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Mechanism of the Pummerer Reaction: A Computational Study

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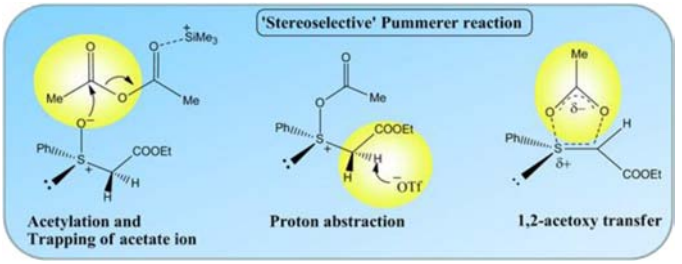
ABSTRACT



DFT calculations are used to investigate the mechanism of the Pummerer reaction between a chiral sulfoxide and acetic anhydride under classical and stereoselective reaction conditions (without and with additives, respectively). The first step involving acetylation of the sulfoxide with release of acetate is found to be rate-determining in both cases. For the stereoselective Pummerer reaction in the presence of trimethylsilyl triflate (TMSOTf) and *N*,*N*-dimethylacetamide (DMAC), TMSOTf- and DMAC-assisted transition states as well as ion exchange reactions are considered to account for the role of TMSOTf and DMAC.

The Pummerer reaction, the conversion of sulfoxides by electrophilic reagents to α-substituted sulfides, has received significant attention as a synthetically useful strategy in organic synthesis.[1]A typical procedure involves the activation of sulfoxide by reagents such as acetic anhydride, trifluoroacetic anhydride, or trifluoromethane sulfonic anhydride, which generates a thionium ion. An ensuing inter- or intramolecular nucleophilic attack at the α-position of the sulfur group leads to the formation of a new carbon−carbon or carbon−heteroatom bond. The most commonly employed nucleophiles are acetate, arenes, alkenes, amides, and phenols. Ring-closing strategies based on the reaction of the generated thionium ion intermediate with internally disposed nucleophiles have broadened the scope of Pummerer-based transformations in the construction of carbo- and heterocyclic rings.[2] The asymmetric Pummerer reaction of chiral sulfoxides with acetic anhydride gives the desired chiral products only with very low enantiomeric excess, presumably due to the formation of achiral intermediates.[3] To improve the enantioselectivity, a variety of practical solutions have been explored, including the addition of 1,3-dicyclohexylcarbodiimide to trap the acetate ion,[4] the use of ethoxy vinyl acetate instead of acetic anhydride,[5] as well as silicon-induced Pummerer-type reactions.[6] A recent simpler procedure involves the use of the reagent trimethylsilyl triflate (TMSOTf) in the presence of additives, such as *N*,*N*-dimethylacetamide (DMAC) or *N*-methyl-2-pyrrolidone (NMP), to enable stereoselective Pummerer reactions.[7]

Despite the widespread synthetic applications of the Pummerer reaction, there have not yet been any in-depth

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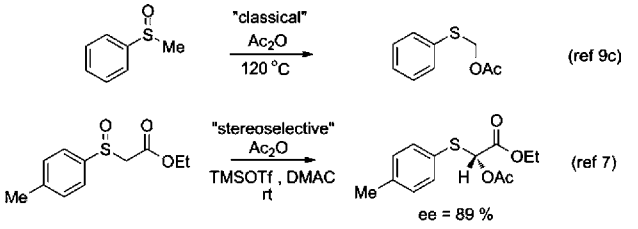
theoretical studies that provide atomistic insight into their mechanism. Understanding the mechanism and selectivity issues could be helpful for further expanding the scope of this important reaction. In this communication, we use density functional theory (DFT) to investigate the mechanism of the Pummerer reaction between acetic anhydride and the chiral sulfoxide (**1**) with a phenyl and a CH_2CO_2Et group, both under classical and stereoselective reaction conditions (Scheme 1). DFT calculations were performed using the B3LYP and M06-2X functionals in combination with the 6-31+G** basis set as implemented in Gaussian09. The results discussed in the text (B3LYP-I level) come from solvent-phase (PCM, DCM) geometry optimizations, with dispersion corrections included through single-point calculations.[8]

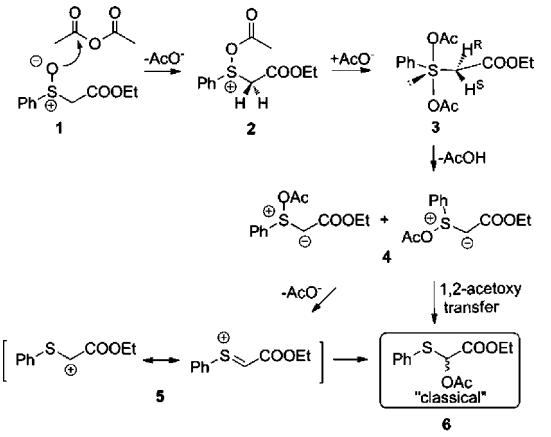
Scheme 1. Classical and Stereoselective Pummerer Reactions



The mechanism of the Pummerer reaction has been studied thoroughly by kinetics and ^{18}O-labeling experiments.[9] The proposed mechanistic scenario is formulated in Scheme 2 for the reaction between **1** and acetic anhydride. The first step is a nucleophilic attack of the sulfoxide oxygen atom of **1** at a carbonyl carbon atom of acetic anhydride that yields the acyloxysulfonium cation **2** and an acetate anion. The latter may add to the positively charged sulfur atom of **2** forming the sulfurane **3**, which may then eliminate acetic acid to produce the sulfonium ylide **4**; in the case of a chiral sulfoxide substrate, this will lead to racemization since the sulfurane is achiral. Alternatively, a base may remove a proton from the α-carbon atom of **2**, which directly leads to **4** and will thus preserve chirality of **1**. The ylide intermediate **4** rearranges to the observed product **6** by 1,2-acetoxy transfer. This rearrangement may proceed either directly or by dissociation of acetate (forming a tight ion-pair **5**) and subsequent nucleophilic addition to the α-carbon atom of the generated thionium cation. The latter may also be attacked by an external nucleophile (not considered here).

Classical Pummerer Reaction. The calculations were performed on the sulfoxide with *R*-configuration at sulfur ((*R*$_S$)-**1**); the corresponding *R*$_S$ and *S*$_S$ intermediates and

Scheme 2. Proposed Mechanism of the Pummerer Reaction



transition states have the same energy (see Supporting Information).

We first modeled the transition state for the initial step, that is, the acetylation of sulfoxide, considering all possible conformers of acetic anhydride. The optimized transition state is shown in Figure 1. The attack of the sulfoxide at one carbonyl group of acetic anhydride releases an acetate ion. The distances of the forming and breaking C−O bonds at the transition state are 1.56 and 1.97 Å, respectively. The resulting acetate ion is stabilized by nonbonded S····O interactions (2.58 Å). NBO analysis suggests a charge delocalization energy of 6.5 kcal/mol. Judging from the relative free energies listed in Table 1, it is clear that this initial acetylation step is rate-determining with an free energy barrier $\Delta G^{\ddagger}$ of 33.9 kcal/mol ($\Delta H^{\ddagger}$ = 20.1 kcal/mol) at the B3LYP-I level.[10] An IRC calculation starting from **TS(1−2)** toward the product indicates that the liberated acetate anion remains coordinated to the acetylated sulfoxide. Binding of this nearby acetate anion to the sulfur atom yields the achiral sulfurane **3**, which assumes a trigonal bipyramidal geometry with both acetate moieties at the apical positions (Figure 1). The two enantiotopic protons (H^R and H^S) on the α-carbon atom in **3** can be removed equally well by the apical acetate groups, via transition states (**TS(3−4)**, see Figure 1) with a free energy ΔG of 20.7 kcal/mol relative to the reactants, which are stabilized through S····O1 (AcO^-) interactions (NBO analysis, delocalization energy of 8.1 kcal/mol). We could not find a direct chirality-retaining pathway from **2** to **4**, since the generated acetate anion remains coordinated to **2** and gets bound to the sulfur atom quickly in a downhill process. The *S*- and *R*-sulfonium ylides **4** have an inversion barrier of 29.4 kcal/mol, which is much higher (by 18.1−22.5 kcal/mol) than the barriers for 1,2-acetoxy transfer via **TS(4−6)**.

For the subsequent 1,2-acetoxy migration from sulfur to the adjacent carbon, we considered the three pathways

(8) See Supporting Information for a detailed description of the applied computational methods.

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(10) Experimental activation parameters at 120 °C for the Pummerer reaction of phenyl methyl sulfoxide with acetic anhydride: $\Delta H^{\ddagger}$ = 21.2 kcal/mol and $\Delta S^{\ddagger}$ = −20.7 e.u. See ref 9c.

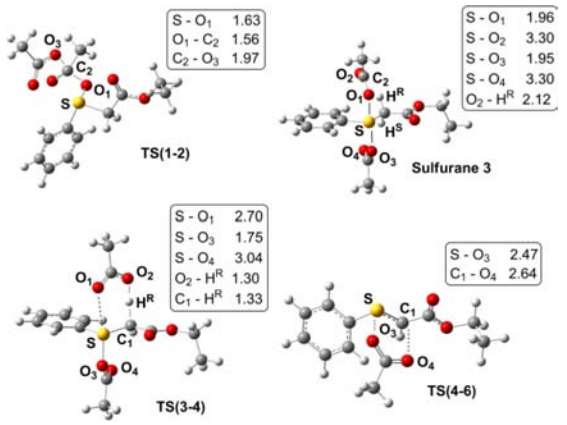


Figure 1. B3LYP-I optimized geometries for intermediate **3** and for the transition states of the classical Pummerer reaction.

Table 1. Relative Free Energies ΔG and Enthalpies ΔH (in kcal/mol) of Intermediates and Transition States Computed at the B3LYP-I Level for the Pathways Shown in Scheme 2[a]

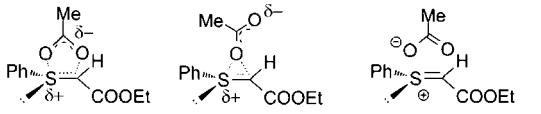
entry	ΔH	ΔG
1 + Ac_2O	0.0	0.0
(**1** + Ac_2O)	−1.9	5.6
TS(1−2)	20.1	33.9
(**2** + AcO^-)	17.6	29.5
3	1.3	13.2
TS (3−4)	8.2	20.7
4 + AcOH	3.4	3.5
5 + AcO^- + HOAc	29.6	18.1
TS (4−6)-cyc + AcOH	5.6	6.9
TS (4−6)-slide + AcOH	11.9	11.3
6 + AcOH	−32.6	−32.0

[a] Entries in parentheses such as (**1** + Ac_2O) denote complexes between the moieties. The M06-2X results are generally similar to the B3LYP-I values given here (see Supporting Information).

shown in Scheme 3. Formation of an intimate ion-pair is often invoked for the Pummerer reaction to explain the uneven distribution of ^{18}O in the Pummerer product that is observed in ^{18}O-tracer experiments. However, all attempts to locate an "intimate" ion-pair **5** of the thionium cation and acetate anion ended up at the sulfonium ylide **4**, both in the gas phase and the solvent phase. This failure to find an ion-pair in solution may be due to the use of a continuum solvation model (instead of explicit solvent molecules). The transition states for the other two modes of 1,2-acetoxy transfer were located successfully (Scheme 3). The cyclic mode (Figure 1) is preferred over the sliding mode by 4.4 kcal/mol (Table 1), presumably due to a better charge delocalization in the five-membered transition state (cyclic mode) as compared to the three-membered transition state (sliding mode).

Stereoselective Pummerer Reaction. Experimentally, high stereoselectivity can be achieved in the Pummerer reaction by using the reagent TMSOTf in the presence of DMAC, which combines with the reagent to form the complex DMAC/TMSOTf.[7] Furthermore, DMAC may also coordinate to the substrate (sulfoxide), whereas the trimethyl silyl group (TMS) of the reagent TMSOTf may trap acetate in the first step of reaction.

Scheme 3. Different Modes of 1,2-Acetoxy Transfer in the Final Step of the Classical Pummerer Reaction via **TS(4-6)**



Accordingly, the transition states were remodeled in the presence of TMSOTf, with and without DMAC being coordinated to the sulfoxide. On the DMAC-assisted pathway, the rate-determining acetylation step is found to be quite complex (Figure 2). It involves formation of the O1····C2 bond (O1 of sulfoxide and C2 of a carbonyl group of acetic anhydride), cleavage of the O3····C2 bond (within acetic anhydride), and formation of the Si····O4 bond (between TMS and acetate). DMAC coordination to the substrate sulfoxide appears to be very weak, since the (sulfoxide)S····O5(DMAC) distance is quite large at the transition state (3.81 Å, Figure 2). On the DMAC-assisted pathway, the overall activation energy of the acetylation step remains rather high ($\Delta G^{\ddagger}$ = 32.0 kcal/mol, Table 2). The analogous transition state [**TS(1−2)** + TMS^+] without DMAC coordination has a lower barrier ($\Delta G^{\ddagger}$ = 28.9 kcal/mol and $\Delta H^{\ddagger}$ = 14.4 kcal/mol). In both cases, the trimethylsilyl group stabilizes the released acetate anion and thus lowers the energy of the transition state compared with the unassisted case ($\Delta G^{\ddagger}$ = 33.9 kcal/mol mol and $\Delta H^{\ddagger}$ = 20.1 kcal/mol, Table 1). The enthalpic gain ($\Delta\Delta H^{\ddagger}$ = 5.7 kcal/mol) due to charge stabilization in these transition states dominates over adverse entropic effects so that the free energy barrier is reduced by 5.0 kcal/mol in comparison to the classical Pummerer reaction.

The acetylation product (**2** + TMSOAc + $^-$OTf) is stabilized by the formation of the complex TMSOAc. Its free energy is only 6.2 kcal/mol above that of the reactants (Table 2) compared with 29.5 kcal/mol in the classical Pummerer reaction (Table 1). Since the liberated acetate is trapped in the complex TMSOAc, the reaction proceeds via abstraction of the α-proton by the available base $^-$OTf to generate ylide **4** followed by 1,2-acetoxy transfer to provide the desired product **6**. The activation barriers for these steps are moderate to small (Table 2). The free energies of the transition states on the DMAC-assisted pathway are again found to be somewhat higher than those in the absence of DMAC (by 3−4 kcal/mol, Table 2), and they always remain below **TS(1−2)**. Given the weak coordination of DMAC and the higher barriers on the DMAC-assisted pathway, our present results do not

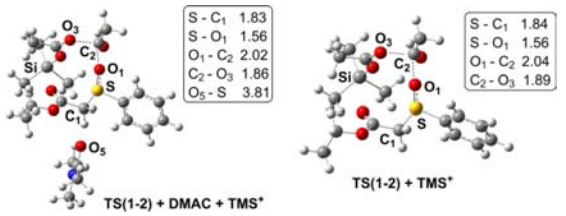


Figure 2. B3LYP-I optimized geometries for the rate-determining transition state **TS(1−2)** of the stereoselective Pummerer reaction with assistance by TMS^+ and DMAC.

Table 2. Relative Free Energies ΔG (in kcal/mol) of Intermediates and Transition States Computed at the B3LYP-I Level in the Presence of TMSOTf, with and without DMAC Assistance[a]

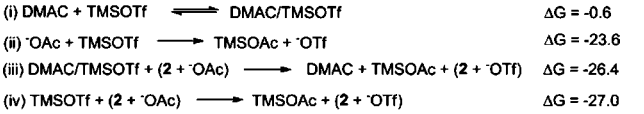
entry	without DMAC	with DMAC
1 + Ac_2O + TMSOTf	0.0	0.0
(**1** + Ac_2O + TMS^+) + $^-$OTf	21.6	25.7
(**TS(1−2)** + TMS^+) + $^-$OTf	28.9	32.0
2 + TMSOAc + $^-$OTf	6.2	6.2
(**2** + $^-$OTf) + TMSOAc	2.5	7.5
(**TS(2−4)** + $^-$OTf) + TMSOAc	16.9	20.7[b]
4 + TfOH + TMSOAc	14.2	14.2
TS (4−6)-cyc + TfOH + TMSOAc	17.6	20.7
TS (4−6)-slide + TfOH + TMSOAc	22.0	26.4
6 + TfOH + TMSOAc	−21.3	−21.3

[a] Entries in parentheses such as (**1** + Ac_2O) denote complexes between the moieties. All compounds have (R_S)-configuration or, in case of **6**, (R_C)-configuration. [b] From single-point calculations at gas-phase optimized geometries.

support DMAC participation in the stereoselective Pummerer reaction, whereas the presence of TMSOTf (TMS^+ and $^-$OTf) is confirmed to be beneficial (lower free energy barriers, see Tables 1 and 2).

To gain further insight into the role of DMAC, we considered several possible exchange reactions (Scheme 4). The exchange of triflate in TMSOTf with acetate is highly exoergic (eq ii) so that TMSOTf will effectively trap acetate. The lack of available acetate anions in the stereoselective Pummerer reaction reduces the chances of forming the achiral sulfurane **3** via **TS(2−3)** and will thus tend to prevent the loss of stereochemical information from the chiral starting material. Instead, the direct chirality-retaining pathway via **TS(2−4)** can be taken.

Scheme 4. Possible Ion Exchange Reactions between TMSOTf and DMAC: Reaction Free Energies (in kcal/mol) Computed at the B3LYP-I Level[a]



[a] Entries in parentheses denote complexes.

Experimentally, the Pummerer reaction between **1** and acetic anhydride in the presence of only TMSOTf (without DMAC) leads to racemic products, however, because of product enolization mediated by the strong Lewis acid TMSOTf.[7] In the presence of DMAC, a complex DMAC/TMSOTf is formed, as confirmed by ^{1}H NMR measurements.[7] This complex exchanges $^-$OTf with $^-$OAc as readily as TMSOTf (see eqs iii and iv in Scheme 4). Hence, a crucial role of DMAC could be to deactivate the Lewis acidity of TMSOTf by forming a complex and thus avoid the racemization of the final products.

In summary, we have provided molecular-level insight into the mechanism of the Pummerer reaction between **1** and acetic anhydride using DFT calculations. The reaction involves three major steps, namely acetylation, proton abstraction, and intramolecular acetoxy transfer. The acetate anion released during the acetylation step can combine with the reactant to form an achiral sulfurane intermediate. Both enantiotopic (H^R and H^S) protons can be abstracted from the α-carbon atom of the achiral sulfurane equally well, and there is also no enantiodistinction in the subsequent 1,2-acetoxy transfer that proceeds equally well on either face of the sulfonium ylide. This rationalizes why the classical Pummerer reaction of phenyl sulfonylacetic acid ethyl ester yields racemic product.[7] In the stereoselective Pummerer reaction, the acetate anion released in the acetylation step can be trapped by TMS^+. This will impede the formation of the achiral sulfurane intermediate and favor the competing pathway toward the sulfonium ylide that retains the stereochemical information.

Supporting Information Available. Computational methods; total and relative energies; Cartesian coordinates of optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.