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Base-Catalyzed Inversion of Chiral Sulfur Centers. A Computational Study

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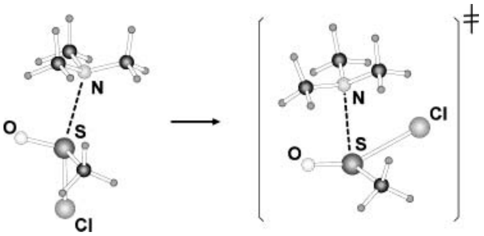
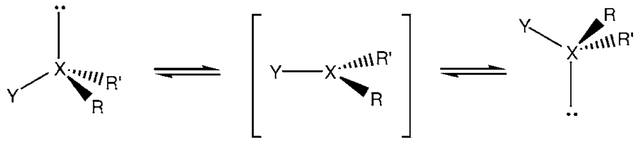
ABSTRACT



A theoretical study on the pyramidal inversion of the chiral sulfur compounds SO(X)(Me) (X = Cl, OMe, *p*-MePh) has been carried out by means of the DFT(Becke3LYP) method. Our results reveal that in the case of X = Cl, an organic tertiary amine such as NMe_3 can catalyze the racemization. The base-catalyzed inversion of SO(Cl)(Me) is proposed as a feasible dynamic kinetic resolution mechanism for the synthesis of chiral sulfoxides by the DAG method.

Chiral amines and sulfoxides can undergo thermal racemization by nitrogen or sulfur pyramidal inversion, respectively. In this mechanism, the absolute configuration of the tetrahedral chiral center is reversed by the intermediacy of a planar nonchiral structure (see Scheme 1). The nitrogen pyramidal inversion has been widely studied with both experimental[1−4] and theoretical[5−8] methods. In many cases, this reaction is fast at room temperature. Nevertheless, both electronic[9,10] and steric effects[11,12] are capable of producing optically active chiral nitrogen compounds by hampering the inversion. On the other hand, the more scarce studies on the pyramidal inversion of chiral sulfoxides, which can be light-induced,[13] pointed out that in most cases this process is very slow in mild conditions. Mislow and co-workers studied the

Scheme 1. Pyramidal Inversion of Amines (X = N, Y = Alkyl or Aryl) and Sulfoxides (X = S, Y = O)



R,R' = alkyl or aryl

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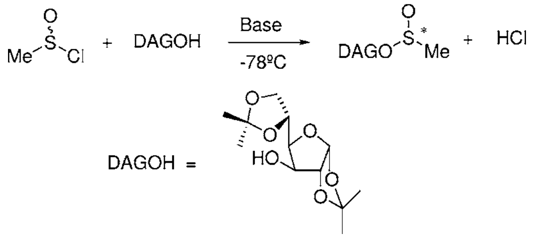
thermal racemization of several chiral sulfoxides.[14] According to these authors, the pyramidal inversion of many diaryl, alkyl aryl, and dialkyl sulfoxides occurs at a significant rate only above 200 °C. Only the racemizations of some arenethiolsulfinates[15] and allyl,[16] benzyl,[17] and vinyl[18] sulfoxides proceed under milder conditions.

Enantiomerically pure sulfoxides are organic compounds of increasing interest due to their application as chiral auxiliaries in asymmetric organic synthesis.[19] During the past 2 decades, different methods have been developed in order to efficiently synthesize optically active sulfoxides.[20] Recently, some of us developed the DAG methodology[21−23] a new and efficient synthetic route to chiral sulfoxides (see Scheme 2). In this method, the dynamic kinetic resolution[24,25] (DKR) of a sulfinyl chloride racemate in the presence of organic nitrogenated bases and the chiral alcohol DAGOH (diacetone-D-glucose) yields enantiomerically pure sulfinates. Subsequent addition of Grignard reagents gives rise to a broad family of optically active sulfoxides. Thanks to the DKR mechanism, high yields were obtained. The spontaneous inversion of the highly unstable sulfinyl chloride reagent has been proposed as a reasonable origin of the DKR. Nevertheless, to the best of our knowledge, the mechanistic details of the racemization of these compounds are unknown. In this paper we present a computational study of this mechanism with the Becke3LYP method,[26] showing that the organic base plays a key role catalyzing the racemization by pyramidal inversion of the sulfinyl chloride.

Scheme 2. DAG Synthetic Method



Before starting the discussion of our calculations on the sulfinyl chloride inversion we will use the kinetic experimental data published by Mislow and co-workers on the racemization of other sulfoxides as a reference in order to validate our theoretical model. These authors determined a free energy barrier ($\Delta G^{\ddagger}$) of 41.4 kcal/mol for the pyramidal inversion of (p-MeC$_6$H$_4$)SO(Me).[14] Using our model, we optimized the stationary point **1** as the minimum energy structure of (p-MeC$_6$H$_4$)SO(Me) (see Figure 1). Furthermore, the planar nonchiral structure **2** was optimized as a transition state of the potential energy surface. The transition vector of this saddle point consists of the oscillation of the sulfur atom above and below the (p-MeC$_6$H$_4$)(O)(Me) plane. Hence, **2** is the transition state for the pyramidal inversion of (p-MeC$_6$H$_4$)SO(Me). The variation of the Me−S−O−Ph dihedral angle from the minimum **1** (101.6°) to the transition state **2** (178.4°) clearly shows the structural mutation of (p-MeC$_6$H$_4$)SO(Me) from a tetrahedral to a trigonal planar geometry. On the other hand, the pyramidal inversion process implies the elongation of the S═O bond (from 1.525 Å in **1**

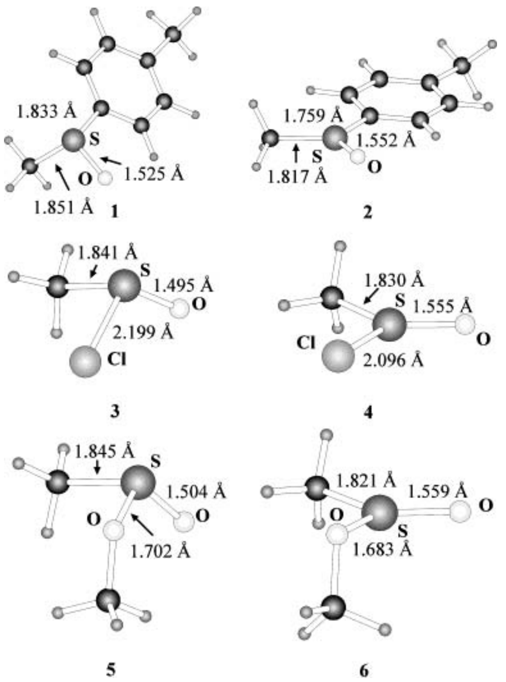


Figure 1. Optimized stationary points for the pyramidal inversion of (p-MeC$_6$H$_4$)SO(Me), SO(Me)(Cl) and SO(Me)(OMe).

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(26) All of the results reported in this paper were obtained using the hybrid Becke3LYP density functional as implemented within the Gaussian 03 package. The 6-31G(d) basis set was used for oxygen, nitrogen, carbon, and hydrogen. An effective core potential was used to replace the 10 innermost electrons of sulfur and chlorine. The valence double-ζ basis set associated to the pseudopotential in the program, with the contraction labeled as LANL2DZ, was used for these two elements, supplemented with a d shell. All optimizations were carried out without imposing geometrical constraints. The stationary points located in the potential energy hypersurface were identified as true minima or transition states through vibrational analysis. The connectivity between transition states and minima was confirmed through IRC calculations. All energetic values reported correspond to free energies at 25 °C and 1 atm. The chiral alcohol and the tertiary amines used in the DAG synthetic method were modeled as methanol and trimethylamine, respectively.

to 1.552 Å in **2**), coupled with the contraction of both S−Me (from 1.851 Å in **1** to 1.817 Å in **2**) and S−(p-MeC$_6$H$_4$) (from 1.833 Å in **1** to 1.759 Å in **2**) bonds. The computed value of the free energy barrier between **1** and **2** was 41.4 kcal/mol, in perfect agreement with the experimental value. The exact coincidence between the computational and empirical values is probably fortuitous but shows the suitability of our theoretical model.

After having confirmed the validity of our computational approach, we proceeded to the computational study of the species involved in the DAG synthetic method. The structures **3** and **4** were optimized as the minimum and the transition state, respectively, for the pyramidal inversion of the reactant sulfinyl chloride, SO(Me)(Cl) (see Figure 1). As in the case of (p-MeC$_6$H$_4$)SO(Me), the minimum has a tetrahedral geometry (∠Cl−S−O−Me = 99.8°), while the saddle point has a trigonal planar geometry (∠Cl−S−O−Me = 180.0°). Furthermore, the S═O bond is also elongated (from 1.495 Å in **3** to 1.555 Å in **4**) while the S−Cl and S−Me bonds are contracted (from 2.199 Å in **3** to 2.096 Å in **4**, and from 1.841 Å in **3**, to 1.830 Å in **4**, respectively). The calculated value of $\Delta G^{\ddagger}$ between **3** and **4** was 63.4 kcal/mol. Thus, the thermal racemization of SO(Me)(Cl) by pyramidal inversion is not a feasible DKR mechanism in the mild reaction conditions of the DAG synthetic method (−78 °C).

The racemization of the reaction product, the sulfinate SO(Me)(OMe), was also explored. The tetrahedral energy minimum **5** (∠MeO−S−O−Me = 103.5°) and the trigonal planar transition state **6** (∠MeO−S−O−Me = −177.2°) were located in the potential energy surface (see Figure 1). As in the case of (p-MeC$_6$H$_4$)SO(Me) and SO(Me)(Cl), the pyramidal inversion of SO(Me)(OMe) implies the elongation of the S═O bond (from 1.504 Å in **5** to 1.559 Å in **6**) coupled with the contraction of the rest of the bonds containing the sulfur atom (from 1.845 Å in **5** to 1.821 Å in **6**, for S−Me, and from 1.702 Å in **5** to 1.683 Å in **6**, for S−OMe). The free energy barrier found for the inversion of SO(Me)(OMe) was 64.1 kcal/mol. Hence, according to our theoretical results, the reaction product should be optically stable in the DAG reaction conditions, as has been observed experimentally.

The reoptimization of the stationary points **3** and **4** introducing a trimethylamine molecule interacting with the sulfur atom converged into the energy minimum **7** and the transition state **8** (see Figure 2). As in the case of **2**, **4**, and **6** the transition vector of the saddle point **8** corresponds to the flipping of the sulfur atom between two imaginary points above and below the (Me)(O)(Cl) plane. Thus, the stationary point **8** is the transition state for the pyramidal inversion of **7**, which is a weak van der Waals complex binding the base with the sulfinyl chloride. The introduction of trimethylamine in this system reduces the S═O bond elongation (from 0.027 Å in the base-free reaction to 0.013 Å) and the S−Me bond contraction (from 0.034 Å in the base-free reaction to 0.004 Å) along the inversion. On the other hand, the S−Cl bond is strongly elongated from 2.250 Å in **7** to 2.560 Å in **8**, instead of being contracted as in the base-free inversion. The long S−N distances of 2.768 Å in **7** and 2.806 Å in **8** seem to indicate a soft long-range interaction between the sulfinyl chloride and the base. Nevertheless, regarding the relative free energies, the introduction of the base results in a surprising reduction of the free energy barrier from 63.4 kcal/mol (base-free inversion) to 22.9 kcal/mol. The long S−Cl distance in **8** suggests a strong anionic character of chlorine, which may require diffuse functions in this atom. Their effect was found to be practically neglectable through a reoptimization of **7** and **8**, with only a slight reduction in the value of $\Delta G^{\ddagger}$ from 22.9 to 22.3 kcal/mol. The meaningful reduction of $\Delta G^{\ddagger}$ by 40.5 kcal/mol associated with the presence of the nitrogenated base clearly points out that trimethylamine catalyzes the inversion of SO(Me)(Cl). Furthermore, the resulting free energy barrier situates this racemization reaction as a feasible DKR mechanism for the DAG synthetic method.

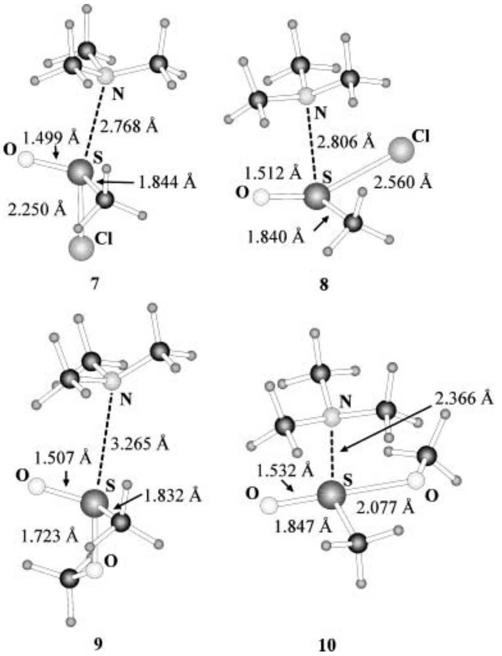

Figure 2. Optimized stationary points for the base-catalyzed pyramidal inversion of SO(Me)(Cl) and SO(Me)(OMe).

The base-catalyzed variant of the SO(Me)(OMe) pyramidal inversion was also computed. The van der Waals complex **9** and the transition state **10** were optimized. The introduction of trimethylamine reduces the elongation of the S═O bond (0.025 Å) and the contraction of the S−Me bond, which suffers a slight elongation (0.015 Å). As for the S−Cl bond of SO(Me)(Cl), the S−OMe bond is strongly elongated (0.354 Å). The main structural difference between the pyramidal inversion of SO(Me)(Cl) and SO(Me)(OMe) comes from the S−N distance, which is clearly longer in **9** (3.265 °A) but significantly shorter in **10** (2.366 Å). Furthermore, regarding the relative free energies, the catalytic effect of the base is rather smaller for the sulfinate. The $\Delta G^{\ddagger}$ of the base-free inversion (64.1 kcal/mol) is reduced to 42.7 kcal/mol giving rise to a $\Delta\Delta G^{\ddagger}$ of 21.4 kcal/mol, clearly smaller than in the case of SO(Me)(Cl) (40.5 kcal/mol). In fact, in this case, the resulting free energy barrier is still capable of keeping the optical activity of the molecule, as observed experimentally in the DAG reaction.

The structures of the transition states **8** and **10** are distorted trigonal bipyramids (TBPs) with the oxygen and the X = Cl, OMe substituents in the axial positions. The O−S−Cl axial angle of 153.0° in **8** and the N−S−C equatorial angle of 95.9° in **8** and 94.2° in **10** reflect the distortion of the ideal TBP geometry. The Berry pseudorotation[27,28] of hypervalent sulfur intermediates[29,30] has also been proposed[23] as a possible DKR mechanism in the DAG synthetic method. Nevertheless, our calculations demonstrate that the pentavalent $SO(Me)(X)(NMe_3)$ species play an important role in the pyramidal inversion of SO(Me)(X) compounds as low-energy transition states instead of intermediates.

To check whether the base has a general catalytic effect toward the pyramidal inversion of SORX ($X = Cl, OR_{alkyl}, R_{aryl}$) we tried to reoptimize the stationary points **1** and **2** introducing a trimethylamine molecule in the system. Although a van der Waals complex analogous to **7** and **9** was found, all attempts to locate the transition state corresponding to the hypothetic base-catalyzed inversion of (p-MeC_6H_4)SO(Me) failed. In all cases the optimization evolves to reactants.

The computational study summarized in this article shows that the reactivity of SO(Me)(X) compounds toward pyramidal inversion follows the trend $X = R_{aryl} > X = Cl \approx X = OR_{alkyl}$. The highest chiral lability of $SO(Me)(R_{aryl})$ is due to the aromaticity of the X substituent, which stabilizes the planar transition state.[31] In all cases, this racemization mechanism implies the structural distortion of the tetrahedral chiral substrate toward a trigonal planar transition state. This distortion is coupled with the S═O bond elongation and the S−Me and S−X bonds contraction. Furthermore, we found that trimethylamine catalyzes significantly the pyramidal inversion of SO(Me)(Cl) and, to a less extent, that of SO(Me)(OMe). To the best of our knowledge, this is the first evidence of the base-catalyzed inversion of chiral sulfur centers. According to our results, the chiral lability in the presence of the base is $X = Cl > X = OR_{alkyl}$, a trend that probably correlates with the strength of such S−X bonds, considering the significant S−X bond elongation in the transition states. In the base-catalyzed inversion, the distortion of the S═O and S−Me bonds is reduced, while the S−X bonds are strongly elongated. In both cases, the tetrahedral structure of SO(Me)(X) is transformed into a TBP transition state.

This theoretical study is being extended in our laboratory with a DFT study on a model system and a QM/MM study on the real system of the full reaction mechanism of the DAG method.

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Supporting Information Available: Potential, enthalpic, Gibbs free energies, and Cartesian coordinates of the 10 stationary points reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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