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Unraveling the Mechanism of Epoxide Formation from Sulfur Ylides and Aldehydes

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Abstract: Sulfur ylides $R_2S^+{-}C^-HR'$ react with aldehydes $R''{-}CHO$ to form epoxides, predominantly as the trans isomers, in a synthetically useful reaction which is increasingly used in its asymmetric variant with chiral sulfides. The mechanisms of the "model" reaction ($R = Me$, $R' = R'' = H$) and the reaction forming stilbene oxide ($R = Me$, $R' = R'' = Ph$) have been studied in detail using density functional theory, the B3LYP density functional, and flexible basis sets. It has been shown that for this reaction involving highly polar intermediates, continuum solvation models need to be used throughout to obtain reasonable results. For the reaction of benzaldehyde with dimethylsulfonium benzylide, the key steps are shown to be quasi [2 + 2] addition of the ylide to the aldehyde to form a betaine $R'{-}CH(S^+Me_2){-}CH(O^-){-}R''$ in which the charged groups are gauche to one another, and torsional rotation around the C−C single bond of the betaine to form its rotamer with the two charged groups anti. The final step, elimination of sulfide from this second rotamer of the betaine, is found to be facile. In the case of the anti pathway, leading to *trans*-stilbene epoxide, the initial addition is found to be rate-determining, whereas for the diastereomeric syn pathway, leading to the *cis*-epoxide, it is instead the torsional rotation which is slowest. These results are in excellent agreement with experiment, unlike previous computational work. The unexpected and apparently unprecedented (for C−C bond-forming reactions) importance of the torsional rotation step, especially in the syn case, is due to the fact that all the barriers involved are low-lying. This novel picture of the mechanism provides a sound basis for the future development of chiral sulfides for enantioselective epoxide synthesis.

Introduction

Given their tremendous importance in synthesis, there has been considerable interest in the development of asymmetric methods to prepare epoxides. Alkene oxidation has long been the most commonly used approach, with the most noteworthy examples being the Sharpless,[1,2] Jacobsen/Katsuki,[3] and Shi[4] epoxidations. Given the functional group and reactivity constraints on the use of these methods, many other approaches have also been used, such as the polyamino acid-based methods developed by Julia,[5−7] the asymmetric phase-transfer mediated epoxidation reactions developed by Lygo,[8] and the metal-catalyzed methods of Enders,[9] Jackson,[10] and Shibasaki.[11] In recent years, we[12] and others[13] have been developing an alternative synthesis based on the reaction of carbonyl compounds with sulfonium ylides.[14] When the ylides are generated in situ under mild, nonbasic conditions from diazocompounds (or, more safely, from the corresponding tosyl hydrazone salts) and chiral sulfides, this represents a versatile, convenient, organic-based,[15] and efficient route to epoxides with high

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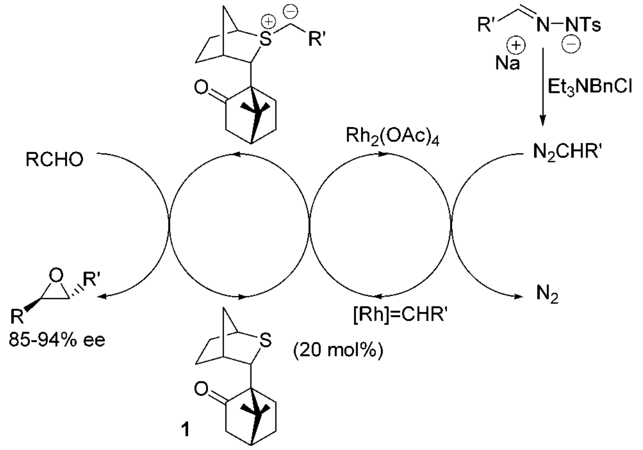
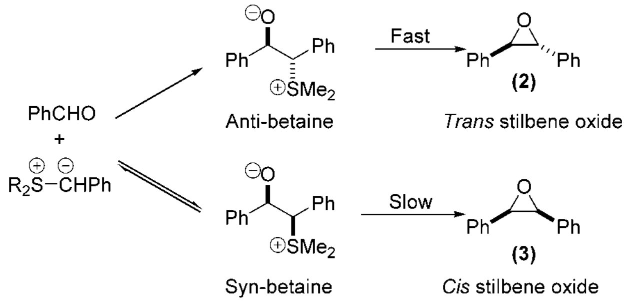
Scheme 1. Catalytic Process for Epoxidation



Scheme 2. Mechanism of Epoxidation Accounting for High Trans Selectivity



enantiomeric excesses. The process used is summarized in Scheme 1.

The efficient design of chiral sulfide catalysts for the asymmetric version of this reaction requires a fundamental understanding of the reaction mechanism. The basic features of this process are well understood, with initial addition of the ylide to the carbonyl group leading to a betaine, which then undergoes elimination of sulfide to yield the epoxide. However, the details are less clear: is it the initial addition or the elimination that is rate-determining? What is the stereoselectivity of these two steps? Some of these issues have been clarified by a recent study[16] in which the supposed betaine intermediates of these reactions were generated independently. From crossover experiments in which the betaines were decomposed in the presence of more reactive carbonyl compounds, and careful study of the cis/trans product ratios in the epoxides, it was possible to show that the two steps in the reaction mechanism are in fact very closely balanced. Thus, the observed diastereoselectivity in favor of *trans*-epoxides is found to be due to the fact that anti betaines undergo elimination without reversion to the ylide and aldehyde, whereas the corresponding syn diastereoisomers decompose back to reactants. In other words, addition of the ylide to benzaldehyde is irreversible in the anti case, leading to *trans*-epoxide, whereas in the syn (cis) case, the ensuing elimination of sulfide from the betaine is slow, resulting in competitive reversion to reactants. It is clear that the relative height of the corresponding barriers must be very finely balanced. It is therefore no surprise that minor changes to the system, such as changing from an aromatic aldehyde to an aliphatic one, can perturb the balance between the two steps.

Despite these extensive experimental investigations,[16] there remain a number of unclear issues relating to the reaction mechanism, and in particular to the structure of the corresponding transition states. Given the increasing availability and accuracy of computational methods, we therefore decided to carry out a thorough study of the reactions of Scheme 2, as a basis for future synthetic work. We are aware of two previous ab initio studies of the sulfur ylide epoxidation reaction. The first of these[17] was a study of the model reaction between formaldehyde and CH_2SH_2. The main focus of this very insightful paper was an attempt to understand the different behavior of sulfur and phosphorus ylides. Because of the very small model system studied, however, and the limited computational accuracy of the gas-phase computations that were possible at that time, the results are of only limited relevance to our interests in the condensed-phase process. The more recent study[18] uses more advanced methods to reinvestigate a slightly more realistic model process ($H_2C{=}O + H_2C{=}S(CH_3)_2$), but also addresses more complex reactions, including the phenyl-substituted reaction of Scheme 2. The results in this paper highlighted some of the severe difficulties involved in the computational study of the sulfur ylide epoxidation reaction. First and foremost, the reaction profile is strongly dependent on the treatment of solvation effects. This is not surprising given the development of separated charges in the betaine intermediates, which must be selectively stabilized by solvation as compared to the highly polar but uncharged reactants and products. Because of computational restrictions, however, the authors were not able to include a description of these solvent effects in anything more than a partial and ad hoc manner, which in turn led to a need to make further approximations. For example, some of the betaine structures do not correspond to minima in the gas phase, when an adequate, correlated, electronic structure method (e.g., density functional theory, DFT) is used. By chance, these structures *are* minima at the Hartree−Fock level of theory, so most of the geometry optimizations were carried out at that level of theory, with final energetics computed using DFT. Clearly, this approach is liable to lead to erroneous results. A further computational restriction came about due to the size of the systems, especially the substituted one of Scheme 2. The authors were not able to carry out full geometry optimization for the transition states involved, and also resorted to the use of small, unpolarized basis sets.

As will be seen below, these necessary compromises prevented Koskinen and Lindvall[18a] from obtaining an accurate picture of the reaction profile for this very complex system. An additional problem with this earlier study is more important and hinges on a fundamental assumption the authors have made concerning the mechanism. Thus, the addition step of the ylide to the carbonyl compound was assumed to be rate-limiting *in all cases*, and was assumed to occur via a transition state with an end-on arrangement of the carbonyl and ylide groups, in which the dialkylsulfonium and oxy groups are in an anti-like relation with respect to the new C−C bond. We shall call this mode of approach “transoid”, with the alternative quasi [2 +

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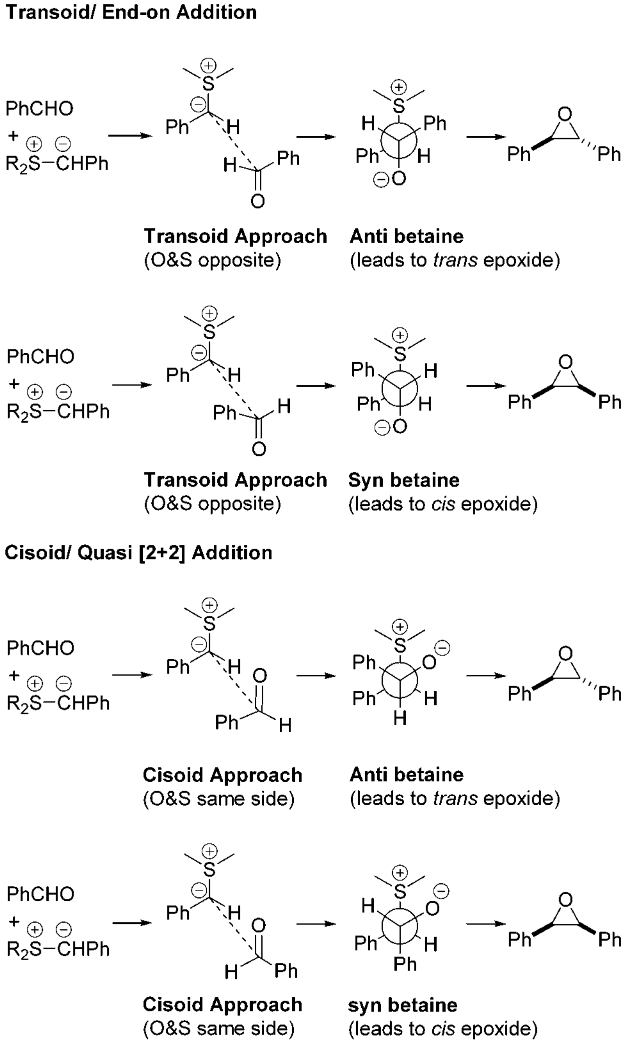
Scheme 3. Different Approaches of the Ylide to the Aldehyde and the Corresponding Stereochemical Outcomes



2] mode of addition, where the sulfonium and oxy groups are gauche or even eclipsed with respect to each other, referred to as "cisoid"(see Scheme 3 for a definition of these terms). We should point out that the authors did carry out computations on the cisoid addition step, as well as on the torsional rotation step we shall discuss below (the latter only for the model system), but ended up concluding that these steps were unimportant in the actual mechanism. The reason for making these two assumptions seems to have been that, taken together, they correctly lead to the prediction that *trans*-epoxides will be the major products. Understandable uncertainties about the accuracy of the computations would have made these assumptions plausible. However, the first of these assumptions is clearly contradictory with the experimental results described above; in the syn betaine diastereoisomers, the initial addition step is *not* rate-limiting and occurs faster than the subsequent elimination of sulfide. As we will see below, the true mechanism actually involves *cisoid* transition states for betaine formation, with the overall trans selectivity arising in a completely different and unexpected manner.

To reach these more reliable conclusions, we have carried out a fundamental computational reappraisal of the potential energy surfaces of the typical benzaldehyde + $PhCHS(CH_3)_2$ reaction shown in Scheme 2. To test our chosen methodology and for comparison with previous results, we have also studied the model reaction between formaldehyde and $H_2CS(CH_3)_2$ at the same level of theory. It is increasingly recognized how important it is to describe solvent effects in an adequate way in the theoretical treatment of such reactions;[19] for example, the mechanism of the Horner−Wadsworth−Emmons reaction has been well reproduced by theory only by including solvation.[20] Accordingly, our study includes the solvent, at the level of a continuum model, throughout. We have also used a reliable electronic structure method, density functional theory using the well-known B3LYP functional, throughout, together with flexible basis sets. This much more accurate approach has been made possible thanks to the development of more efficient algorithms[21] and of more powerful computers.

Computational Details

The bulk of the computations has been carried out using the Jaguar 4.0 pseudospectral program package.[22] All species have been fully geometry optimized, and the Cartesian coordinates are supplied in the Supporting Information. In most cases, the "loose" geometry convergence parameters within Jaguar (which correspond to rms gradients below 0.0015 hartree/au) have been used. Test calculations using the standard convergence criteria led to insignificant changes in bond lengths, angles, and energies, but were much more time-consuming due to very slow convergence of some floppy dihedral angle coordinates. 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 for the geometry optimization (additional diffuse functions on heavy atoms, that is, the 6-31+G* basis, were used for the model reaction; nearly identical geometries were obtained for this system without these diffuse functions). Because of the importance of solvent effects, the optimization was carried out on the basis of solution-phase total energies including free energies of solvation computed using the polarizable continuum−Poisson method as incorporated in Jaguar.[23,24] To model the properties of the solvents used in experimental studies, the continuum was assigned a dielectric constant of 39.5 (8.93), and a solvent probe radius of 2.18 (2.34) Å, corresponding to the properties of acetonitrile (dichloromethane, respectively). Frequency calculations for large molecules of the type studied here, especially if solvation effects 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 either include 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 else than minima (or transition states). Zero-point vibrational energies are expected to be more or less constant for the different species so that their neglect should be of little consequence.

Single-point energy computations at a variety of levels have been carried out at the B3LYP/6-31+G* or 6-31G* geometries obtained from optimization in acetonitrile. For the model system, gas-phase B3LYP/6-311+G* and MP2/6-311+G**, and solvated B3LYP/6-311+G**, energies have thus been obtained. The MP2 calculations were carried

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Table 1. Relative Energies (kcal/mol) of the Stationary Points for the Reaction between Dimethylsulfonium Ylide and Formaldehyde

level, basis set, solvent	B3LYP 6-31+G* acetonitrile	B3LYP 6-31+G* CH_2Cl_2	MP2 6-311+G** gas phase[a]	B3LYP 6-311+G** gas phase[a]	B3LYP 6-311+G** acetonitrile[a]
H_2CSMe_2, CH_2O	0.0	0.0	0.0	0.0	0.0
cisoid betaine (**6**)	−29.5	−26.5	−11.0	−8.0	−27.5
torsional TS (**7**)	−26.1	*b*	6.5	8.0	−24.2
cis elimination TS (**12**)	10.7	*b*	23.8	13.9	12.3
ransoid betaine (**8**)	−29.6	−25.2	1.8	3.7	−27.5
trans elimination TS (**9**)	−16.0	−14.7	−6.9	−8.0	−14.0
$CH_2CH_2(O)$, Me_2S	−36.6	−37.8	−39.4	−39.7	−30.0

[a] Single points at the B3LYP/6-31+G* (acetonitrile) optimized geometries. [b] Not studied at this level of theory.

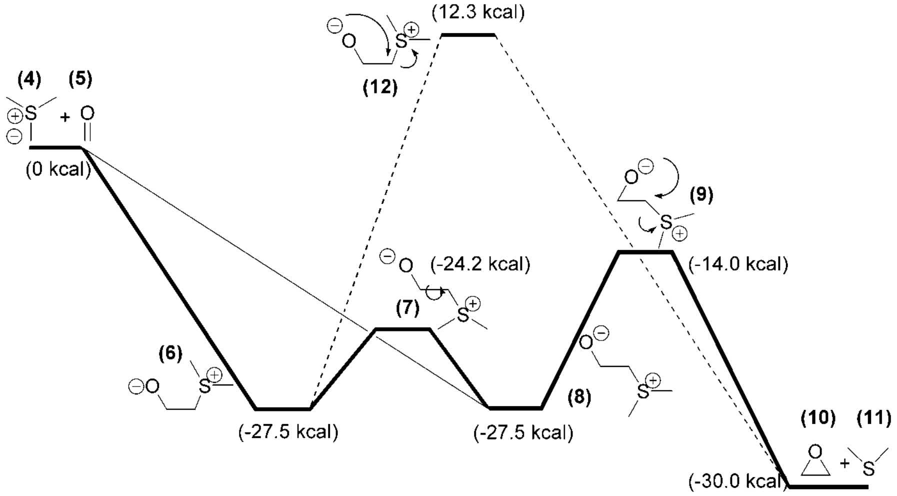

Figure 1. Computed potential energy surface for the model epoxidation reaction in acetonitrile. Energies are obtained at the B3LYP/6-311+G** (acetonitrile)//B3LYP/6-31+G* (acetonitrile) level and are given in kcal/mol relative to reactants.

out using the Gaussian 98 program package.[25] For the larger, substituted system, single-point energies have been derived at the gas-phase B3LYP/6-311+G** and acetonitrile-solvated B3LYP/6-311+G** levels. Note that in an exact reversal of the usual practice, the gas-phase energies computed for these systems are thus obtained as single points computed at the solution-phase geometries. This is because some of the stationary points do not exist in the gas phase. All the single-point total energies computed are given in the Supporting Information.

For the large reaction system coupling dimethylsulfonium benzylide with benzaldehyde, there are several local minima or saddle points corresponding to each intermediate or transition state. This is due to the possibility of forming different rotamers around the C−S bond. For example, there are two rotamers of the starting ylide, as discussed in ref 18a. We have, in most cases, explicitly located *all* these local minima, but the data presented refer to the lowest one only except where otherwise mentioned.

As discussed below, we found the key point along the potential energy surface to be the TS's for torsional rotation around the newly formed C−C single bond of the betaines. Because rotation from cisoid to transoid rotamers can, in principle, occur in both directions, it was crucial to identify the lowest energy pathway. Accordingly, we first determined a rough energetic profile as a function of the O−C−C−S dihedral angle, θ. This was done by optimizing the geometry at the B3LYP/6-31G* (acetonitrile) level of theory, while holding the value of θ frozen at values between −180° and 180°, and with 20° intervals. This allowed us to identify which pathway was at lower energy. We then refined the geometry and energy of the corresponding transition state by normal geometry optimization. The two torsional rotation profiles are attached as Supporting Information.

Results

In this section, we will first present our results concerning the model reaction between dimethylsulfonium methylide (**4**) and formaldehyde (**5**) to give ethylene oxide (**10**) and dimethyl sulfide (**11**). We shall then discuss the reaction of dimethylsulfonium benzylide with benzaldehyde, shown in Scheme 2. This part of the section will be further divided into an initial discussion of the general features of the potential energy surface, and how it differs from that of the model reaction, followed by the results concerning the differences between the two diastereomeric pathways, which lead to the overall experimental stereoselectivity.

A. Model Reaction. Our results for this system are on the whole very similar to those of ref 18a, and are summarized in Table 1, with the reaction profile at the most accurate B3LYP/6-311+G** (acetonitrile)//B3LYP/6-31+G* (acetonitrile) level of theory shown in Figure 1. Addition of the ylide to formaldehyde leads to formation of a betaine. As previously discussed (see Scheme 3), the ylide and aldehyde can approach in an "end-on" (transoid) or quasi [2 + 2] (cisoid) way. Although we were able to locate low-lying transition states for these C−C bond-formation steps in the gas phase, these barriers disappear upon inclusion of solvation effects. A set of constrained geometry optimizations at successively smaller values

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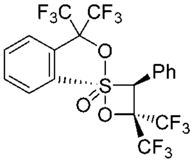

Figure 2. Okazaki's stable oxathietane.

of the C−C distance was carried out to check that the interaction between reactants is indeed uniformly attractive in solution.

The first intermediate in the reaction, which is a β-oxy dimethylsulfonium ion or betaine, is thus formed without barrier. There are, in fact, two distinct rotamers of this betaine, corresponding respectively to the cisoid and transoid approach pathways. We will refer to these different conformers of the betaine as the cisoid (**6**) and transoid (**8**) rotamers. As expected, the stability of both betaine rotamers, which are zwitterionic structures, is strongly enhanced by solvation relative to the fairly polar but uncharged reactants. This large stabilization accounts for the fact that no addition barrier leading to these intermediates could be found in solution.

It is to be noted that the epoxidation mechanism has sometimes[18a,26,27] been considered to involve an oxathietane, which is a cyclic intermediate related to the cisoid betaine but with an S−O single bond instead of separated charges. The proposed intermediacy of these structures in epoxidation is based on the observation of some oxathietanes as stable compounds,[26,27] and on the fact that they yield epoxides upon heating. The structure of one of these stable compounds, as proven by X-ray crystallography,[26] is shown in Figure 2. This compound has an endocyclic S−O bond length of 1.82 Å, clearly indicating the existence of a chemical bond between these atoms. It should, however, be noted that this oxathietane is chemically distinct from those which would be formed in the standard sulfur ylide reaction, in that the sulfur atom has one alkoxy and one aryl substituent, instead of two alkyl groups, and also bears an additional oxo ligand. We were able to reproduce the X-ray structure of this intermediate in a B3LYP/6-31G* geometry optimization (e.g., $r_{S-O} = 1.845$ Å), confirming that there is no computational bias which disfavors such cyclic structures. However, the electronic structure of this compound is so different from that in our systems that this observation is not relevant to the standard epoxidation mechanism. Thus, for both the model reaction considered here and the substituted reaction discussed below, both gas-phase and solvated geometry optimizations of the cisoid structure lead to a structure that is clearly best described as that of a betaine. The optimized S−O distance in acetonitrile, for instance, is of 2.81 Å, well above the value which would correspond to a bond between these atoms. We also attempted geometry optimization starting from an oxathietane-like structure to explore the stability of this putative isomer, but the same betaine-like geometry was obtained. Clearly, the energetic gain associated with bonding between these atoms is more than offset by the ring strain it would entail.

In the gas phase, the transoid betaine (**8**) is not a minimum on the potential energy surface, with all attempts at geometry optimization leading instead directly to the products, dimethyl sulfide and ethylene oxide via S_N2-like substitution at carbon by the oxy group (**9**). In solution, however, the charges on oxygen and sulfur are extensively stabilized, and elimination now involves passing over a significant barrier of 13.5 kcal/mol. In the single-point gas-phase computations, this barrier lies *lower* in energy than the betaine! Elimination from the cisoid betaine can take place *via* two different pathways. The first of these involves torsional rotation around the C−C bond to form the transoid betaine, followed by elimination as above. As expected for rotation around an unhindered C−C single bond, the barrier to torsional rotation (**7**) in solution is very low. In the gas phase, this rotation involves an unfavorable separation of the negatively and positively charged groups, and is therefore endothermic, with a small supplementary barrier in excess of the overall energy change. The other elimination pathway from the cisoid betaine is via direct, cis elimination corresponding to a "frontside" S_N2 substitution step with retention of configuration (**12**). This step, however, involves a significant activation barrier.

The relative energies in the first and last columns of Table 1, obtained respectively at the B3LYP/6-31+G* (acetonitrile) and B3LYP/6-311+G** (acetonitrile)//B3LYP/6-31+G* (acetonitrile) levels, can be seen to be rather similar, suggesting that basis set effects are not enormous in this system. Comparison of the first and second columns shows that the overall effect of solvation is rather similar in dichloromethane and in acetonitrile. This is in reasonable agreement with experiment, where both solvents have been used for this reaction without observation of major changes in reactivity. It is also encouraging for the accuracy of the continuum solvation model, because these two solvents correspond to rather different parameters (dielectric constant and cavity shape) and yet yield similar results, showing that the results obtained do not have an exaggerated sensitivity to the details of the solvent model. Finally, the single-point calculations in the gas phase at the B3LYP/6-311+G** and MP2/6-311+G** levels are in reasonable agreement, except perhaps for the barrier to cis elimination of dimethyl sulfide (which is anyway only of limited relevance to the overall mechanism). This suggests that the present system does not constitute one of the occasional cases for which density functional theory gives unreliable results.[28,29]

B. Reaction of Phenyl-Stabilized Ylide. In this second and most important part of our work, we have addressed a much more realistic reaction, in which the nature of the substituents is very similar to those used in the asymmetric version: the production of *cis*- or *trans*-stilbene oxide from dimethylsulfonium benzylide and benzaldehyde (see Scheme 2). The introduction of substituents can be expected to exert a considerable effect on the reaction profile, due to stabilization of the partial charges in the reactants, steric effects, and the fact that the betaine intermediates can now have multiple diastereoisomers as well as rotamers. These factors, combined with the much greater computational expense associated with the much larger system, mean that previous work on this system[18a] has

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(26) Ohno, F.; Kawashima, T.; Okazaki, R. *J. Am. Chem. Soc.* **1996**, *118*, 697−698.

(27) Kawashima, T.; Ohno, F.; Okazaki, R.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **1996**, *118*, 12455−12456.

(28) For a critical survey of the application of density functional theory methods to chemical systems, see: Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2000.

(29) For a recent example, see: Brönstrup, M.; Schröder, D.; Kretzschmar, I.; Schwarz, H.; Harvey, J. N. *J. Am. Chem. Soc.* **2001**, *123*, 142−147.

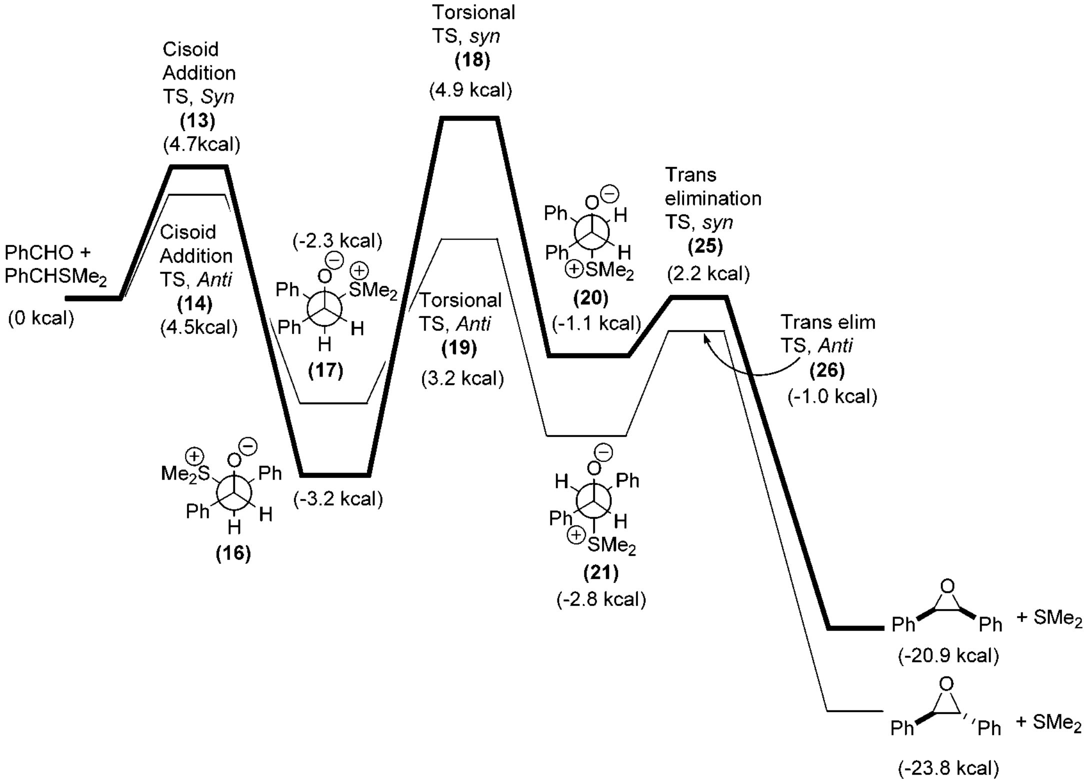

Figure 3. Computed potential energy surface for the epoxidation reaction between benzaldehyde and dimethylsulfonium benzylide. Energies are obtained at the B3LYP/6-311+G** (acetonitrile)//B3LYP/6-31G* (acetonitrile) level and are given in kcal/mol relative to reactants. For clarity, some of the stationary points have been omitted; see Table 2 for a complete set of energies.

Table 2. B3LYP Relative Energies (kcal/mol) of the Stationary Points for the Reaction between Phenyl Dimethylsulfonium Ylide and Benzaldehyde, with the Indicated Basis Set and Treatment of Solvation

	6-31G* acetonitrile	6-311+G** gas phase[a]	6-311+G** acetonitrile[a]
$PhCHSMe_2$, PhCHO	0.0	0.0	0.0
cisoid add TS, syn (**13**)	4.3	5.0	4.7
cisoid add TS, anti (**14**)	5.2	6.9	4.5
cisoid add TS, anti (rotamer) (**15**)	6.5	7.4	6.8
transoid add TS, syn (**22**)	7.9	13.2	6.3
transoid add TS, anti (**23**)	9.5[b]		
cisoid betaine, syn (**16**)	−4.6	0.7	−3.2
cisoid betaine, anti (**17**)	−2.8	3.0	−2.3
torsional TS, syn (**18**)	8.2	18.9	4.9
torsional TS, anti (**19**)	8.0	16.5	3.2
cis elimination TS, syn (**24**)	14.3	15.1	16.2
transoid betaine, syn (**20**)	3.7	15.6	−1.1
transoid betaine, anti (**21**)	2.3	15.1	−2.8
trans elimination TS, syn (**25**)	5.2	13.6	2.2
trans elimination TS, anti (**26**)	2.7	12.4	−1.0
PhCHCH(O)Ph (cis), Me_2S	−27.4	−27.0	−20.9
PhCHCH(O)Ph (trans), Me_2S	−30.9	−29.9	−23.8

[a] Single points at the B3LYP/6-31G* (acetonitrile) optimized geometries. [b] It was not possible to fully converge this structure. The energy was obtained as the maximum for a set of partial geometry optimizations with fixed C−C distances (see Supporting Information for this profile).

been much less systematic and at an overall lower level of theory than that on the model reaction.

Our results concerning the potential energy surface for this reaction are shown in Table 2, with the reaction profile at the B3LYP/6-311+G** (acetonitrile)//B3LYP/6-31G* (acetonitrile) level illustrated in Figure 3. The profiles corresponding to the distinct diastereoisomeric pathways leading to *cis*- and *trans*-stilbene oxide are rather similar.

A striking feature of the potential energy surface is how close in energy all the stationary points lie in the solution calculations, with the exception of the final products, and of the cis elimination transition state (**24**). Our computations therefore need to be very accurate to be able to predict the course of the reaction through the different competing steps. It is perhaps appropriate to start with a brief discussion of the accuracy of our results. The most obvious source of error is the choice of the B3LYP DFT electronic structure method. This is known to lead in some cases to errors on relative energies as large as 10 kcal/mol,[28,29] with errors of 5 kcal/mol not at all uncommon. In the present case, however, the key energy differences concern diastereoisomers with nearly identical electronic structures, and the errors on their relative energies should cancel. Another source of error is the limited size of the 6-311+G** basis set used for final energy computations and the use of the modest 6-31G* basis for geometry optimization. Here, past experience together with the good agreement between the small and large basis set energies suggests that basis set effects are not a major problem. Next, the energies in Table 2 are electronic energies, while the kinetics depend instead on the corresponding free energies. However, the difference between the electronic energy and free energy profiles should be rather predictable; unimolecular species on the energy surface will be selectively destabilized by roughly 10 kcal/mol in terms of free energy, with respect to the "bimolecular" reactants and products.[30] The error involved in assuming that this off-shift will be the same for all the intermediates and transition states, and especially for the two diastereoisomers of the same stationary point, will typically be very small. Finally, there are two sources of possible error in the solvation model we use. First, the use of the continuum model may yield errors of several kcal/mol in the worst cases,[23] but comparison of our results with different solvents suggests the method is behaving well, and error cancellation can anyway be expected to occur. The second problem is that our electronic structure computations assume an adiabatic relaxation of the solvation at the transition state, neglecting the solvent reorganization dynamics.[19] This effect may well lead to small differences between, for example, the initial addition step, during which separate charges develop and solvation effects increase significantly, and the torsional rotation step in which the charges merely move around. Overall, even after taking all these possible sources of inaccuracy into account, we believe that our calculated energy differences are probably reliable to within 2−3 kcal/mol and that the crucial energy differences between diastereoisomeric systems are even more accurate. The main qualitative conclusions drawn from our study should thus be reliable, although the apparent excellent agreement with experiment is certainly in part fortuitous.

B1. General Features and Reactivity. The first step in the reaction mechanism, C−C bond formation to give the betaine, is much less exothermic than in the model reaction. This can be readily understood since the phenyl groups significantly stabilize both the ylide and the aldehyde, whereas stabilization of the betaine by these substituents is likely to be negligible. In fact, the steric bulk of the phenyl groups also decreases the extent of solvent stabilization of the betaines by partially impeding solvent access to the charged groups. Because the addition is less exothermic, there is now a barrier to addition, although it is rather “early” in nature, with critical C−C bond lengths close to 2.1 Å, and also lies very low in energy relative to the reactants. As mentioned above, a *free energy* profile analogous to the electronic energy profile of Figure 3 would look somewhat different for this first step. The loss of translational and rotational degrees of freedom upon bringing the reactants together is unfavorable, so that the addition transition state and all subsequent stationary points (except the products) should be mentally shifted upward by ca. 10 kcal/mol[30] to obtain the profile in terms of the free energy.

Only the barriers leading to the cisoid rotamers of the betaines are shown in Figure 3 (for a definition of the “cisoid”, “transoid”, etc. terminology used, see Scheme 3). This is because the barriers leading to transoid betaine formation [(**22**) and (**23**)] lie higher in energy, as shown in the Table,[31] and are not expected to play any role in the mechanism. The reason for this preferred orientation of the reactants during the initial addition step seems to be the favorable Coulombic interaction between the dipoles of the polar reactants.

This Coulombic preference carries over onto the betaines themselves; the cisoid rotamers of both diastereoisomeric betaines are found to be more stable than their transoid congeners, especially in the gas phase, of course, but also, albeit to a much lesser extent, in solution. This is different from the situation in the model reaction, where the two rotamers were nearly isoenergetic in solution. This is partly due to the steric effect already discussed above. The close spatial proximity of the oxy and dimethylsulfonium groups in the cisoid rotamers means that these groups interact favorably both in the model and in the “real” systems. In the model system, solvent access to these groups in the transoid rotamer is excellent, and the higher solvation energy for this rotamer (46 kcal/mol) is enough to compensate for the Coulombic stabilization of the cisoid rotamer (solvation energy 34 kcal/mol). In the present, more sterically hindered, system, solvation of both rotamers is less favorable, and the differential solvation effect, while still large (e.g., for the syn diastereoisomers, the solvation energies of the transoid and cisoid rotamers are respectively of 31 and 21 kcal/mol), is no longer large enough to compensate for the intrinsic lower stability of the transoid rotamer.

The overall epoxidation reaction is only slightly less exothermic for production of stilbene oxide than it is for the model reaction. However, betaine formation is much less exothermic. Therefore, elimination to form products is more exothermic in the present reactions. On the basis of the Hammond postulate, it is therefore not surprising that the barrier to elimination from the transoid rotamers is lower than in the model system. As can be seen in the scheme, this activation energy is in fact *extremely* low, at only 1−2 kcal/mol. Expressed in other terms, the ring-forming nucleophilic substitution is more facile for the substituted betaines than for the model system, probably because of benzylic stabilization of the TS and maybe also because the oxy group of the betaine is somewhat less stabilized by solvation. As in the model system, there is no barrier to elimination in the gas phase, so that gas-phase optimization of transoid betaines leads directly to products, and the gas-phase single-point computations show the barrier to lie *lower* in energy than the betaines.

An interesting situation arises concerning the pathway leading by cis-elimination (“frontside” S_N2 substitution of the dimethylsulfonium group, TS **24**, see (**12**) in Figure 1) from the cisoid betaines directly to the products. In the gas phase, this is actually the lowest-energy route to products from reactants! Even in solution, the barrier to this “frontside” nucleophilic substitution step is relatively low by the standards of many chemical reactions. However, it is not substantially stabilized in solution, whereas the barriers to the “normal” anti elimination via the transoid betaines [(**25**) and (**26**)] are well solvated, and thus lie well below it in energy, so that this latter mechanism is clearly the preferred one in solution. This highlights the vital importance of accounting correctly for solvation effects in reactions like the present one which involve highly polar intermediates − gas-phase results would lead to misleading conclusions!

Because all the main transition states along the reaction pathway are so low, it is obvious that the epoxidation reaction should be very fast. This is in excellent qualitative agreement with experimental observations. Indeed, when preformed sulfur ylides are used, the reaction is often complete within 30 min,

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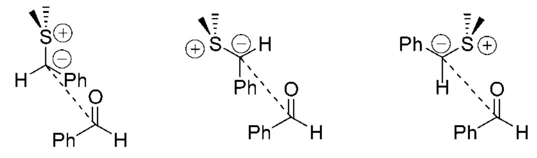
(30) This figure of 10 kcal/mol results from standard gas-phase statistical mechanics. Upon going from two molecules to form one complex, intermediate, or transition state, there is a large (ca. 30 cal/mol/K) decrease in entropy, due to the loss of rotational and, especially, translational degrees of freedom. This correlates to the mentioned increase in free energy. In solution, the situation is slightly different for two reasons: (i) the solvent may undergo a change in entropy due to the different solvation of reactants and intermediates. This effect is treated, at least approximately, by the continuum model of ref 23. (ii) Estimates based on gas-phase formulae of the translational entropy loss occurring in solution may be somewhat too large and thus not directly appropriate (for a discussion, see, for example: George, P.; Siegbahn, P. E. M.; Glusker, J. P.; Bock, C. W. *J. Phys. Chem. B* **1999**, *103*, 7531−7541). This is why the 10 kcal/mol we mention is only a rough estimate. However, for the important energy differences between diastereoisomers, only small differences can be expected.

(31) Geometry optimization of the transoid transition states was marred with considerable difficulties, with many jobs reverting to cisoid geometries or failing to converge altogether.

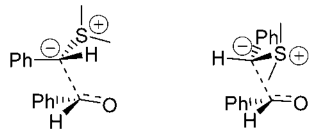


Cisoid Addition TS, *Syn* **(13)**

Cisoid Addition TS, *Anti* **(14)**

Cisoid Addition TS, *Anti* (rotamer) **(15)**

Figure 4. Addition transition states giving rise to lowest energy betaines.



Cisoid Addition TS, *Anti* **(14)**

Cisoid Addition TS, *Anti* (rotamer) **(15)**

Figure 5. Different views of addition transition states **14** and **15**.

even at −78 °C. Another consequence of the low energy barriers to the key C−C and C−O bond-forming steps is that the height of the barriers to rotation around the central C−C bond of the betaines is no longer negligible. In fact, the activation barriers of 8.1 and 5.5 kcal/mol (for the syn and anti systems, respectively) for isomerization of the initially formed cisoid rotamers to give the transoid isomers, which can then undergo elimination, are the largest of all the energy barriers along the reaction profiles!

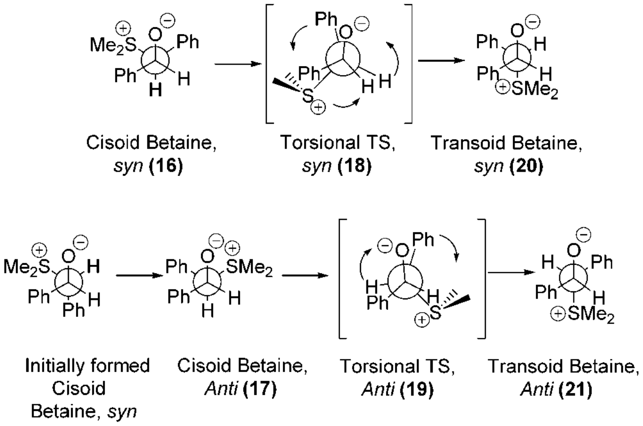
B2. Differences between Diastereomeric Pathways. 1. Formation of Betaines. We now turn to a discussion of the differences between the formation of the syn and anti betaines which lead respectively to *cis*- and *trans*-stilbene epoxide. The activation barriers involved in the initial addition step are very similar, with a very slight preference for the anti betaine. It is instructive to examine the structure of these TS's, as illustrated in Figure 4. As can be seen, the syn TS adopts a geometry in which the substituents on the two reactants are close to being eclipsed (with an S−C−C−O dihedral angle of only 12°). This is presumably the preferred orientation for the addition TS, since it maximizes the favorable Coulombic interactions between the dipoles on the two reactants. Steric repulsion between the other groups is not too large in this diastereoisomer, partly of course due to the distance between the two moieties in this very early transition state, and partly because the phenyl group of the aldehyde is eclipsed with the hydrogen atom of the ylide, and vice versa. The lowest-lying anti TS, in contrast, is more staggered (S−C−C−O dihedral angle of 74°). This must reflect the fact that the eclipsed orientation would be sterically unfavorable, due to interaction between the two phenyl groups; a tradeoff between this factor and the Coulombic factor favoring the eclipsed orientation leads to the observed staggered orientation. Overall, the transition state appears to be fairly flexible, since this observed deformation does not lead to any significant difference in energy. In this case, we have included a higher-lying rotamer of the anti cisoid transition state. In the lower-lying TS just discussed, the phenyl group of the aldehyde lies gauche to both the dimethylsulfonium and the phenyl groups, which might be expected to be less favorable than the other rotamer, in which it is the "small" oxy group which lies gauche to these two more bulky groups. We were slightly surprised, therefore, to find that this other TS (**15**), which is closer to the eclipsed geometry (S−C−C−O dihedral angle of 18°), lies somewhat higher in energy. Careful inspection of the structures suggests that this higher energy is due to steric hindrance between the dimethylsulfonium group and the *hydrogen* atom on the aldehyde. This interaction occurs because the sulfur ylide and the aldehyde do not approach each other with an exactly parallel arrangement of the two molecular planes. Instead, the ylide approaches the aldehyde with a C- - -C═O angle of 108°, and with the approximate plane around the ylide carbon atom tilted also. This means that some of the substituents interact more than others. These features are common to all the addition TS's, but the pattern of substituents is such that of the three transition states mentioned here, only the a priori more favorable rotamer of the anti transition state is significantly sterically hindered (Figure 5). These and all other optimized structures are deposited as Supporting Information.

We now turn our attention to the betaines. These will initially be formed as cisoid rotamers. For both the syn and the anti diastereoisomers, there are in fact *two* cisoid rotamers, corresponding to O−C−C−S dihedral angles θ of approximately +60° or −60°, respectively. The energies in Table 2 correspond to the more stable of these two forms in each case. As can be seen, the syn betaine is found to be slightly more stable than the anti diastereoisomer. This is due to the fact that once the C−C bond is completely formed, steric hindrance becomes larger, and there are more gauche interactions in the anti diastereoisomer.

2. Carbon−Carbon Bond Rotation To Form Transoid Betaine. Elimination occurs from the transoid betaines, in which the O−C−C−S dihedral angle is near 180°. To reach this rotamer starting from the cisoid betaines, it is necessary, as discussed above, to pass over a torsional rotational barrier. It might appear at first that there are *two* alternative barriers, depending on whether one starts from the rotamer of the cisoid betaine with $\theta = +60°$, or that with $\theta = -60°$. In fact, these two cisoid rotamers should interconvert very readily, in both the syn and the anti betaines, because the corresponding torsional rotation barrier near $\theta = 0$ lies at very low energy in both cases, due to the favorable interaction between the negative oxy and positive sulfonium groups. The rotation will therefore occur through whichever of the two barriers at $\theta \approx \pm 120°$ lies lowest in energy. As mentioned in the Computational Details section, in both cases, we have computed a rough profile of the energy as a function of θ to ensure that we have indeed located the lowest rotational barrier.

Crucially, the energetic situation at the cisoid betaine minima, favoring the syn form, is *reversed* at the rate-limiting torsional rotation barriers; the barrier for the syn system lies significantly higher, at +4.9 kcal/mol, versus +3.2 kcal/mol for the anti case. It should again be stressed that the *only* difference between these two systems is the relative orientation of the substituents around the two carbon atoms, so that any errors arising from the electronic structure methods should be by and large identical, and thus cancel out when the relative energy of these points is considered. We therefore believe that this energy difference, though quite small, is reasonably reliable. Because the syn cisoid betaine is more stable to start with, the difference between the overall activation barriers for torsional rotation between the two diastereomeric systems is even larger, at 8.1 and 5.5 kcal/mol, respectively, for the syn and anti cases. The difference in energy

Scheme 4. Lowest Energy Pathways from Initially Formed Betaines to Transoid Betaines



can again be rationalized on the basis of Newman projections, as shown in Scheme 4. In the barrier for the anti diastereoisomer, there are eclipsed interactions between phenyl and H, dimethylsulfonium and H, and oxy and phenyl. None of these interactions is expected to be particularly repulsive. For the syn diastereosiomer, on the other hand, there is an eclipsed interaction between a phenyl group and the dimethylsulfonium group, which is likely to be quite destabilizing.

Discussion

The results discussed above for the phenyl-substituted version of the ylide + aldehyde epoxidation reaction lead to very clear conclusions concerning the likely mechanism. There are two important steps along each of the diastereoisomeric pathways leading to cis and trans products: The first one is addition of the ylide to the aldehyde to form a betaine. The preferred quasi [2 + 2] or cisoid approach of the two polar groups, with an eclipsed or near-eclipsed orientation of the dimethylsulfonium group and the oxygen atom at the addition transition state, is due to favorable Coulombic interactions, and explains why the betaine will be formed in what we call a "cisoid" conformation initially. Although we also found transition states for an "end-on" mode of approach of the reactants, leading directly to the "transoid" rotamers, these barriers lie higher in energy and are unlikely to play a significant role in the mechanism. We note that this conclusion about the initial addition step is consistent[32] with the empirical predictions by Seebach et al.[33] concerning the stereochemical features of transition states for addition of nucleophilic species $RR'C^{\delta-} = X^{\delta+}$ to electrophilic ones $RR'C^{\delta+} = Y^{\delta-}$.

In ref 18a, the authors have in fact *assumed* that, contrary to our results, the transoid addition pathway is preferred, as this is one way to explain the observed trans selectivity of the overall epoxidation process. However, this model for the reaction mechanism cannot account for the experimental results, as discussed in the Introduction.

Addition of the ylide to benzaldehyde leads to the cisoid rotamers of the syn and anti betaines. On the basis of the small difference in energy between the two corresponding transition states, formation of the anti betaine is predicted to slightly dominate, but the difference should be very small. This means that the addition step cannot be product-determining, since if it was, the anti betaine, which leads to *trans*-stilbene oxide, would be formed in similar quantities to its syn diastereoisomer, and thus the trans/cis ratio of the products would be very low, whereas the trans selectivity is known experimentally to be large. We have indeed found a second step which also involves a significant activation barrier, rotation around the C−C bond to lead from the cisoid rotamer of the betaine to the transoid rotamer. The barriers for these two steps lie at very similar energies, and the small difference in steric effects in the syn and anti systems means that the rate-determing step is different in the two cases.

For the anti system, the initial addition *is* the slowest step, with the ensuing torsional rotation and ring-forming nucleophilic substitution occurring faster. The situation along the syn pathway is different; the relatively high barrier for the torsional rotation step means that this is the highest energy point, in terms both of electronic and of free energies. Although this second transition state is only slightly (0.2 kcal/mol) higher in energy than the initial one for C−C bond formation, it is very plausible, given the computational uncertainties, that rotation around the C−C bond to form the corresponding transoid betaine is the rate-determing step in this case. Given that this is also the interpretation which is most consistent with the experimental results,[16] we think it is reasonable to make this assumption. This is a remarkable conclusion − almost the first thing one learns as a chemistry undergraduate is that rotation around C−C single bonds is extremely facile. In fact, we believe that the present case in which such a step is rate-determining is the first of its kind.[34] This exceptional behavior is not due to the barriers for rotation being particularly high − we wish to underline that there is no unusual electronic contribution hindering rotation. Instead, this barrier comes to dominate because all the other, a priori far more complicated reaction steps, involving C−C, C−O, and/or C−S bond formation or breaking, occur with such unusually low barriers.

The origin of the diastereoselectivity can best be understood by re-expressing the above discussion of the rate-limiting steps in slightly different form; thus, both cisoid betaines are formed at roughly the same rate. Each of them can then undergo one of two competing steps: reversion to reactants, and rotation around the C−C bond. Because the activation energies for these two steps are close, this competition, which will ultimately determine the ratio of trans to cis products, is finely balanced. Our computations are in excellent (although certainly partly fortuitous) qualitative agreement with the experimental results. Thus, in the anti system, the barrier for reversion to reactants (6.8 kcal/mol) is somewhat higher than that for rotation (5.5 kcal/mol) and subsequent trans elimination, so that the latter step should predominate. This is in agreement with the experimental observation[16] that, upon independent generation from the corresponding β sulfonium alcohol, this betaine

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[32] However, the lowest-lying addition transition state we have found is not the one predicted from the rules given in that reference, which is actually the one we have called "add TS anti (rotamer)". This is due to the particular features of the present system, essentially the nature of the steric interactions arising as a consequence of the fact that the addition transition states deviate from the ideal quasi [2 + 2] geometries assumed in the model of ref 33.

[33] Seebach, D.; Golinsky, J. *Helv. Chim. Acta* **1981**, *64*, 1413−23.

[34] This rather strong claim may be incorrect as despite a thorough literature search, we cannot exclude the fact that a similar observation may have been made elsewhere. We do, however, point out that rotation around bonds with partial multiple bond character would be a different case, as do also the many cases where C−C bond rotation plays a role in, for example, selectivity without being rate-limiting. In any case, our mechanistic conclusions remain valid whatever the truth of this claim.

converts quantitatively to products, that is, dimethyl sulfide and *trans*-stilbene epoxide. In contrast, for the syn cisoid betaine, reversion to reactants over a barrier of 7.9 kcal/mol is slightly more easy than torsional rotation (8.1 kcal/mol), and should thus dominate over slower conversion to products. This is in agreement with the observation[16] that this betaine yields *trans*-epoxide upon independent generation (other related betaines give a mixture of *cis*- and *trans*-epoxide), and also gives rise to crossover products upon reaction in the presence of a more electrophilic aldehyde.

One interesting prediction to emerge from these computations concerns solvent effects on the diastereoselectivity. Part of the reason for the high barrier to rotation around the C−C bond is that the transoid betaines resulting from this rotation are slightly less stable than the starting cisoid betaines. It might be expected that more polar solvents, for example, protic ones, may provide better stabilization for the transoid betaines. The cisoid rotamers will be less affected, because the close attractive interaction between the negative oxy and positive dialkylsulfonium groups means that these groups are less in need of solvation. However, this interaction is essentially completely lost at the torsional rotation transition states, so that these too will be stabilized relative to the initially formed cisoid betaines. This should lead to a decrease in the diastereoselectivity of the reaction, because the syn betaine may not undergo near-exclusive reversion to reactants. Indeed, preliminary experiments have supported this prediction.[35] In general, the balance between the different transition states is so delicate that other small changes in the conditions, such as small changes in the bulk of the aryl or alkyl chains, or of the substituents on sulfur, may affect the height of the rotational barriers and so could change the diastereoselectivity.

In the *chiral* version of the reaction, where the sulfide is asymmetric, the diastereoselectivity will be defined, as in the present case, by the relative height of the barriers corresponding to C−C rotation and C−C bond breaking leading back to products. These barriers should not depend too much on the chirality of the sulfonium group, provided it is not too bulky, so that the overall trans selectivity should be similar to that obtained in the nonchiral version of the reaction. The enantioselectivity, on the other hand, is entirely defined during the first addition step, depending on which of the enantiotopic faces of the ylide reacts with the aldehyde. The key transition state is thus that for anti cisoid addition, and future computational work to elucidate and rationalize the enantioselectivity with chiral sulfide catalysts can focus on this point. It is to be noted that this transition state adopts a quasi [2 + 2] configuration. The computations reported on asymmetric induction with chiral sulfides in ref 18b may lead to misleading results, since they make the assumption[18a] that the rate-limiting and enantioselectivity-defining step has instead an “end-on” transoid structure. Indeed, we[12a,b,36] and all others[37] have previously used this same incorrect model to account for the enantioselectivity in epoxidation reactions with chiral sulfonium ylides.

Conclusions

In this study, we have first shown that it is necessary to use very sophisticated computational methods to provide a consistent description of the potential energy surfaces for epoxidation of aldehydes by sulfur ylides. Thus, one needs to use realistic, large-scale systems so as to capture all the steric and stereochemical effects involved, a correlated electronic structure method such as density functional theory to describe the difference in energy between the various stationary points, and, above all, a systematic treatment of solvent effects because the gas-phase potential energy surfaces are completely different from the solution surfaces. Our study has been the first to meet all these criteria throughout and emerges with a strikingly new picture of the overall reaction mechanism. Thus, the step which is experimentally known to be rate-limiting in the syn case, elimination of the sulfide from an intermediate betaine, has been shown to consist in *two* separate steps: initial rotation around the C−C single bond of the initially formed cisoid betaine to form its transoid rotamer, and ring-forming elimination via S_N2-like substitution from the latter. Most unexpectedly, we have shown that it is, in fact, the former of these two steps which is truly rate-determining, an observation which we believe to be unprecedented. The well-known trans selectivity of epoxidation is explained as follows: initial C−C bond-formation step proceeds *at a similar rate* to form the two diastereoisomeric cisoid betaines, so that this *is not* the key step for establishing the selectivity. Along the anti pathway, it is the rate-determining step, with subsequent C−C bond rotation occurring relatively easily. Along the syn pathway, leading to the minor, cis product, C−C bond rotation is slow, and reversion to reactants occurs instead. Our predicted mechanism should assist in the design of chiral sulfide catalysts for the enantioselective version of the reaction.

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Supporting Information Available: Tables with optimized Cartesian coordinates for all species discussed in the text, together with corresponding total energies at the different levels of theory. Torsional rotation profiles for the syn and anti betaines (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) In the reaction between PhCHO and $PhCHSMe_2$, the diastereoselectivity is 97:3 in CH_3CN but only 62:38 in CH_3OH. We thank Imhyuck Bae for carrying out this work. The lower diastereoselectivity when ylide reactions are carried out in protic solvent has also been observed in the reaction of (2*R*, 5*R*)-2,5-dimethylthiolane, benzyl bromide, KOH, and PhCHO (see Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731−735). The diastereoselectivity was 94:6 in CH_3CN-H_2O (9:1) and 87:13 in H_2O.

(36) In our communications (ref 12a,c) and the full paper below, only end-on additions were considered, but in ref 12b we did discuss the relative merits of the quasi [2 + 2] versus end-on addition. The experimental data did not allow us to propose which of the two modes of addition is likely to be favored. Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, J. G.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604−2622.

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