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Synthesis of anticonvulsant sulfamides. Theoretical study of the related mechanism

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Abstract. A theoretical study of the mechanisms associated with the synthesis of anticonvulsant symmetric *N*,*N*′-substituted sulfamides is presented. Two possible synthetic routes are compared, which mainly differ in the use of pyridine as a nucleophilic agent in the reaction mechanism. Geometry optimization techniques and transition-state detection at the B3LYP/6-31G** level, modeling the solvent by means of an isodensity polarizable continuum approach, allow the most suitable method for the experimental process to be discerned.

Keywords: Anticonvulsant sulfamides – Density functional calculations – Reaction mechanisms

1 Introduction

Sulfonamide and sulfamide functionalities are considered sometimes as parent-derived related structures [1]. In addition to their structural similarity, they show the same pattern of interaction with carbonic anhydrase (CA), responsible in part for triggering the anticonvulsant activity. The amine group, with its particular electronic characteristics, imparted by the proximal sulfur heteroatom, is the anchoring group that coordinates the catalytic Zn in CA [2, 3].

In addition to their interaction with CA, other mechanisms, such as blockade of sodium channels and kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, as well as enhancement of γ-aminobutyric acid ergic transmission, have also been reported, or hypothesized, as being involved in their therapeutic action [3, 4].

Sulfonamides have been largely used in the treatment and prevention of a variety of diseases or pathological states, like open-angle glaucoma, osteoporosis, epilepsy, Parkinson and other neurological conditions. However, side effects such as augmented diuresis, fatigue, paresthesias and anorexia have been reported [1, 2, 3, 4, 5]. Sulfamides, on the other hand, play an important role in the field of medicinal chemistry, as nonhydrolyzable components in peptidomimetics [6], active components in epinephrine analogues [7], agonists of the 5-HT_{ID} receptor [8] and HIV protease inhibitors [9]. They are also important units in supramolecular-chemistry engineering processes. Hydrogen-bonded sulfamides have been used to construct 2D layered or 3D network structures [10], whereas sulfamide and glycoluril functionalities have been successfully coordinated to build self-assembled capsules [11].

Among the different applications of sulfonamides and sulfamides, our research is mainly centered on those compounds of therapeutic interest, focusing on the design of new antiepileptic (AE) related structures [12, 13]. We have recently designed anticonvulsant sulfamides following a nonclassical bioisosteric substitution of the carboxylic function (–CO_2H) by sulfonamide (–SO_2NH–) [14] in the pharmacophore associated with a sodium channel blockade mechanism [12, 13, 15, 16]. Although their AE mechanism is, at present, not completely known, the efficiency of sulfamides against convulsion challenges the traditional drugs used for the treatment of epilepsy. Accordingly, drugs of this pharmacological class are under constant development.

Efficient synthetic procedures become relevant for rational drug design methodologies. We analyze, in this research, the synthetic routes that yield symmetric *N*,*N*′-substituted sulfamides, which are based on the reaction

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of sulfuryl chloride with the corresponding amines. To this end, we have used quantum chemical calculations to evaluate the energy requirements associated with different proposed reaction pathways. The theoretical study models the synthesis of *N*,*N*′-dibutylsulfamide, which was chosen as a test example. The comparative evaluation of the mechanisms under consideration is used to determine the most suitable route to be followed in the synthesis.

Synthetic routes

N,*N*′- symmetric sulfamides have been traditionally synthesized following the method of Ohme and Preuschhof [17]. According to these authors, pyridine (Py) has to be used as a nucleophilic agent in order for the reaction to proceed. Py, which attacks the sulfur atom of the sulfuryl moiety, should be further replaced by the corresponding amine (Scheme 1). However, Bermann et al. [18], and subsequently other researchers [6, 10, 19] have successfully obtained *N*,*N*′-substituted sulfamides with no Py participating in the reaction (Scheme 2)

We have synthesized several *N*,*N*′-symmetric sulfamides, which we predicted to have anticonvulsant activity. According to the results reported in this article, we decided to follow a direct procedure, without the addition of Py. Nevertheless, we also tested the Py-mediated mechanism for the *N*,*N*′-dibutylsulfamide case, in order to validate the theoretical predictions. Both syntheses were conducted in dichloromethane, following the usual experimental procedure. The presence of Py in the reaction media severely complicates product isolation, consequently lowering the reaction yield.

The *N*,*N*′- symmetric sulfamides manifest sizeable anticonvulsant activity, a fact that validates the pharmacophore on which basis they have been designed [20].

Calculation procedure

Calculations were done at the B3LYP/6-31G** level, using Gaussian 98 [21]. Full geometry optimizations were conducted for reactants, products, stable intermediates and transition states of the reaction paths under comparison. Transition states were detected using a quadratic synchronous transit approach (QST2) [22]. Critical points were further characterized by analytical computation of the harmonic frequencies at the same level of theory. Bulk solvent effects (dichloromethane) were described via an isodensity continuum polarizable model (IPCM) [23]. Single-point IPCM calculations were performed on the optimized (in vacuum) geometries. Atomic charges were computed according to the Merz–Kollman approximation [24], keeping the same level of theory.

Results and discussion

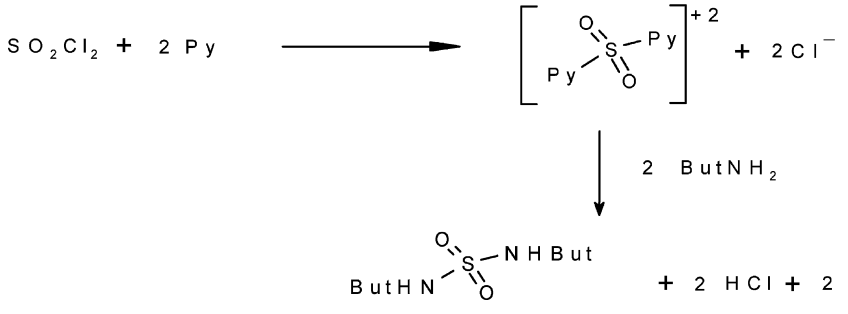
The potential-energy hypersurfaces were analyzed, for both the Py-mediated and the direct reactions, at the same level of theory.

Py-mediated reaction mechanism

Two main steps can be considered in the Py-mediated reaction mechanism. The first one is associated with the nucleophilic substitution of chloride by Py in the SO_2Cl_2 molecule, whereas the second one is related to the substitution of Py by butylamine.

The first step of the reaction initially proceeds through nucleophilic attack of Py to the sulfur center, which, according to our calculations, bears a positive charge of 0.7 e.u.

The displacement of a chloride anion renders the stable intermediate SI1 (Fig. 1). The process is not favored energetically ($\Delta E^{*} = 10$ kcal/mol) as regards the destabilization of the products ($SI1 + Cl^{-}$) relative to the reactants (Scheme 3). The transition-state structure that results from QST2 calculations is 54 kcal/mol less stable than the reactants. The associated energy for this reaction is strongly dependent on the simulated solvent (Table 1). A dichloromethane environment strongly stabilizes the positively charged species. The geometries of TS1 and SI1 are characteristic of an S_N2 mechanism. TS1 is a sulfur-centered trigonal bipyramid with the releasing chloride in line and opposite to the incoming Py. All the S–*X* bonds (where X represents the different ligands) are longer than the corresponding ones in reactants or products (Fig. 1). In SI1 the tetrahedral (T_d) geometry is achieved, although it is distorted in the N–S–Cl angle, which is stabilized at 94°. A second Py molecule, acting again as a nucleophile, displaces the remaining chloride ion, and generates the stable



Scheme 1. Mechanistic path for the reaction with pyridine (Py).

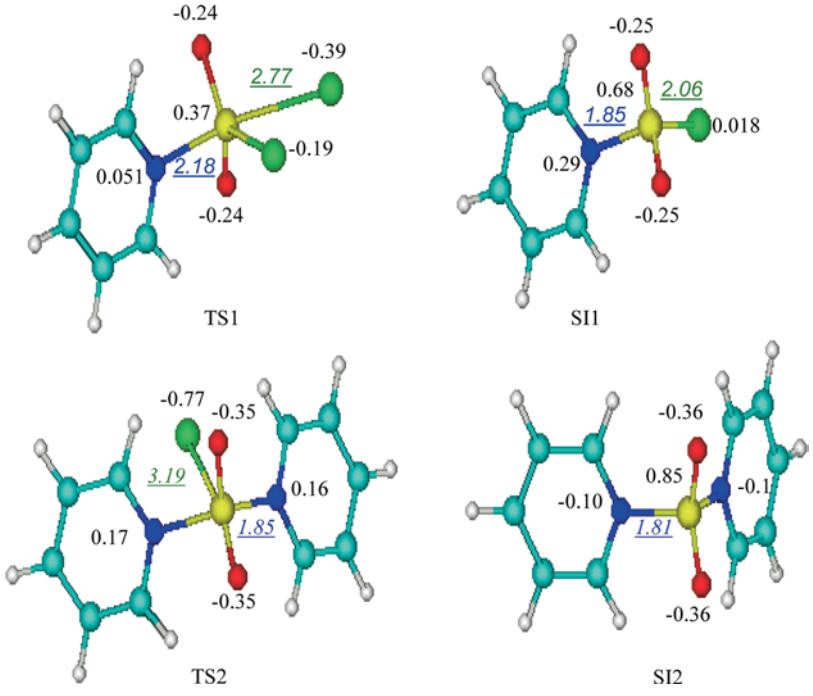
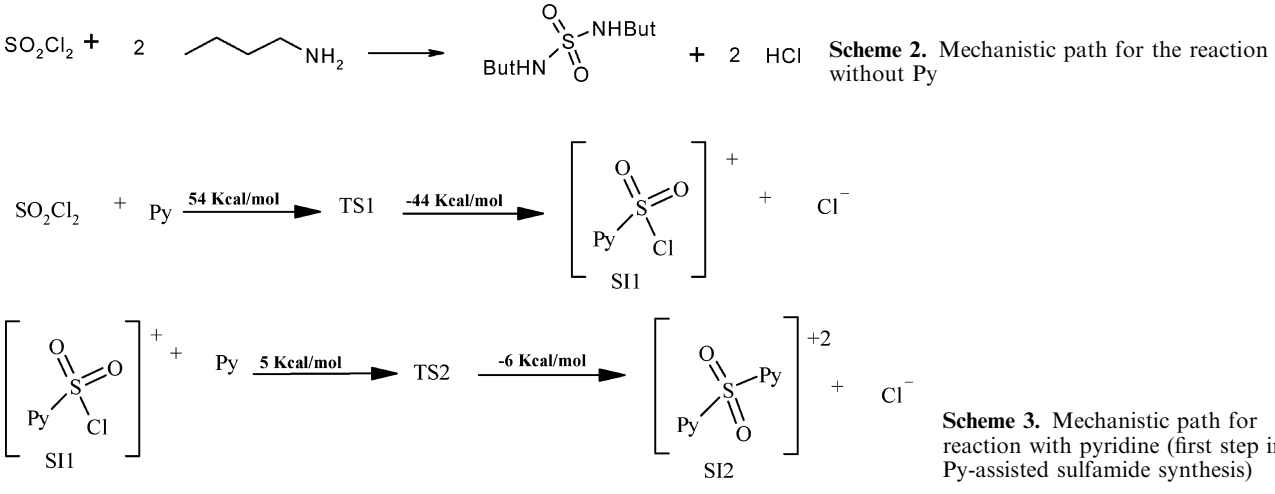


Fig. 1. Geometries of the stable intermediates and transition states associated with the first step of the pyridine (*Py*)-mediated sulfamide synthesis. Calculated charges (e.u.) and relevant interatomic distances (Å) are shown

intermediate (SI2) going through the transition structure TS2 (Fig. 1). TS2 can be described as a distorted trigonal bipyramid, with the oxygen and chlorine atoms defining a planar triangle. The distortion is defined by an N–S–N angle of 125° that deviates from 180° and gets closer to the value in SI2. In SI2 the chloride is already separated and the N–S–N angle (103°) better adjusts to the T_d value. This intermediate has been previously proposed by Ohme and Preuschhof [17], although no details of its geometry were reported. This second substitution is favored energetically according to our calculations, and needs an energy close to 5 kcal/mol to proceed through the TS2 structure (Scheme 3). The progress of the reaction is favored as the products are separated from the media by precipitation of the cationic intermediate with chloride.

The second step of the reaction is related to the nucleophilic replacement of Py by the primary amine (butylamine). The attack of the first amine molecule to the electrophilic S atom generates a stable intermediate (SI3, Fig. 2) where the pentavalent sulfur atom is in the center of a structure intermediate between a square pyramid and a trigonal bipyramid with Py and oxygen in the apical vertex. It results from the distortion of the T_d SI2 after binding the amine molecule. The hydrogen atom of the incoming amine has already been transferred to the sulfuryl oxygen in this structure. The energy implied in the formation of this intermediate shows that the reaction is far from being favored (Scheme 4), but can be stabilized by elimination of a protonated PyH^+, which is separated as a chloride salt, rendering the stable T_d intermediate SI4 (Fig. 2).



Scheme 2. Mechanistic path for the reaction without Py

Scheme 3. Mechanistic path for reaction with pyridine (first step in the Py-assisted sulfamide synthesis)

Table 1. Pyridine (*Py*)-mediated reaction. Calculated electronic energies for reactants, products, stable intermediates and transition states. Energy changes for the different steps of the reaction are included in columns 5 and 6

Reaction with Py					
Species	E (au)[a]	E (au)[b]	Description	ΔE (kcal/mol)[a]	ΔE (kcal/mol)[b]
SO_2Cl_2	−1,468.94198	−1,468.94636			
Py	−248.29260	−248.29981			
SO_2Cl_2 + Py	−1,717.23458	−1,717.24617			
TS1	−1,716.91935	−1,717.15980	TS1—(SO_2Cl_2 + Py)	197.81	54.20
SI1	−1,256.78694	−1,256.85969			
Cl^-	−460.52223	−460.36955			
SI1 + Cl^-	−1,717.30917	−1,717.22924	SI1 + Cl^-−TS1	−244.62	−43.57
SI1 + Py	−1,505.07953	−1,505.15950			
TS2	−1,505.05806	−1,505.15231	TS2—(SI1 + Py)	13.48	4.51
SI2	−1,044.52335	−1,044.79233			
SI2 + Cl^-	−1,505.04558	−1,505.16188	SI2 + Cl^-—TS2	7.83	−6.01
H_2NBut	−213.81629	−213.82210			
SI2 + H_2NBut	−1,258.33964	−1,258.61443			
SI3	−1,258.23179	−1,258.48371	SI3—(SI2 + H_2NBut)	67.68	82.03
SI3 + Cl^-	−1,718.75403	−1,718.85326			
SI4	−1,009.84570	−1,009.92570			
HCl	−460.80078	−460.80477			
SI4 + Py + HCl	−1,718.93907	−1,719.03027	SI4 + Py + HCl—(SI3 + Cl^-)	−116.12	−111.07
SI4 + H_2NBut + Cl^-	−1,684.18422	−1,684.11734			
SI5	−975.00829	−975.02626			
SI5 + Py + HCl	−1,684.10166	−1,684.13084	SI5 + Py + HCl—(SI4 + H_2NBut + Cl^-)	51.81	−8.47

[a]Calculations in vacuo
[b]Bulk solvent (dichloromethane)modeled within an isodensity continuum polarizable model approach

The substitution of the remaining Py by a second amine molecule, to give the product SI5 (Fig. 2), should imply two consecutive steps, following a mechanism similar to that found for the coordination of the first amine to the sulfur atom. However, we have not succeeded in identifying any pentavalent intermediate, similar to SI3, as all the attempts evolved to give the reaction products. We conclude that this reaction, far

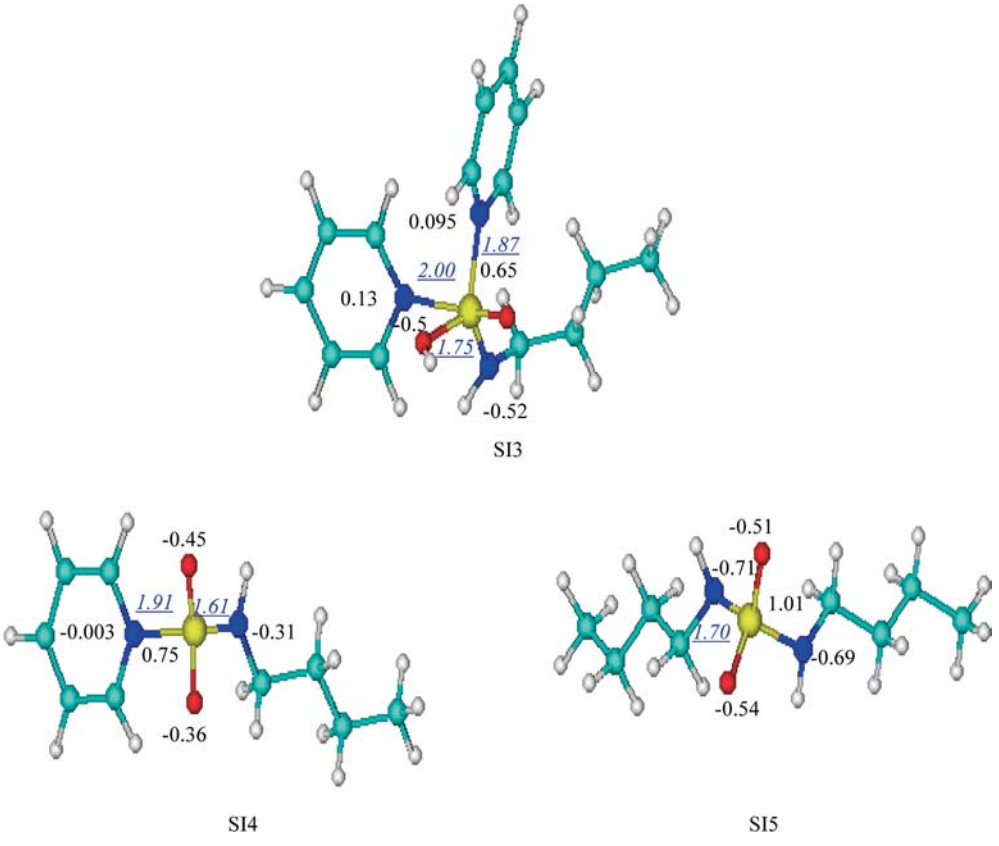
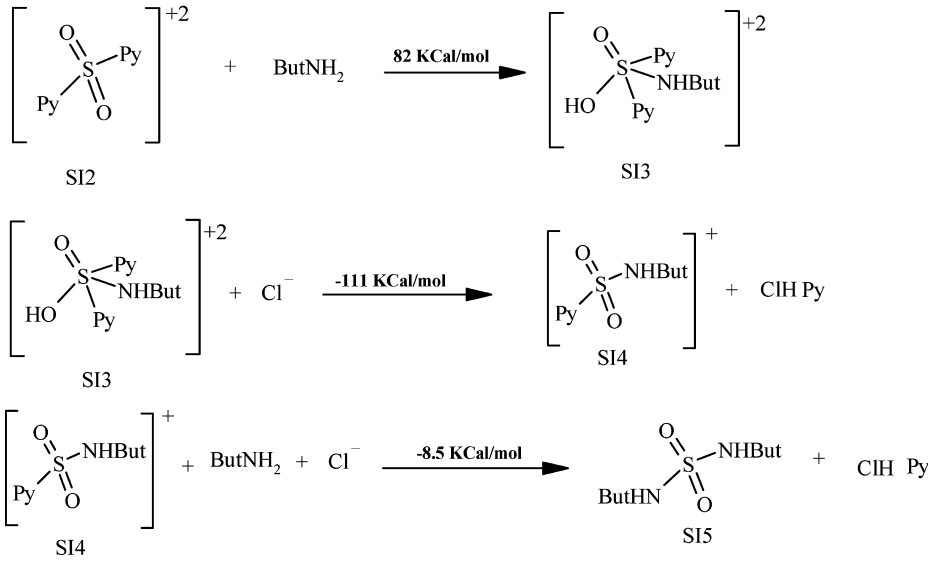


Fig. 2. Geometries of the stable intermediates associated with the second step of the Py-mediated sulfamide synthesis. Calculated charges (e.u.) and relevant interatomic distances (Å) are shown



Scheme 4. Mechanism associated with the second step of the Py-assisted sulfamide synthesis

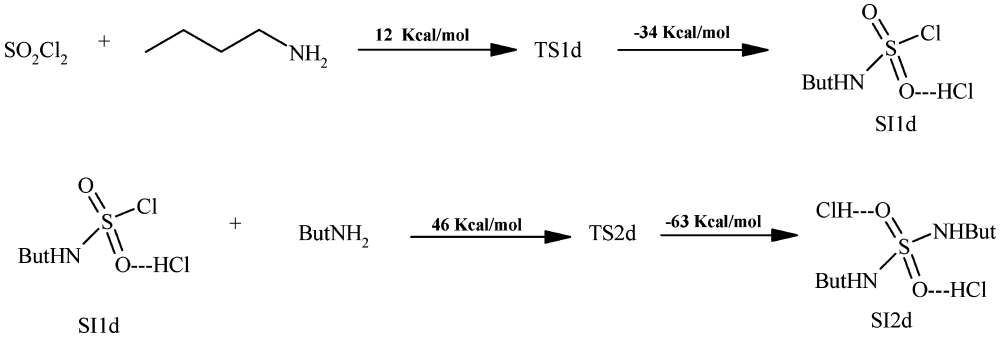
from occurring downhill, as could be inferred from the data in Scheme 4, is again associated with an energy increase (Scheme 4). The activation energy for the substitution of Py by butylamine is, then, higher than 82 kcal/mol, if not equal to this value. The reaction is experimentally favored by the displacement of the equilibrium towards the products as they are separated from the reaction media.

Direct reaction

The potential-energy surface for the reaction taking place with no Py in the media was also calculated (Scheme 5).

The nucleophilic attack to the sulfuryl chloride is directly effected by a molecule of butylamine, generating a stable intermediate (SI1d, Fig. 3), which is 22 kcal/mol stabler than the reactants. The potential-energy hypersurface is less complex for this direct reaction, with a calculated transition state for the first amine substitution (TS1d, Fig. 3) which is only 12 kcal/mol uphill in energy (Table 2), a figure that defines the activation energy for this reaction The transition-state structure TS1d is similar to that previously found for the first step of the Py-mediated reaction (TS1). It can be described as a distorted trigonal bipyramid, with the nonreleasing chloride and the amine nitrogen in apical positions, and the oxygen atoms defining with the other chloride a planar triangle. The geometry is, however, closer to the products than that of TS1, with one S–Cl elongated to 2.97 Å. This Cl atom is already hydrogen-bonded to one of the amine hydrogens. The release of hydrogen chloride to give SI1d is favored by the stabilization of a hydrogen bond between HCl and the sulfuryl oxygen that promotes product formation.

In the second stage, another amine molecule, acting as a nucleophile, attacks the sulfur center with simultaneous transfer of a proton to the nonprotonated sulfuryl oxygen. The process is similar to that previously described, going through a transition state TS2d (Fig. 3) that defines an activation energy of 46 kcal/mol (Scheme 5). The final product (SI2d, Fig. 3) is stabilized as chlorhydrate, and is 17 kcal/mol lower in energy than SI1d. In TS2d an O–H bond between the amine hydrohen and a sulfuryl oxygen is stabilized. Rotation about the SO bond allows the final coordination of the hydrogen atom to chloride, allowing the releasing of HCl to give the final product SI2d. As previously described for SI1d, the releasing HCl molecules are stabilized by coordination to the sulfuryl oxygen atoms.



Scheme 5. Mechanistic path for reaction without pyridine

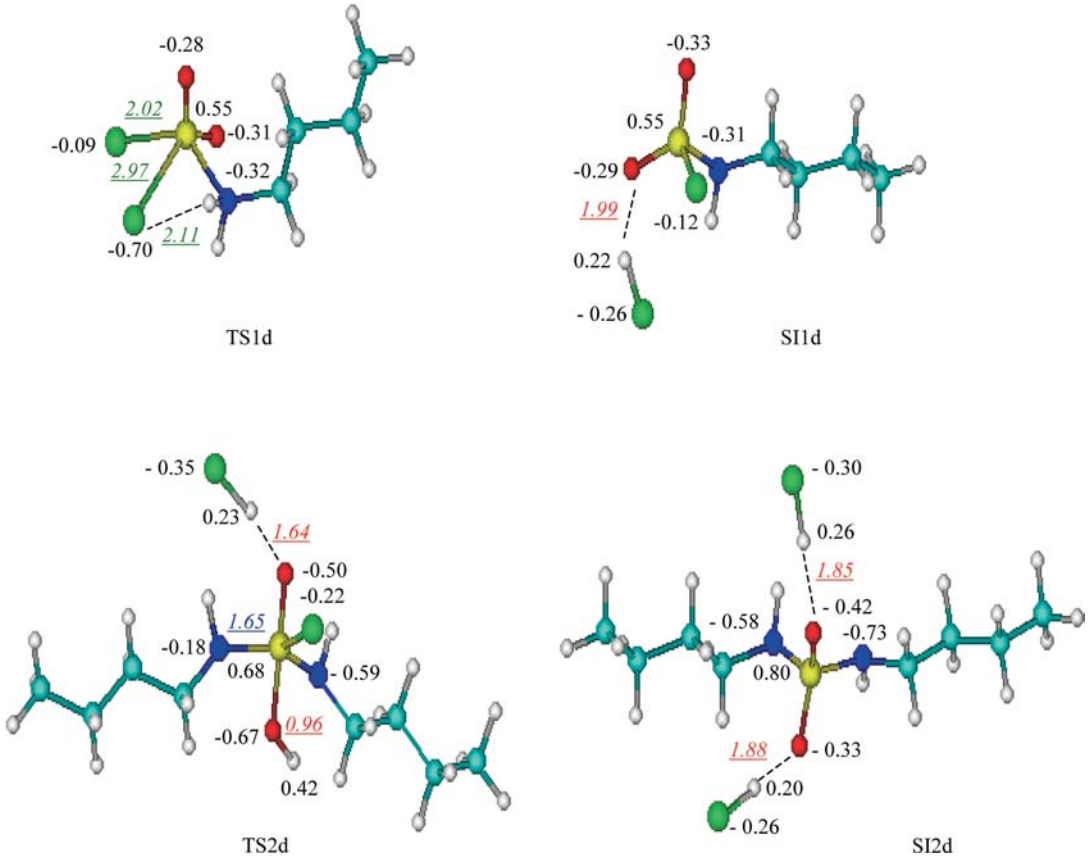


Fig. 3. Geometries of the stable intermediates and transition states associated with the direct sulfamide synthesis. Calculated charges (e.u.) and relevant interatomic distances (Å) are shown

Table 2. Direct reaction. Calculated electronic energies for reactants, products, stable intermediates and transition states. Energy changes for the different steps of the reaction are included in columns 5 and 6

Direct reaction					
Species	E (au)[a]	E (au)[b]	Description	ΔE (kcal/mol)[a]	ΔE (kcal/mol)[b]
SO_2Cl_2	−1,468.94198	−1,468.94636			
H_2NBut	−213.81629	−213.82210			
$SO_2Cl_2 + H_2NBut$	−1,682.75827	−1,682.76846			
TS1d	−1,682.72524	−1,682.74970	TS1d—($SO_2Cl_2 + H_2NBut$)	20.73	11.77
SI1d	−1,682.79462	−1,682.80348	SI1d—TS1d	−43.54	−33.75
$SI1d + H_2NBut$	−1,896.61092	−1,896.62558			
TS2d	−1,896.53281	−1,896.55281	TS2d—($SI1d + H_2NBut$)	49.01	45.67
SI2d.2HCl	−1,896.63277	−1,896.65277	SI2d.2HCl—TS2	−62.73	−62.73

[a]Calculations in vacuo
[b]Bulk solvent (dichloromethane)modeled within an isodensity continuum polarizable model approach

Conclusions

The mechanisms calculated and discussed in this article provide valuable information about the influence of Py in the synthesis of *N*,*N*′-symmetric sulfamides, for which no experimental data have been found in the literature. The Py-mediated mechanism has a larger activation energy than the direct reaction. The formation of charged species in the Py-assisted mechanism defines it as more energy-demanding. The solvent, however, exerts a sizeable effect in decreasing the energy associated with the latter, as it stabilizes the positively charged species. This effect is not enough, however, to reverse the observed trend. The unfavorable effect associated with the use of Py is manifested, in the experimental procedure, in a lower yield, measured for the same reaction time (62% versus 80% with and without Py, respectively).

According to the calculations, the displacement of the chloride ion may become relevant in both cases. For the Py-mediated mechanism, the chloride salt of the cationic intermediate should be formed as a way to promote the displacement of the reaction towards the products.

When no Py is used, the chloride ion is stabilized by coordination to the protonated species, and lowers, in this way, the energy involved in the different steps of the reaction. Moreover, the final product (*N*,*N*′-symmetric sulfamide) is stabilized by the coordination of two molecules of HCl, which are generated in the reaction media.

The consideration of the energies associated with the different steps of each reaction, for the model mechanisms proposed, has allowed us to determine that the direct reaction is the most suitable method to be followed in the experimental process. This can be acknowledged considering that the presence of Py in the reaction media does not facilitate the formation of the products. Moreover, it remains in the media as an additional impurity, a drawback that can be easily avoided by simply following the direct reaction.

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