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Mechanism and Diastereoselectivity of Aziridine Formation from Sulfur Ylides and Imines: A Computational Study

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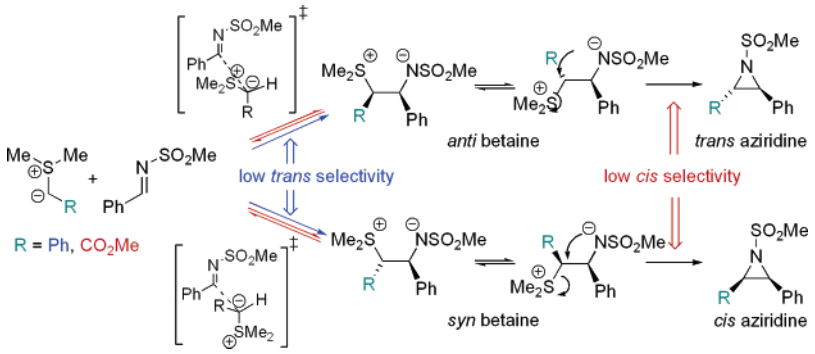
Received December 13, 2005



A computational investigation of the title reaction involving semistabilized (R = Ph) and stabilized (R = CO_2Me) sulfur ylides has been performed using DFT methods including a continuum model of solvent. Our results provide support for the generally accepted mechanism and are in very good agreement with observed *cis*/*trans* selectivities. This study shows that betaine formation is nonreversible, and that selectivity is thereby determined at the initial addition step, in the case of semistabilized ylides. Our analysis indicates moreover that addition TS structures are governed by the steric strain induced by the *N*-sulfonyl group, which favors the *transoid* approach in the case of *syn* betaine formation and the *cisoid* mode of addition in *anti* TSs. The observed low *trans* selectivity is accounted for by the favorable Coulombic interactions and stabilization by C−H···O hydrogen bonding allowed in the *cisoid anti* addition TS. In the case of stabilized ylides, the endothermicity of betaine formation combined with the high barrier to ring closure render the elimination step rate- and selectivity-determining. Accordingly, the low *cis* selectivity observed in stabilized ylide reactions is explained by the lower steric strain in the elimination step generated by the formation of the *cis* aziridine (as compared to the *trans* case).

Introduction

Aziridines are versatile functional groups that have found numerous applications in the synthesis of biologically important compounds.[1] The majority of attention with respect to developing an efficient aziridination protocol has focused on the aziridination of alkenes.[2] An efficient alternative strategy has also been developed independently by the groups of Aggarwal[3] and Dai,[4] namely, the reaction of sulfur ylides with imines (Scheme 1).[5,6] This strategy has proved to enable access, in high

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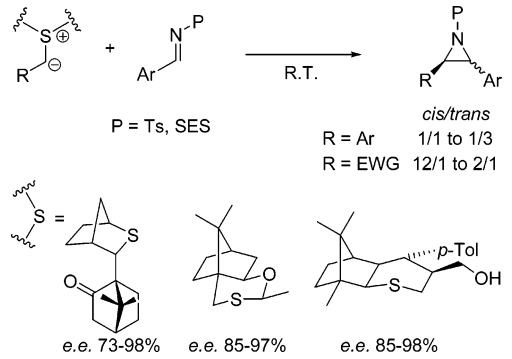
(2) For reviews, see: (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919.

(3) (a) Aggarwal, V. K.; Abdelrahman, H.; Thompson, A.; Mattison, B.; Jones, R. V. H. *Phosphorus, Sulfur Silicon* **1994**, *95*, 283−292. (b) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368−8369. (c) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *Phosphorus, Sulfur Silicon* **1997**, *120*, 361−362. (d) Aggarwal, V. K.; Alonso, E.; Fang, G. Y.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433−1436. (e) Aggarwal, V. K.; Ferrara, M.; O'Brian, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, *14*, 1635−1643. (f) Aggarwal, V. K.; Charment, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brian, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 3159−3166. (g) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335−2344. (h) Aggarwal, Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987−3990.

10.1021/jo052559t CCC: $33.50
Published on Web 02/28/2006

SCHEME 1. Synthesis of Aziridines from Sulfur Ylides and Imines



yields, to a wide range of optically active substituted aziridines under mild reaction conditions. Although high enantiomeric excesses can be achieved by using a chiral sulfide (up to 98%), the *cis*/*trans* diastereoselectivity in this process is, in most cases, poor. Imines protected by a sulfonyl group (the most commonly used in this reaction[7]) react with semistabilized ylides (R'_2-SCHR; R = Ar, alkene) to give aziridines with either no or low *trans* selectivity, whereas their reaction with stabilized ylides (R = CO_2Et, CO_2NEt_2, CH=$CHCO_2Me$) yields *cis* aziridines with low to good selectivity.

The generally accepted mechanism for aziridine formation from sulfur ylides and imines involves two key steps (Figure 1).[3f,4g] The first one is addition of the ylide to the imine to form a betaine intermediate. Two isomeric betaines can be formed during this step: an *anti* and a *syn* diastereoisomer. The *transoid* conformer (aza and sulfonium groups *antiperiplanar* to each other) of each of these betaines can then ring close to yield a *trans* and a *cis* aziridine, respectively.

Using crossover experiments (independent generation of betaines in the presence of a more reactive imine), Aggarwal et al. have shown that the first step, betaine formation, was nonreversible in reaction of *N*-sulfonyl imines with semistabilized ylides (R = Ar), which would therefore also be the selectivity-determining step.[3f] In trying to explain the observed selectivity, the authors have thus suggested that *anti* betaine

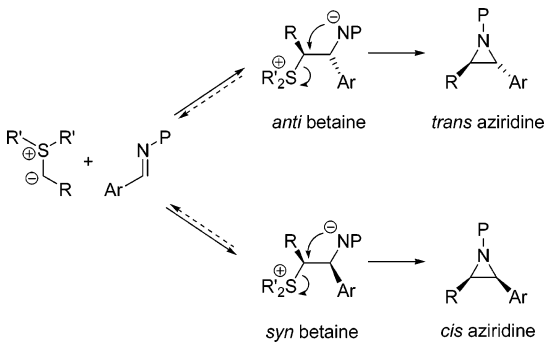


FIGURE 1. Generally accepted mechanism for aziridine formation from sulfur ylides and imines.

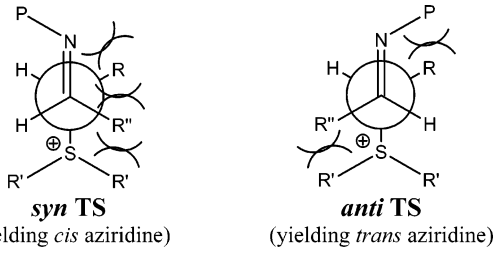


FIGURE 2. Addition TS structures proposed by Aggarwal to account for *trans* selectivity.

(leading to the *trans* aziridine) was formed preferentially due to steric strain in the TS leading to the *syn* betaine. In this model, ylides add to imines via transition states with a *transoid* arrangement of the aza and sulfonium groups as depicted in Figure 2 (see Figure 3 for a definition of the terminology used). Comparing the two diastereomeric TSs, *syn* and *anti*, it was suggested that the lesser steric encumbrance between the ylidic substituent (R) and the approaching imine in the *anti* TS accounts for the preferential formation of *anti* betaine and hence *trans* aziridine.

The geometry of the addition TSs, i.e., involving a *transoid* arrangement of the reactants, was suggested by Aggarwal et al. by analogy with what was described at that time for the reaction of sulfur ylides with aldehydes, based on computational (gas phase) calculations.[8] Since then, more detailed DFT calculations by Harvey and Aggarwal including solvent effects have suggested, however, that transition states for the addition of sulfur ylides to aldehydes (X = O in Figure 3) involve actually a quasi [2 + 2] approach of the reactants, referred as *cisoid* addition (see Figure 3).[9−11] A transition state involving a *transoid* arrangement was also found but was lying ca. 3 kcal/mol higher in energy.[9] This preferred *cisoid* geometry of the TS is accounted for by the stabilizing Coulombic interactions between the negatively charged oxygen and the positively charged sulfur atom in such a geometry; for geometrical reasons, a *transoid* approach does not allow such stabilizing interactions. In the case of aziridination reactions (additions onto imines) the presence of a protecting group on the nitrogen (P) induces

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(6) For some other recent studies, see: (a) Saito, T. Sakairi, M.; Akiba, D. *Tetrahedron Lett.* **2001**, *42*, 5451−5454. (b) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Synlett* **2003**, *13*, 1985−1988. (c) Solladié-Cavallo, A.; Roje, M.; Welter, R.; Sunjiæ, V. *J. Org. Chem.* **2004**, *69*, 1409−1412. (d) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Org. Lett.* **2005**, *6*, 2377−2380.

(7) Diastereoselecitivity has been shown to depend on the nature of the activating group on the nitrogen of the imine (P). The large majority of the reactions between ylides and imines involve however *N*-sulfonyl-protected imines (i.e., ArCH=NSO_2R). The present study will thereby focus only on reactions involving such imines. The nature of the imine group (Ar) has usually little effect on selectivity.

(8) (a) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1−14. (b) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4596−4606.

(9) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5757−5856.

(10) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468−5471.

(11) Silva, M. A.; Bellenie, B. R.; Goodman, J. M. *Org. Lett.* **2004**, *6*, 2559−2562.

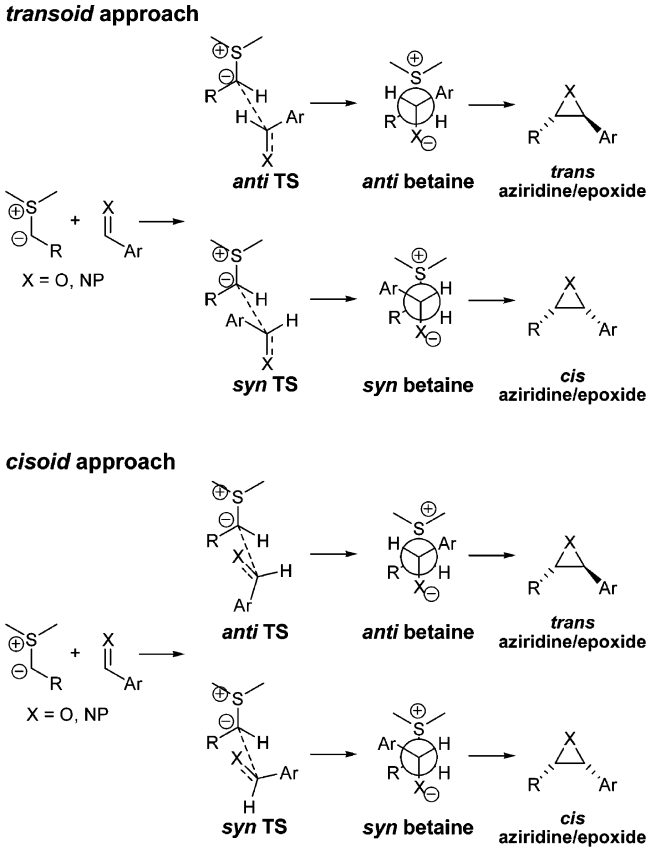

FIGURE 3. Different approaches of the ylide to the imine/aldehyde and the corresponding stereochemical outcomes.

additional steric effects. Moreover, the Coulombic interactions involving a negatively charged nitrogen bearing an electron-withdrawing group is likely to differ from the one induced by an alkoxy group (as in epoxidation reactions). It is thus not clear if the transition states for addition of ylides onto imines have a geometry similar to those for the corresponding epoxidation process (i.e., a *cisoid* geometry) or involve a *transoid* approach.

For stabilized ylide reactions, crossover experiments reveal a reversible betaine formation and hence that selectivity must be determined in a subsequent step.[3f,4g] It was thereby suggested[3f] that preference for *cis* aziridine formation in stabilized ylide reactions is due to the product-like character of the elimination TS, which favors the formation of the more stable aziridine, the *cis* isomer.[12]

In summary, a detailed atomistic account of the mechanism and selectivity of aziridine formation from sulfur ylides and imines is still lacking. Particularly unclear issues concern the geometry of the addition transition states, the cause of the different level of reversibility with different degree of stabilization of the ylide, and the nature of factors governing selectivity in reaction of semistabilized and stabilized ylides. The present work addresses these issues, focusing on the reaction of a benzilic *N*-sulfonylimine, $PhCH{=}NSO_2Me$, with Me_2SCHPh and Me_2SCHCO_2Me ylides (respectively, semistabilized and stabilized).[7]

To validate our methodology, we have also studied the model reaction between CH_2SMe_2 ylide and $CH_2{=}NSO_2H$ imine at a variety of different levels of theory. It is increasingly recognized that solvent effects should be included, at least with a continuum treatment, for organic reactions of polar species (as ylides) if accurate results are needed. For example, the mechanism and selectivity of the Wittig[13] and Horner−Wadsworth−Emmons[14] reactions can only be rationalized by including solvation effects, and previous calculations on mechanism and stereoselectivity of ylide reactions[9−11] that needed to be carried out using continuum solvent as the gas-phase potential energy surface are not at all meaningful. Accordingly, the present study includes the solvent, at the level of a continuum model, throughout.

Computational details

The bulk of the computations has been carried out using the Jaguar 4.0 pseudospectral program package.[15] All species have been fully geometry optimized, and the Cartesian coordinates are supplied in Supporting Information. In the case of transition states, the "loose" geometry convergence parameters within Jaguar (which correspond to rms gradients below 0.0015 hartree/au) have been used.

The grids used for integration in Jaguar are partly determined by the covalent radius on each atom, among other parameters. Using the standard covalent radius for sulfur lead to discontinuities in the potential energy surface as the breaking C−S bond length is varied as a result of changes in the density of the grid. The corresponding changes in energy were small (max 2 kcal/mol) but prevented successful geometry optimization in some cases. Accordingly, the covalent radius of the sulfur atom was set to 1.5 Å for optimization calculations of ring closure TSs. Tests showed that changing this parameter had no impact on calculated energies for other species.

Geometry optimization was carried out using the well-established B3LYP hybrid density functional as implemented in Jaguar. The standard split valence polarized 6-31G* basis set was used. Because of the importance of solvent effects, the optimization was carried out using the polarizable continuum-Poisson method as incorporated in Jaguar.[16,17] The results are not expected to depend strongly on the parameters used for the continuum solvent, so we have used a single set of parameters, i.e., a dielectric constant of 37.5 D and a solvent probe radius of 2.179 Å, which are suitable for acetonitrile (CH_3CN), one of the most common solvents used in these reactions. All given energies are obtained after corresponding single point calculations at the B3LYP/6-311+G**(CH_3CN) level using the fine grid and high accuracy parameters within Jaguar. Additional single point calculations on each addition TS using parameters corresponding to THF (dielectric constant = 7.43 D; radius = 2.522 Å) were carried out (see Supporting Information) in order to check the validity of our analysis of transition state structure.

Frequency calculations have been performed on every stationary points for the model reaction in order to guarantee the quality of the obtained results. Frequency calculations for large molecules of the type studied in the other reactions, especially if solvation effects

(12) It has been shown computationally and experimentally that *N*-substituted *cis* aziridines are thermodynamically more stable than the corresponding *trans* isomers. See: (a) Mimura, N.; Ibuka, T.; Akaji, M.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fijii, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, *3*, 351−352. (b) Lutz, R. E.; Turner, A. B. *J. Org. Chem.* **1968**, *33*, 516−518.

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(15) *Jaguar*, ver. 4.0; Schrödinger, Inc.: Portland, OR, 1991−2000.

(16) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honing, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875−11882.

(17) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honing, B. *J. Phys. Chem.* **1996**, *100*, 11775−11788.

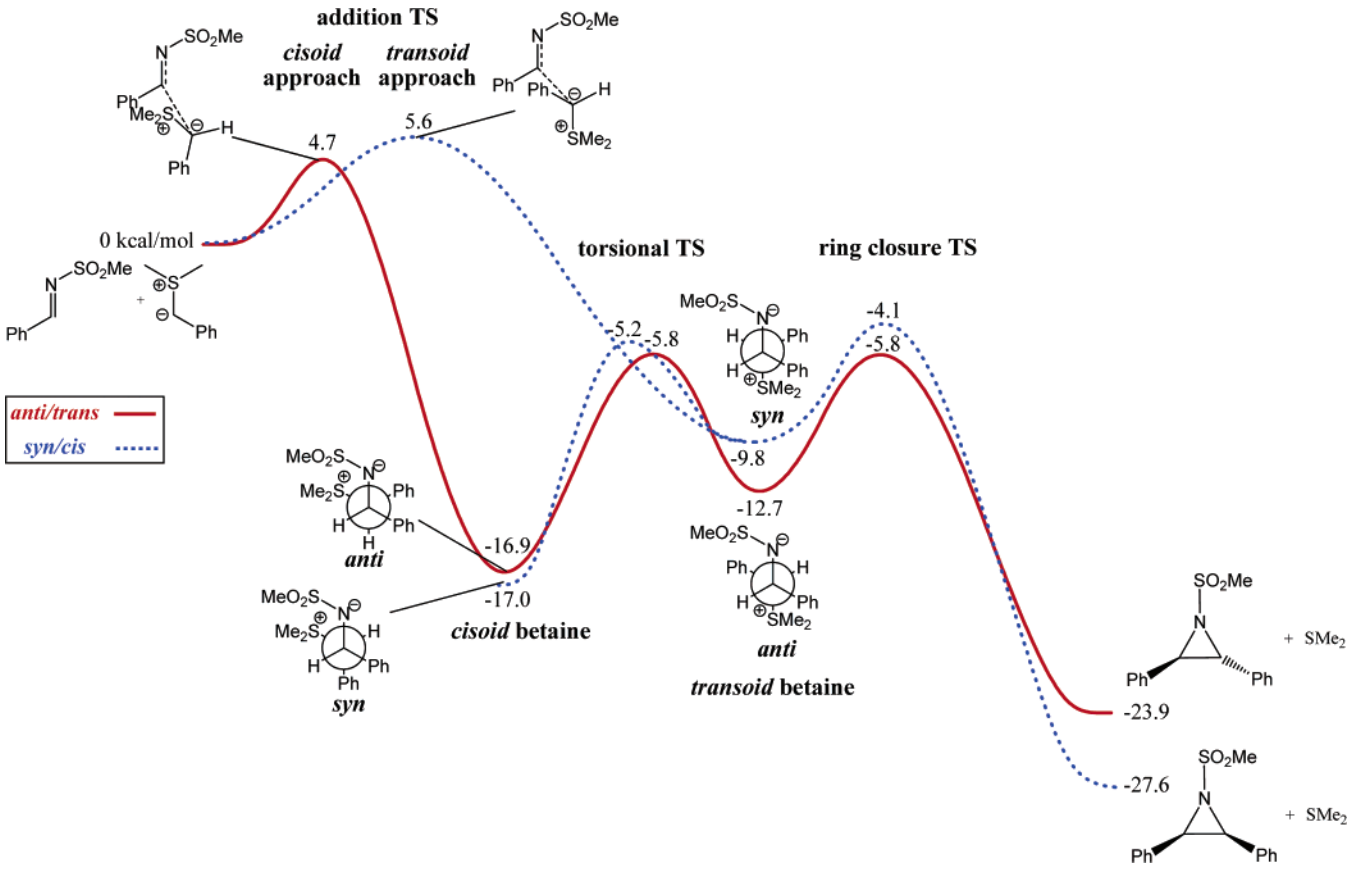

FIGURE 4. Computed potential energy surface for the aziridination reaction between *N*-mesylbenzaldimine (PhCH=NSO_2Me) and dimethylsulfonium benzylide ($PhCHSMe_2$). Energies are obtained at the B3LYP/6-311+G**(CH_3CN)//B3LYP/6-31G*(CH_3CN) level and are given in kcal/mol relative to reactants.

need to be taken into account, are of prohibitive computational expense and have not been performed, so that we cannot be absolutely certain that the optimized structures have the desired character as minima or transition states and cannot include either zero-point energy or thermal corrections. However, given the low symmetry of the molecules, it is extremely unlikely that the optimized structures correspond to anything other than minima or transition states. Zero-point energy corrections and entropic effects are expected to be near identical for isomeric pathways leading to *cis* and *trans* aziridine so that their neglect should be of little consequence.

For the model reaction $CH_2SMe_2 + CH_2{=}NSO_2H$, single point energies at the B3LYP/6-31G*(CH_3CN) geometries have been evaluated at several levels of theory: B3LYP/6-31G*, B3LYP/6-311+G**, B3LYP/6-31G*(CH_3CN), B3LYP/6-311+G**(CH_3CN), MP2/6-311+G**, and QCISD(T)/6-31G*. G3(MP2)//B3LYP/6-31G* single point energies[18] have also been calculated. MP2 calculations were performed using the Gaussian 03 program package,[19] with the QCISD(T) single-points calculations obtained using the MOLPRO program package.[20]

For the large reaction systems there are usually several local minima or saddle points corresponding to each intermediate or transition state. This is due to the possibility of multiple conformations of substituents. We have made a systematic attempt to locate all possible local minima and saddle points, with the data presented in the text referring to the lowest energy form unless mentioned otherwise (see Supporting Information for the other conformers).

(18) Badoul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650−7657.

(19) *Gaussian 03*, Revision B.04; Frisch, M. J. et al.; Gaussian, Inc.: Pittsburgh, 2003.

(20) *MOLPRO*, Version 2002.3; Werner H.-J et al.

Results

A. Model Reaction. Our results for the model reaction ($CH_2SMe_2 + CH_2{=}NSO_2H$) are on the whole very similar to those reported for the corresponding epoxidation reaction ($CH_2SMe_2 + CH_2{=}O$), and we will restrict here the discussion to the main points, with the full results presented in Supporting Information.

The initial addition step for the model reaction occurs without any enthalpic barrier. This means that preference for a *transoid* or a *cisoid* mode of addition cannot be examined in this simple case.

The relative energies obtained vary significantly according to the method. The most important discrepancy concerns the relative energy of betaines and the activation energy of the ring-closure step. Taking the accurate G3(MP2)/B3LYP energies as a reference, we find that MP2 method highly overestimates the stabilization of betaines and does not estimate correctly the ring closure barrier. B3LYP method, on the other hand, was found to reproduce satisfactorily G3(MP2) energies, although it underestimates slightly the height of the ring-closure barrier. The relative energies obtained respectively at the B3LYP/6-31G*(CH_3CN) and B3LYP/6-311+G**(CH_3CN) levels can be seen to be rather similar, suggesting that basis set effects are not large in this system. We have therefore selected the B3LYP/6-311+G**//B3LYP/6-31G* method using the continuum model of CH_3CN both for the optimization and the single point calculation, although even at this level the gas-phase energy of the elimination TS is underestimated by about 2−3 kcal/mol as compared to reactants.

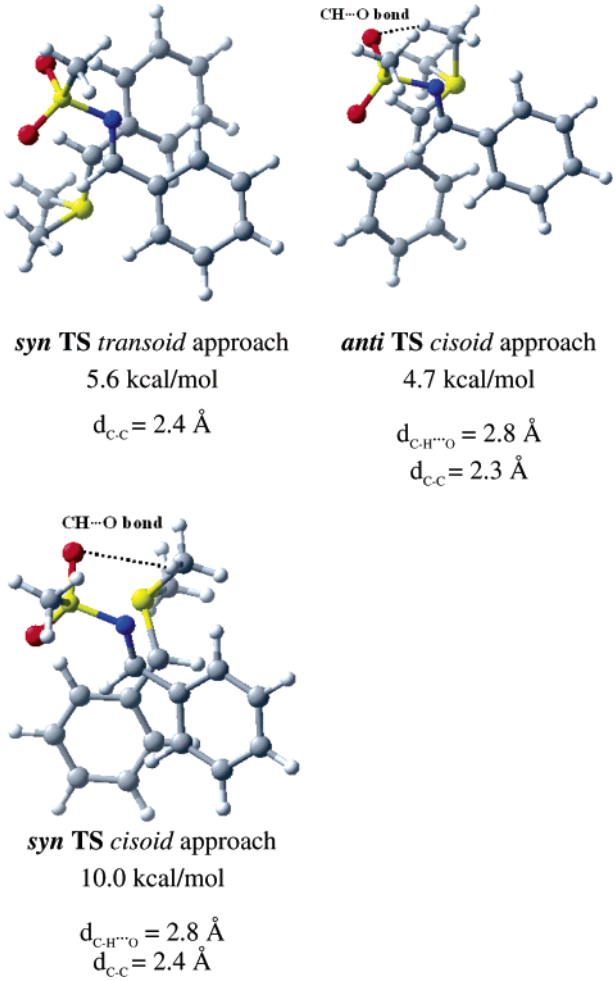

FIGURE 5. Transition state structures and selected structural parameters (C−H···O and C(imine)−C(ylidic) bond distances) for the addition of Me_2SCHPh to $PhCH{=}NSO_2Me$.

B. Semistabilized Ylides Reaction. In this section we will discuss the reaction of *N*-mesylbenzaldimine ($PhCH{=}NSO_2Me$) with dimethylsulfonium benzylide ($PhCHSMe_2$). The computed energy profile of the reaction is shown in Figure 4.

As for the model reaction, our calculations provide support for the generally accepted mechanism of aziridination. The addition of the ylide to the imine leads to formation of two diastereomeric betaines, *syn* and *anti*. As discussed in the Introduction, the respective addition TSs can hypothetically occur either via a *cisoid* or a *transoid* approach.

In the case of *anti* betaine formation, only a TS involving a *cisoid* mode of addition was obtained (Figure 5); every attempt to localize a TS with a *transoid* structure, as in Aggarwal's original model (see Figure 2), revealed the higher energy of such a geometry and led to a *cisoid* TS. Similarly to the addition onto aldehydes,[9] this preference for a *cisoid* approach of the reactants can be attributed to the favorable Coulombic interactions between the negatively charged oxygen/nitrogen and the positively charged sulfur allowed by such a geometry. However, an additional important factor responsible for the *cisoid* geometry in this case is the steric encumbrance a *transoid* approach of the reactants would provoke. Such a mode of addition would indeed involve a close spatial proximity of the ylidic phenyl and the sulfonyl group (see Discussion).

In the case of *syn* betaine formation, the influence of steric effects is the reverse, that is, the *cisoid* approach would generate a steric encumbrance between the sulfonyl and the ylidic phenyl groups whereas this interaction is absent in the *transoid* TS (see Discussion). Accordingly, two different TSs have been found for the formation of the *syn* betaine: one with a *cisoid* approach (at 10.0 kcal/mol) and another one, more stable, with a *transoid* mode of addition (at 5.6 kcal/mol) (see Figure 5; for clarity sake, only the lowest barrier is shown in Figure 4). The *cisoid* structure benefits from the favorable Coulombic interactions between the polar reactants but involves a steric hindrance between the ylidic phenyl and the sulfonyl group. The release of this steric strain by adopting a *transoid* mode of addition decreases the barrier, even though it prevents stabilization by favorable Coulombic interactions.

A careful analysis of the structures allows pointing out another feature of transition states involving a *cisoid* mode of addition, the presence of a C−H···O hydrogen bond between one of the oxygens of the sulfonyl function and a hydrogen of the dimethylsulfonium group of the approaching ylide (see Figure 5).[21] The short H···O distances (2.4−2.8 Å) and the C−H···O angles (120−155°) observed in the addition TS structures are indicative of stabilizing C−H···O hydrogen bonds.[22,23] As for Coulombic interactions, this stabilizing interaction is not present in the case of a *transoid* approach (for geometrical reasons) and favors thereby the *cisoid* mode of addition.

The *anti* TS leads thus to the *anti* betaine in its *cisoid* conformation, whereas the *syn* betaine is initially formed in its *transoid* conformation. The barrier for the latter to equilibrate with its *cisoid* conformer is however lower than the barrier to ring closure (or to reversal) and indicative of a rapid conformational equilibrium. In the case of the *anti* betaine, obtained barrier height to rotation is close in energy to the ring-closure TS. One has to keep in mind however that B3LYP method underestimates slightly the barrier to ring closure, by 2−3 kcal/mol (see section A above). Taking this bias into account, the rotation step is thus expected to be fully reversible in this case also.

For both diastereomeric betaines the *cisoid* conformer lies lower in energy than its corresponding *transoid* form (by 4−7 kcal/mol). This can be accounted for by the favorable electronic interactions (Coulombic interactions and C−H···O hydrogen bonding) between the two polar groups, sulfonium and NSO_2Me, present in the *cisoid* rotamers. It is worth noting as well that steric interactions induced by the sulfonyl group are lower in betaines than they are in addition TSs. This is due to the possibility, in betaines, of rotation around the carbon−nitrogen bond, which enables the sulfonyl group to move away and release steric strain (the double bond character of this bond in addition TSs did not allow such rotation).

The *cis* aziridine is found to be substantially more stable than its *trans* isomer (by 3.7 kcal/mol). This is in good agreement with previous ab initio calculations and equilibration reactions.[12] The larger stabilization of the *cis* isomer is explained in terms

(21) Even after a careful examination of the TS structures, no CH/π or π/π interactions could be observed in any of them.

(22) (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441−449. (b) Grabowski, S. J. *J. Phys. Org. Chem.* **2004**, *17*, 18−31.

(23) It is recognized that C−H···O hydrogen bonding is justified if the fragment under consideration satisfies the following range of parameters: H···O distance = 2.0−2.8 Å; C−H···O angle = 110−180°; C=O···H angle = 120−140° (see ref 21 and references therein). All C−H···O hydrogen bonds considered in this study follow this range.

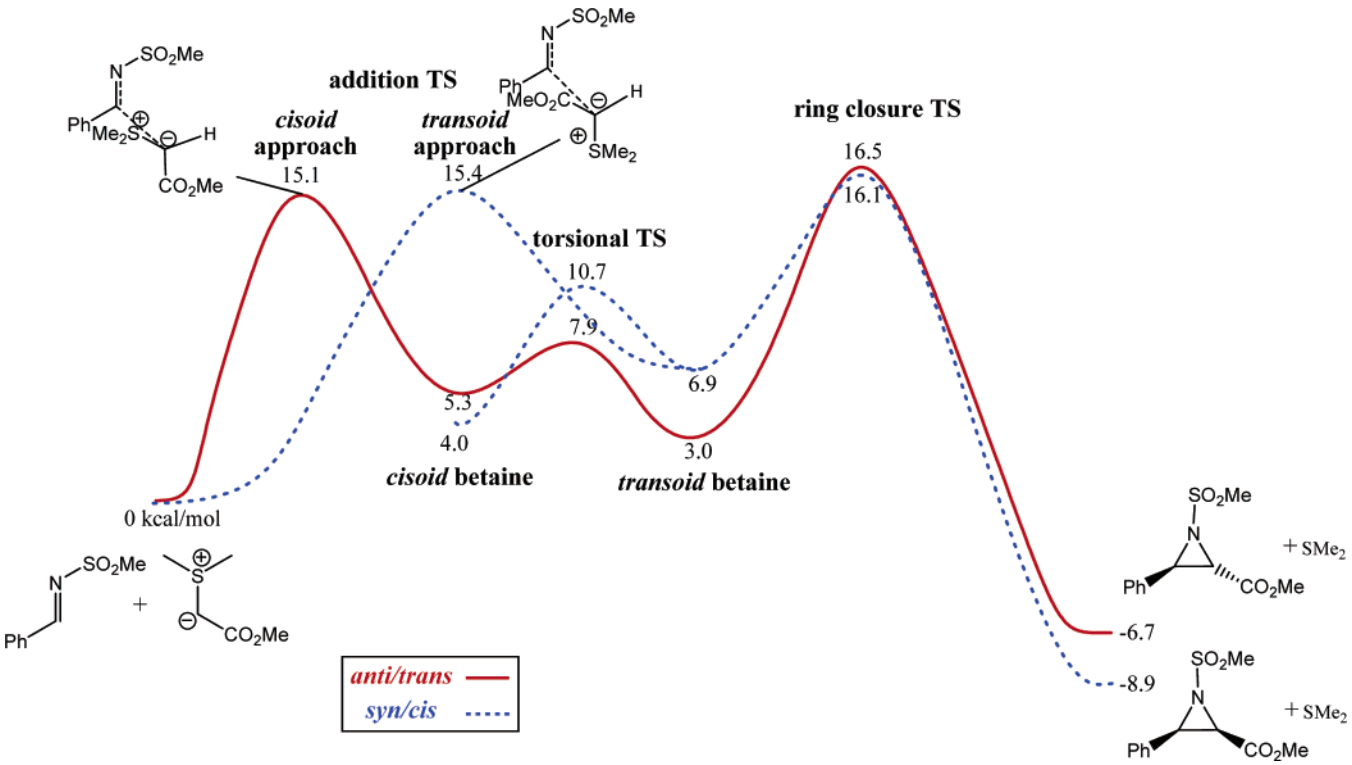

FIGURE 6. Computed potential energy surface for the aziridination reaction between $PhCH{=}NSO_2Me$ and Me_2SCHCO_2Me. Energies are obtained at the B3LYP/6-311+G**(CH_3CN)//B3LYP/6-31G*(CH_3CN) level and are given in kcal/mol relative to reactants.

of steric hindrance:[3f] the largest group on the three-membered ring is the sulfonyl group and this will prefer to be *trans* to the other substituents to minimize 1,2 steric interactions, which force the two remaining groups to be *cis* to each other. This lower steric encumbrance in the *cis* aziridine can account as well for the lower barrier to its formation (5.7 kcal/mol from *transoid* betaine) as compared to the one in the case of the *trans* isomer (6.9 kcal/mol).

Even taking into account the fact that the energy of the elimination TS is likely to be underestimated relative to the addition step at the level of theory used (as in the model reaction; see section A above), the addition TS is the highest point on both energy profiles. This means that betaine formation is completely nonreversible and that the overall *cis*/*trans* selectivity must thereby be exclusively ruled by the relative energy of *syn* and *anti* addition TSs. This is in good agreement with crossover experiments, which give no incorporation product when generating independently *syn* and *anti* intermediate betaines in the presence of a more reactive imine.[3f] Our calculations predict a low *trans* selectivity for the reaction of semistabilized $PhCHSMe_2$ ylide with $PhCHNSO_2Me$ (barrier to *anti* betaine formation is lower than for *syn* betaine). This is too in good agreement with experiment which gives a ratio of 1/3 of *cis* and *trans* aziridine in reaction of $PhCHSMe_2$ with PhCHNTs at room temperature.[3f]

C. Stabilized Ylides Reaction. We have investigated in this part the reaction of *N*-mesylbenzaldimine ($PhCH{=}NSO_2Me$) with a stabilized ylide, Me_2SCHCO_2Me. The potential energy surface differs significantly from the one obtained for semistabilized ylides (Figure 6).

Given the stabilization of reactants, betaine formation is now slightly endothermic. Accordingly, the barrier to addition is higher than in the semistabilized case. For both diastereomeric additions, two TSs, corresponding respectively to a *cisoid* and *transoid* approach, have been found (see Figure 7; for clarity sake, only the lowest barriers are shown in Figure 6). The localization of a *transoid* TS (lying at 16.4 kcal/mol) for *anti* betaine formation in this case can be accounted for by the stabilization of this latter geometry by a C−H···O hydrogen bond between the methyl of the ylidic ester group and one oxygen of the sulfonyl function on the imine.[21] The *cisoid* TS is however still the lowest lying transition state (Figure 7). For *syn* betaine formation it is in the *cisoid* TS that the ester group is close to the sulfonyl group and thus ther C−H···O hydrogen bonding is possible. The *transoid* TS (15.4 kcal/ml) is however still slightly favored over the *cisoid* one (16.0 kcal/mol).

The low barrier to rotation indicates again a rapid conformational equilibrium for both betaines. The energy discrimination between the two conformations, *cisoid* and *transoid*, of the betaines is much lower than in the semistabilized cases; the *transoid* conformer becoming even more stable for *anti* betaine. This can be attributed to the different steric and electronic effects of the ester group as compared to a phenyl.

The barrier to ring closure of both diastereomeric betaines is substantially larger than in the semistabilized case, 9.6 and 13.1 kcal/mol for the *syn* and *anti* isomer, respectively, from the corresponding *transoid* betaine (those barriers are respectively 5.7 and 6.9 kcal/mol in the case of semistabilized ylides). Similar increases in the barrier height of the elimination step by the presence of a carbonyl group α to the sulfonium group has been observed previously in epoxidation processes.[24,25] The consequence is that the ring-closure TS is now found to be the highest

(24) a) Robiette, R.; Fang, G. Y.; Harvey, J. N.; Aggarwal, V. K. *Chem. Commun.* **2006**, 741−743. (b) Aggarwal, V. K.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105−2114.

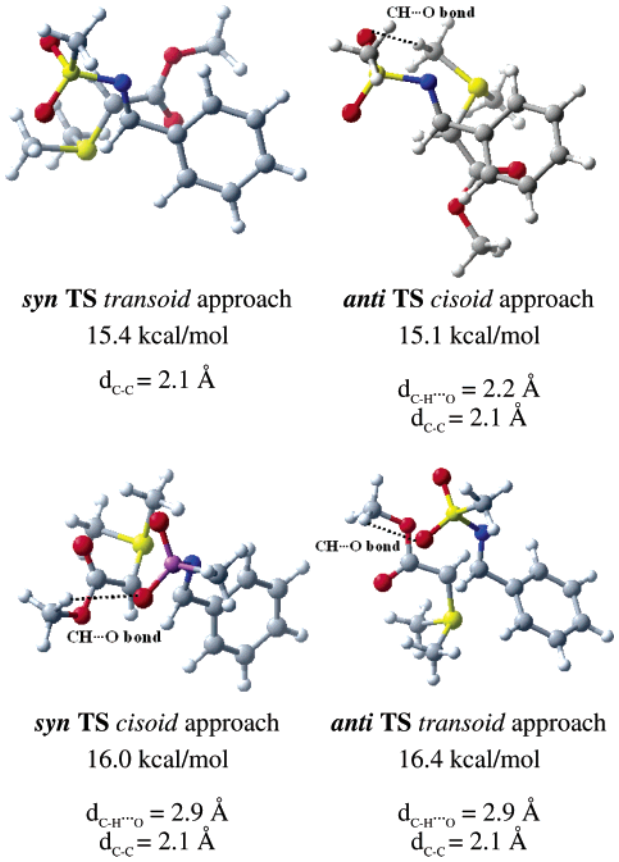

FIGURE 7. Transition states structures and selected structural parameters (C−H···O and C(imine)−C(ylidic) bond distances) for the addition of Me_2SCHCO_2Me to $PhCH{=}NSO_2Me$.

point on the energy profile in both diastereomeric pathways (especially taking into account the underestimation of the relative energy of the ring-closure TS by the B3LYP method, as for the model reaction). Thereby, the addition and rotation steps are completely reversible, and the ring-closure step constitutes the rate- and selectivity-determining step. This is in good agreement with crossover experiments carried out by Aggarwal et al., which gave >80% incorporation product when generating independently *syn* and *anti* intermediate betaines in the presence of a more reactive imine (*p*-nitrobenzaldimine).[3f,4g]

The computed relative energy of *syn* and *anti* ring-closure TSs predicts a very low selectivity for *cis* aziridine formation. Experimentally reaction of *N*-tosylbenzaldimine with stabilized Me_2SCHCO_2Et ylide gives a ratio of 3/1 of *cis* and *trans* aziridine,[3f] in agreement with our predictions.

Discussion

A. Mechanism. Our calculations using a computational method including solvent effects provide support for the generally accepted mechanism of aziridine formation from sulfur ylides and imines. There are two important steps along each of the diastereoisomeric pathways leading to *cis* and *trans* aziridines.

The first key step is the addition of the ylide onto the imine to form a betaine intermediate. This step is found to be more exothermic (or less endothermic) than in the case of corresponding additions onto aldehydes (epoxidation processes).[9−11,24] This can be accounted for by the lower bond energy of C═N versus C═O bond and the stabilization of the betaine by delocalization of the negative charge on the nitrogen into the electron-withdrawing (sulfonyl) group in the case of aziridination reactions. It is worth noting that experiment has shown that the presence of this electron-withdrawing group to activate the imine function was required: imines bearing an aryl or alkyl group on the nitrogen atom do not react with sulfur ylides unless activated by addition of a Lewis acid.[4g]

Betaines formed can lie in two different conformations, *cisoid* or *transoid*. In contrast to epoxidation reactions, this conformational equilibrium has no importance on the rate and the selectivity of the aziridination process. Indeed, in all cases, the energy discrimination between the two conformers and the barrier to rotation are much lower than the barrier to reverse to reactants or to ring close to products (Curtin−Hammett principle conditions[26]).

The barrier to ring closure of *transoid* betaines has been found to depend strongly on the nature of the ylidic substituent. In reactions of phenyl-substituted (semistabilized) ylides, this barrier is 5.7 and 6.9 kcal/mol for *syn* and *anti* betaine, respectively, whereas the presence of a carbonyl group (CO_2-Me) on the ylide increases this barrier by 4−6 kcal/mol. Similar observation has already been made in the context of epoxidation reactions.[24,25]

Because of the high stabilization of betaines and the low activation energy to elimination, the initial addition step is found to be completely nonreversible (for both diastereoisomeric pathways) in the case of semistabilized ylides. Selectivity is therefore determined at this step. This is not the case in the corresponding epoxidation process in which reversibility in formation of the *syn* betaine is observed.[9] In stabilized ylides reactions, the situation is different: endothermicity of the betaine formation (due to stabilization of the reactants) together with the increase in the barrier to ring closure (due to the presence of a carbonyl group) make the addition and rotation steps totally reversible. These observations are in good agreement with crossover experiments, which revealed no reversibility in betaine formation in semistabilized ylide reactions, whereas the initial addition step was shown to be completely reversible in the aziridination reactions of ester stabilized ylides.[3f,4g]

B. Structure of Addition TS. The geometry of the transition state for the initial addition step has been found to depend on steric and electronic interactions involving the substituents of the imine and the ylide. These interactions are as follows:[21]

Coulombic Interaction. As previously described in the context of addition of sulfur ylides onto aldehydes (epoxidation process), the *cisoid* approach of the reactants involves a spatial proximity between the positively charged sulfonium group and the negatively charged oxygen/nitrogen atom, which makes possible a favorable Coulombic interaction between those two polar groups. A *transoid* mode of addition moves away those two groups and hence does not allow such a stabilizing interaction.[27] This interaction thereby favors the *cisoid* mode of addition over the *transoid* one, in all cases.

C−H···O Hydrogen bond. A *cisoid* mode of addition enables C−H···O hydrogen bonding to occur between one of

(25) This surprising observation is in contradiction with the high reactivity usually observed for α-halogenated carbonyl compound in S_N2 reaction (see for instance (a) Bordwell, F. G.; Brannen, W. T. *J. Am. Chem. Soc.* **1964**, *86*, 4645−4650. (b) Lee, K. S.; Kumar, K. Lee, H. W. Lee, B.-S.; Lee, I. *Org. Biomol. Chem.* **2003**, *1*, 1989−1994). We are currently carrying out studies aiming at understanding this dissimilarity.

(26) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

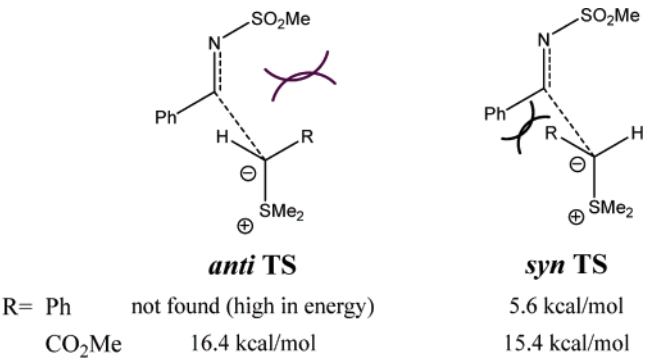

FIGURE 8. Illustration of steric interactions in *transoid* addition TSs.

the oxygens of the SO_2Me function and a hydrogen of the dimethylsulfonium group of the approaching ylide. The strength of this type of interaction in other systems has been reported to range from 0.5 to 4 kcal/mol, depending on the acidity of the hydrogen and the topology of the bond.[22b,23] For geometrical reasons (nonproximity of the two groups), this type of C−H···O hydrogen bonding is not possible in the *transoid* TS structures. It constitutes thereby also an important factor favoring the *cisoid* mode of addition (over the *transoid* approach).

In the case of ester-stabilized ylides, C−H···O hydrogen bonding between one of the oxygens of the SO_2Me function and a hydrogen of the methyl of the ylidic ester group is also possible. This stabilizing interaction occurs in stabilized ylide reactions when the ester group and the sulfonyl function are close to each other. This is the case in the *transoid* TS for *anti* betaine formation while for *syn* TS this is in the *cisoid* approach.

Steric Effects. The approach of the two reactants engenders a steric strain between their respective substituents. In semistabilized ylide epoxidation processes, the main steric interaction involves the aldehydic substituent and the aromatic ring of the ylide.[9] In the case of aziridination (addition to imines), however, the presence of a sulfonyl group on the nitrogen atom of the imine induces additional steric hindrance. The importance of this steric strain can be investigated by comparing the *transoid* structure of the *syn* and *anti* TSs (Figure 8). The fact that the *syn* isomer is found to be more favorable than the *anti* TS reveals that the ylidic substituent prefers to be *gauche* to the phenyl of the imine rather than to point toward the SO_2Me group. This indicates that the steric interactions involving the SO_2Me group are the dominating steric effects in TSs of addition of ylides to imines. This is especially true for semistabilized ylides; in the case of stabilized ylides, this destabilizing interaction is partly compensated by the presence of a C−H···O hydrogen bond between the sulfonyl group and a hydrogen of the methyl of the ester function (vide supra). Thus, overall, steric interactions disfavor TS structures involving a close proximity between the ylidic substituent and the *N*-sulfonyl group, namely, the *transoid* approach for *anti* betaine formation and the *cisoid* structure for *syn* TS.

Addition TS: Summary. The structure of the addition TS is dictated by an interplay of electronic and steric factors (Figure 9). Both Coulombic and C−H···O hydrogen bonding interactions (electronic factors) between the NSO_2Me and sulfonium groups favor the *cisoid* mode of addition, in all cases. The influence of steric effects on the contrary differs for the two diastereomeric pathways. For *anti*, as the electronic effects, they favor the *cisoid* approach. This explains the systematic preference for a *cisoid* approach in *anti* TSs. In the case of *syn* betaine formation the steric interactions favor, on the contrary, the *transoid* mode of addition. The electronic and steric effects act thus in an opposite manner in these cases. The lower energy of the barrier involving a *transoid* approach shows, however, that steric effects dominate over the electronic ones.

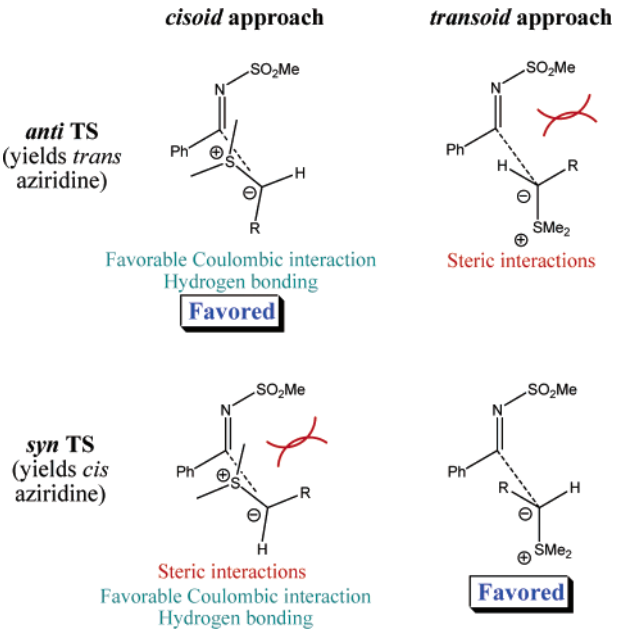

FIGURE 9. Transition state model.

The magnitude of electronic effects (C−H···O bonding and Coulombic interactions) can be investigated by examining the addition TS of CH_2SMe_2 onto $PhC{=}NSO_2Me$, since no important steric effects are expected in this particular case. Optimization of the *cisoid* and *transoid* TSs gives a *transoid* TS that is only 0.8 kcal/mol higher in energy than its *cisoid* conformer. This confirms the *intrinsic* preference for a *cisoid* mode of addition.[27] The low energetic discrimination supports however the fact that electronic effects are not very strong and can be easily overcome by steric effects.

In the case of stabilized ylides, the close proximity of the ylidic substituent (CO_2Me) and the sulfonyl group is less destabilizing. The steric strain induced by the SO_2Me group can indeed be partly compensated by the presence of a C−H···O hydrogen bond between this latter and a hydrogen of the methyl of the ester group. The discrimination between the two TS structures, *cisoid* and *transoid*, is consequently lower (∼1 kcal/mol) than in semistabilized ylide reactions, and *transoid anti* TS and *cisoid syn* TS may well play a role in the mechanism of addition of stabilized ylides in some cases (depending on substitution or reaction conditions).

C. Selectivity. Crossover experiments have suggested that selectivity was determined at the initial addition step in semistabilized ylide reactions but at a later stage in the case of stabilized ylides.[3f,4g] Computed energy profiles obtained in this study are in very good agreement with these experimental

(27) The favorable Coulombic interactions present in the *cisoid* TSs can be expected to be competing with the higher solvation energy for the *transoid* structures (due to a better access to the polar groups). This difference in solvation energy, while large (for instance, for *syn* TS in the case of semistabilized ylide, solvation energy is 24.2 and 17.9 kcal/mol for *transoid* and *cisoid* TS, respectively), is however not large enough to compensate for the intrinsic lower stability of the *transoid* structure.

observations. Our calculations reveal moreover that in the case of stabilized ylides it is the elimination step that is the selectivity-determining step.

For semistabilized ylides, overall selectivity is thus determined exclusively by the relative energy of *syn* and *anti* addition TSs. Our results indicate a low preference (0.9 kcal/mol) for *anti* betaine formation and hence predict a low *trans* selectivity. This is in good agreement with experiment, which gives a ratio of 1/3 of *cis* and *trans* aziridine in reaction of $PhCHSMe_2$ with PhCHNTs at room temperature. It was previously believed that ylide additions occur via a *transoid* approach in both diastereomeric pathways, and selectivity was explained by a lower steric strain in the *transoid anti* TS (compared to *transoid syn* TS; see Figure 2). Our calculations reveal however that if addition TS leading to *syn* betaine has indeed a *transoid* geometry, due to steric interactions (see section B), the *anti* TS involves actually a *cisoid* approach of the reactants. Our study shows that the lower energy of the *anti* TS, and hence the overall *trans* selectivity, can be accounted for by the favorable Coulombic interaction and the stabilization by C−H···O hydrogen bonding made possible by the *cisoid* geometry of this TS. Note that switching from a *transoid* to a *cisoid* geometry in the case of *syn* TS would make possible favorable Coulombic interactions and enable C−H···O hydrogen bonding as well. This structure has however a significant steric interaction between the ylidic phenyl and the sulfonyl group as illustrated in Figure 9.

Interestingly, the identification of the geometry of the two diastereomeric addition TSs suggests a rationalization for the observed solvent effect on *cis*/*trans* selectivity in reaction of semistabilized ylides. Polar protic solvents give more *cis* aziridine,[6a] presumably because the more polar *transoid syn* TS is better solvated than its *anti* isomer, which has a *cisoid* geometry.

In the case of stabilized ylides, the addition and rotation steps being reversible, it is the relative energy of *syn* and *anti* elimination TSs that determines the overall selectivity. Our calculations predict a very low *cis* selectivity; *syn* elimination TS lies 0.4 kcal/mol lower than its *anti* isomer. This is in good agreement with experiment, which gives a ratio of 3/1 of *cis* and *trans* aziridine for the reaction of *N*-tosylbenzaldimine with stabilized Me_2SCHCO_2Et ylide. The lower barrier to ring closure of the *syn* betaine can be explained by the lower steric hindrance around the sulfonyl group generated by the formation of the *cis* aziridine (as compared to the *trans* case).[12] Indeed, it has been shown, theoretically and experimentally, that *cis* aziridines are thermodynamically more stable than the corresponding *trans* isomers as a result of less steric encumbrance.

Conclusion

We have conducted the first computational investigation of the mechanism and the origin of diastereoselectivity of aziridine formation from semistabilized and stabilized sulfur ylides and imines. Our results are in very good agreement with previous crossover experiments and bring a considerable improvement of our picture of the overall reaction mechanism. Furthermore, our calculations reproduce the observed *cis*/*trans* selectivities and give a detailed insight into the origin of these selectivities.

In semistabilized ylide reactions, betaine formation is completely nonreversible (for both diastereoisomeric pathways). Selectivity is thus determined at the initial addition step. It was previously believed that *anti* selectivity at this step, and hence *trans* aziridine selectivity, were due to less steric encumbrance in the *transoid* addition TS during formation of *anti* betaine rather than *syn* betaine. However, we have shown that the structure of addition TSs does not always involve a *transoid* approach of the reactant. Relative stability of TS structures are influenced by hydrogen bonding, Coulombic interactions, and steric effects. Our calculations suggest however that addition TS geometries are mainly governed by the steric strain between the *N*-sulfonyl group and the ylidic substituent. Consequently, the *syn* TS has a *transoid* geometry, whereas the lowest lying *anti* TS involves a *cisoid* mode of addition. Accordingly, the observed low *trans* selectivity in semistabilized ylide reactions is explained by the favorable Coulombic interactions and stabilization by C−H···O hydrogen bonding in the *anti* TS made possible by its *cisoid* structure. The *syn* TS having a *transoid* structure does not allow those stabilizing interactions. The identification of TS structures and the better understanding of the origin of selectivity now allows us to rationalize experimental observations relative to solvent effect in aziridination reactions of semistabilized sulfur ylides.

In the case of stabilized ylides, calculations confirm the experimentally observed reversibility of betaine formation. Computed energy profiles indicate moreover that the rate- and selectivity-determining step is the ring closure. This difference in mechanism, as compared to semistabilized ylides, is accounted for by the endothermicity of the betaine formation (due to stabilization of reactants) combined with the high barrier to ring closure. In stabilized ylide reactions, selectivity is thus determined solely by the relative energy of the two diastereomeric elimination TSs. Accordingly, the *cis* selectivity is explained by the lower steric strain around the *N*-sulfonyl group generated by the formation of the *cis* aziridine (as compared to the *trans* case).

Our analysis of reactivity and factors governing selectivity in reaction of semistabilized and stabilized sulfur ylides with imines should assist in the design of new reagents for highly stereoselective synthesis of aziridines.

Acknowledgment. Part of this work was carried out while the author was at the University of Bristol, and the author thanks Dr. Jeremy Harvey and Prof. Varinder Aggarwal for access to computer resources during that time and for helpful and pertinent comments then and since. The author is indebted to Profs J. Marchand-Brynaert and D. Peeters for their unconditional support. F.N.R.S. is acknowledged for financial support (R.R. is a "Collaborateur scientifique F.N.R.S.").

Supporting Information Available: Complete refs 19 and 20, full results on model reaction, tables with optimized Cartesian coordinates and corresponding energies for all species discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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