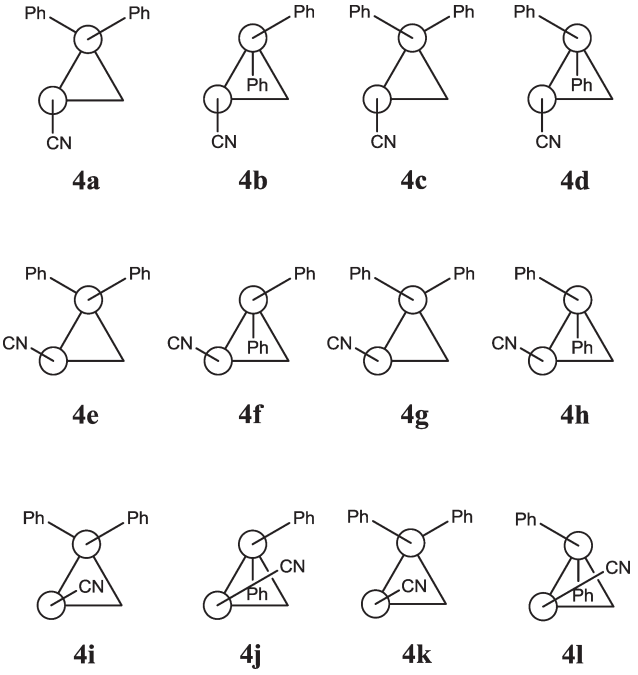
TABLE 5. Conformers of Aziridinium Ions 4 and Mulliken, CHELPG, NPA, and Hirshfeld-I Charges (MPW1B95/6-31++G(d,p)) for Aziridine Carbons C2 and C3

	MPA		CHELPG		NPA		Hirshfeld-I	
	C2	C3	C2	C3	C2	C3	C2	C3
4a	0.082	−0.095	0.044	−0.223	−0.040	−0.226	0.066	−0.261
4b	0.038	−0.287	0.076	−0.160	−0.049	−0.225	0.064	−0.255
4c	0.325	−0.150	0.116	−0.218	−0.039	−0.225	0.066	−0.261
4d	−0.206	0.040	0.024	−0.109	−0.045	−0.230	0.071	−0.261
4e	0.280	−0.199	0.109	−0.269	−0.037	−0.229	0.067	−0.260
4f	0.009	−0.254	0.059	−0.144	−0.047	−0.227	0.065	−0.253
4g	0.324	−0.177	0.116	−0.198	−0.034	−0.231	0.072	−0.262
4h	−0.199	0.076	0.036	−0.115	−0.043	−0.234	0.074	−0.260
4i	0.143	−0.113	0.043	−0.114	−0.038	−0.227	0.075	−0.262
4j	0.437	−0.545	0.105	−0.134	−0.047	−0.228	0.071	−0.261
4k	0.335	−0.109	0.042	−0.192	−0.039	−0.228	0.072	−0.264
4l	0.032	−0.076	−0.026	−0.098	−0.044	−0.233	0.078	−0.263
mean	0.133	−0.157	0.062	−0.164	−0.042	−0.229	0.070	−0.260
std dev	0.211	0.161	0.044	0.055	0.005	0.003	0.005	0.003



The three-dimensional Fukui function is usually approximated using a finite difference methodology, resulting in three different Fukui functions, $f^+(r)$, $f^-(r)$, and $f^0(r)$, that correspond to nucleophilic, electrophilic, and radical attacks, respectively. For the nucleophilic ring opening of aziridinium ions, the following three-dimensional Fukui function was utilized:

$$f^+(r) \approx \rho_{N+1}(r) - \rho_N(r) \approx \rho_{\mathrm{LUMO}}(r)$$

The final approximation results from the idea that the Fukui function generalizes the frontier molecular orbital (FMO) concept developed by Fukui.[102−104] This approximation is valid whenever the orbital relaxation effects are small, which is usually the case. Practical use of three-dimensional indicators is tedious, and therefore condensed values of the Fukui function, which provide a value for the local indicator at the position of the atomic center, are more often applied.[105] The atom-based Fukui function is defined as:

$$f_k^+ = q_k(N+1) - q_k(N)$$

where $q_k(N)$ is the electron population on the kth atom of a molecule with N electrons. The resulting values, which are condensed-to-atoms, are inevitably influenced by population analysis methods.[106−109] However, DFT-based indicators have shown little dependency on the DFT functional

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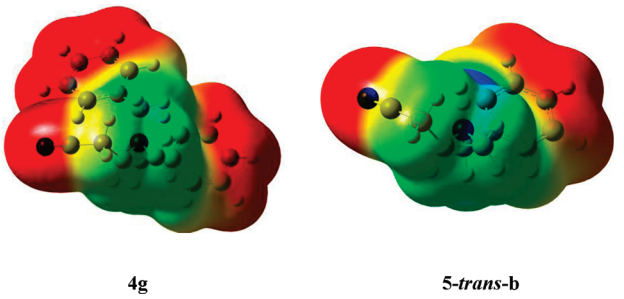

FIGURE 5. MPW1B95 electrostatic potential mapped on the electron-density surface [isovalue 0.0004] for aziridinium ions **4g** and **5-*trans*-b**. Color code: [+0.100 au; +0.212 au] where red corresponds to electron-rich and blue corresponds to electron-poor regions. The choice of a positive range is motivated by the cationic nature of the aziridinium ions.

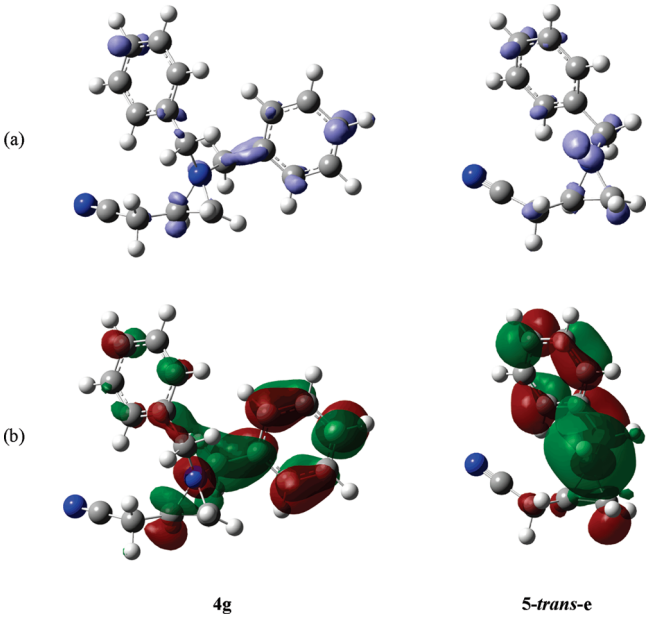

FIGURE 6. (a) Nucleophilic Fukui functions [isovalue 0.003 au] and (b) LUMOs [isovalue 0.03 au] for aziridinium ions **4g** and **5-*trans*-e**.

and/or the basis set utilized, qualitative trends are shown to be unaltered.[110,111]

In the present work, nucleophilic Fukui functions as well as LUMO orbitals were calculated for all conformers of **4** and **5-*trans*** (see Supporting Information for a complete list of figures). The main focus is on the difference in the reactivity between aziridine carbons C2 and C3 in each aziridinium ion. The largest (positive) value of the Fukui function indicates the most reactive site, while FMO suggests that a site where the LUMO is localized is a good electrophilic site, susceptible to nucleophilic attack. For some conformers no clear preference for either of the aziridine carbons was observed; however, the overall picture of the nucleophilic Fukui functions shows a significant preference for the substituted (C2) and unsubstituted (C3) carbon atoms, for structures **4** and **5-*trans***, respectively. These results are in line with the experimentally observed regioselectivities, albeit with one exception (**5-*trans*-c** with preference for the substituted carbon atom).

Fukui functions and LUMOs for aziridinium ions **4g** and **5-*trans*-e** are shown in Figure 6. Both properties show that aziridinium ion **4g** and **5-*trans*-e** have a clearly opposite preference, i.e., nucleophilic attack at the substituted versus the unsubstituted aziridine carbons, respectively. These results indicate that the experimentally observed regio preference can be rationalized in terms of frontier orbital concepts.

In terms of Fukui functions condensed-to-atoms, the type of population analysis method used dramatically influences the results obtained, as in the case of atomic charge analysis (see Supporting Information for a detailed list of results). For aziridinium ion **5-*trans***, the Hirshfeld-I method shows for all conformers the largest f_k^+ values for the C3 atom, in agreement with the experimentally observed regioselectivity. In case of ion **4**, the differences between the f_k^+ values for the C2 and C3 atoms are much smaller, and no definite conclusions can be drawn.

Conclusions

The ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines with HBr (33% acetic acid solution) in acetonitrile or dichloromethane was shown to afford 3-(arylmethyl)amino-4-bromobutanenitriles via regiospecific ring opening at the unsubstituted aziridine carbon. The aziridine ring system and nucleophilic ring opening of the corresponding aziridinium ion obtained through N-protonation at both aziridine ring carbons has been studied by means of computational methods in order to rationalize the experimentally observed regioselectivity. The investigation of the PES with explicit solvent molecules (acetic acid) solvating the bromide ion has revealed a clear preference of attack at the unhindered aziridine carbon, indicating kinetic control. HBr versus benzyl bromide ring opening was analyzed through comparison of the electronic structure of corresponding aziridinium intermediates. Although the electrostatic picture indicates that charge distribution and electrostatic potential surfaces of aziridinium ions is influenced by the difference in N-substituents, it fails to explain the opposite regiospecific nature of the reaction. However, frontier molecular orbital analysis of LUMOs and nucleophilic three-dimensional Fukui functions show a clear preference of attack for the substituted aziridine carbon in aziridinium **4** and for the unsubstituted aziridine carbon in aziridinium **5**, successfully rationalizing the experimentally observed regioselectivity. This shows that the outcome of aziridinium ring-opening reactions is dictated by orbital control rather than electrostatics.

Experimental Section

Synthesis of 3-*N*-(Arylmethyl)amino-4-bromobutanenitriles 3. To a stirred solution of 2-(cyanomethyl)aziridine **1** (16 mmol) in dichloromethane (15 mL) was added a hydrogen bromide solution (4.65 g, 1.2 equiv, 33% in acetic acid) at 0 °C. The resulting solution was further stirred at room temperature for 1 h, after which the reaction mixture was poured into a saturated $KHCO_3$ solution (40 mL). Extraction with dichloromethane (3 × 25 mL), drying ($MgSO_4$), and removal of the solvent afforded 3-*N*-(arylmethyl)-amino-4-bromobutanenitrile **3**, which was purified by means of filtration through a pad of silica gel (hexane/EtOAc 2:1). The initially orange oil turned black upon prolonged preservation.

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4-Bromo-3-[*N*-(phenylmethyl)amino]butanenitrile 3a. Orange oil, yield 87%. R_f = 0.39 (hexane/EtOAc 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 and 2.68 (2H, 2×d×d, J = 16.9, 6.7, 5.9 Hz); 3.11−3.18 (1H, m); 3.60 (2H, ∼d, J = 4.7 Hz); 3.82 and 3.88 (2H, 2 × d, J = 13.2 Hz); 7.26−7.44 (4H, m). ^{13}C NMR (75 MHz): δ 22.4 (CH_2); 35.3 (CH_2); 50.7 (CH_2); 53.7 (CH); 117.3 (C); 127.5 (CH); 128.1 (CH); 128.6 (CH); 138.9 (C). IR (NaCl, cm^{-1}): ν_{NH} = 3324, ν_{CN} = 2250. MS (70 eV): m/z (%) 253/5 (M^++1, 30); 173 (100). Anal. Calcd for $C_{11}H_{13}BrN_2$: C 52.19, H 5.18, N 11.07. Found: C 51.94, H 4.93, N 10.86.

4-Bromo-3-{*N*-[(4-methylphenyl)methyl]amino}butanenitrile 3b. Orange oil, yield 51%. R_f = 0.40 (hexane/EtOAc 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (3H, s); 2.60 and 2.66 (2H, 2 × d × d, J = 17.0, 6.7, 5.8 Hz); 3.11−3.18 (1H, m); 3.59 (2H, ∼d, J = 4.7 Hz); 3.77 and 3.83 (2H, 2 × d, J = 13.2 Hz); 7.14−7.48 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.2 (CH_3); 22.5 (CH_2); 35.5 (CH_2); 50.6 (CH_2); 53.7 (CH); 117.4 (C); 128.1 (CH); 129.4 (CH); 135.9 (C); 137.3 (C). IR (NaCl, cm^{-1}): ν_{NH} = 3341, ν_{CN} = 2250. MS (70 eV): m/z (%) 267/9 (M^+ + 1, 55), 187 (100). Anal. Calcd for $C_{12}H_{15}BrN_2$: C 53.95, H 5.66, N 10.49. Found: C 53.68, H 5.49, N 10.33.

4-Bromo-3-{*N*-[(4-chlorophenyl)methyl]amino}butanenitrile 3c. Orange oil, yield 82%. R_f = 0.45 (hexane/EtOAc 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 and 2.66 (2H, 2 × d × d, J = 16.7, 6.5, 5.9 Hz); 3.10−3.17 (1H, m); 3.59 (2H, ∼d, J = 4.4 Hz); 3.78 and 3.85 (2H, 2 × d, J = 13.5 Hz); 7.28−7.35 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.6 (CH_2); 35.3 (CH_2); 50.1 (CH_2); 53.8 (CH); 117.3 (C); 128.9 (CH); 129.5 (CH); 133.4 (C); 137.5 (C). IR (NaCl, cm^{-1}): ν_{NH} = 3340, ν_{CN} = 2250. MS (70 eV): m/z (%) 287/89/91 (M^+ + 1, 38); 207/9 (100). Anal. Calcd for $C_{11}H_{12}BrClN_2$: C 45.94, H 4.21, N 9.74. Found: C 45.78, H 4.06, N 9.91.

4-Bromo-3-{*N*-[(4-methoxyphenyl)methyl]amino}butanenitrile 3d. Orange oil, yield 66%. R_f = 0.49 (hexane/EtOAc 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 and 2.66 (2H, 2 × d × d, J = 16.7, 6.5, 5.9 Hz); 3.11−3.18 (1H, m); 3.52−3.68 (2H, m); 3.72−3.84 (2H, m); 3.80 (3H, s); 6.80−6.92 and 7.22−7.30 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 22.5 (CH_2); 35.4 (CH_2); 50.2 (CH_2); 53.7 (CH); 55.4 (CH_3); 114.1 (CH); 117.4 (C); 129.4 (CH); 130.9 (C); 159.1 (C). IR (NaCl, cm^{-1}): ν_{NH} = 3346, ν_{CN} = 2250. MS (70 eV): m/z (%) no M^+; 203 (M^+ − Br, 100). Anal. Calcd for $C_{12}H_{15}BrN_2O$: C 50.90, H 5.34, N 9.89. Found: C 50.74, H 5.55, N 9.72.

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Supporting Information Available: Cartesian coordinates (B3LYP/6-31++G**), imaginary and low frequency modes, and absolute energies (MPW1B95/6-31++G(d,p)) of transition states; condensed-to-atoms atomic Fukui functions for aziridinium ions **4** and **5**; nucleophilic Fukui functions and LUMOs for aziridinium ions **4** and **5-*trans***; full ref 50. This material is available free of charge via the Internet at http://pubs.acs.org.