

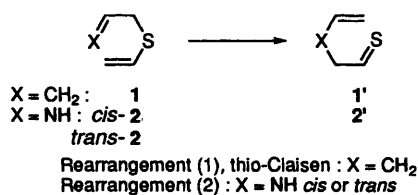
# Theoretical study of the thio-Claisen rearrangement. Can vinylthioethanimine undergo a [3,3]-sigmatropic shift?

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An *ab initio* study of the [3,3]-sigmatropic rearrangements of allyl vinyl sulfide **1** and vinylthioethanimine **2** has been carried out. To this end, geometries of stationary points were optimized at the HF, DFT (B3LYP) and MP2 (fc) levels using the 6-31G\* basis set, while relative energies were estimated using post-HF calculations up to  $\sim$ QCISD(T)/6-311 + G(2df,2p)//MP2/6-31G\* level and corrected for zero-point energies. Progress of the charge distributions and delocalization interactions (NBO analysis) along the reaction have been investigated by employing the intrinsic coordinate method. Solvent effects on these processes have been simulated by the mean of SCRF computations associated to a continuum model. The results show that **2** is predicted to be less reactive than **1**, the calculated enthalpy of activation for *cis-2* and *trans-2* rearrangement being respectively 4.5 and 10.0 kcal mol<sup>-1</sup> higher than for the rearrangement of compound **1**. The thio-Claisen rearrangement is calculated to be slightly exothermic ( $\Delta_r H = -1.5$  kcal mol<sup>-1</sup> at our best level of calculation) while the rearrangement from vinylthioethanimine is calculated to be endothermic [ $\Delta_r H(\textit{cis-2}) = 7.0$  kcal mol<sup>-1</sup>;  $\Delta_r H(\textit{trans-2}) = 9.1$  kcal mol<sup>-1</sup>]. Unlike the thio-Claisen rearrangement, the results obtained considering the polarizable continuum approach indicate that no significant rate enhancement of rearrangement from compound **2** can be expected on going from the gas phase into solution. NBO analysis is a tool for the mechanistic study of these rearrangements and is a guideline in the research of electronic effects in order to improve their feasibility.

Since its first description by Brandsma and co-workers,<sup>1,2</sup> the thio-Claisen rearrangement of allyl vinyl sulfides has received much attention (Scheme 1, X = CH<sub>2</sub>). It produces a new



Scheme 1

carbon-carbon bond,  $\alpha$  to a thiocarbonyl function and thus is an alternative to the generally unfeasible direct  $\alpha$ -alkylation of thiocarbonyl compounds.<sup>3</sup> This methodology has been used by Corey *et al.* to synthesize  $\gamma$ -unsaturated aldehydes.<sup>4</sup> More recently, the attention has been focused on the stereoselectivity of this sigmatropic rearrangement.<sup>5</sup> Good selectivities are often observed and have been interpreted in terms of a chair-like cyclic transition state. The first goal of this paper is to present theoretical calculations concerning this rearrangement.

With the exception of the rearrangement of divinyl disulfides,<sup>3,6</sup> no dihetero-[3,3]-sigmatropic rearrangement has been reported in the sulfur series. Here, we present theoretical results concerning a sulfur nitrogen system (Scheme 1, X = NH). To the best of our knowledge, this rearrangement is still unknown. It would create a carbon-nitrogen bond  $\alpha$  to a thiocarbonyl group, thus allowing, *inter alia*, the synthesis of thiono analogues of amino acids. Furthermore, this carbon-nitrogen bond formation would involve a nucleophilic carbon and an (at least formally) electrophilic nitrogen. This rearrangement can thus be regarded as an electrophilic amination of an enolate equivalent.<sup>7</sup> The second goal of this paper is to study the feasibility of this rearrangement.

Quantum chemical calculations on parent Cope and Claisen rearrangements have received a great deal of attention. The mechanism and transition structure of the former [3,3]-

sigmatropic shift has been subject to controversy. Semiempirical methods favoured a two stage mechanism involving a biradical-like TS.<sup>8</sup> In contrast, *ab initio* calculations at the SCF or MCSCF levels with small basis set predicted a concerted process with an aromatic transition structure.<sup>9</sup> More recently, however, CASSCF (6,6)/6-31G\* calculations indicated a very flat potential energy surface and suggested an alternative reaction channel involving a biradicaloid intermediate.<sup>10</sup> Very recently, the mechanism of the Cope rearrangement has been revisited using multireference perturbation theory;<sup>11,12</sup> these independent studies showed that the CASSCF surface is in error and established that the Cope rearrangement is concerted and does not involve the formation of a diradical intermediate. In addition, Houk *et al.*<sup>13</sup> reported a density functional study of this process using non-local gradient corrections (B3LYP); DFT results also predict a single concerted aromatic transition state.

The Claisen rearrangement has been theoretically investigated by Houk *et al.*<sup>13-15</sup> An appreciable C-O bond breaking is found in the transition structure, and the chair conformation is preferred at the RHF/6-31G\* level. CASSCF/6-31G\* calculations<sup>15</sup> predict a concerted process with a much looser 'aromatic' transition structure. Non-local DFT methods yield also an aromatic chair transition structure and a good estimate of activation energy.<sup>13</sup> Another fundamental issue concerning the reaction is the effect of solvation on the reaction rate. Theoretical models including Monte Carlo simulations,<sup>16</sup> continuum representation of the solvent<sup>17,18</sup> and combined quantum mechanical and molecular mechanical<sup>19</sup> approaches have been employed to study the effect of water on reaction rate. In addition to these simulations of aqueous solution, the continuum models in *ab initio* calculations were used to predict the effect of solvation by dibutyl ether on the Claisen rearrangement.<sup>17</sup> In this work, they compare the polarizable continuum model (PCM) developed by Tomasi and co-workers<sup>20</sup> with a model using elliptical cavity and truncated multipole expansion developed by Rivail and co-workers.<sup>21</sup>

We report a comparative study of the two elementary

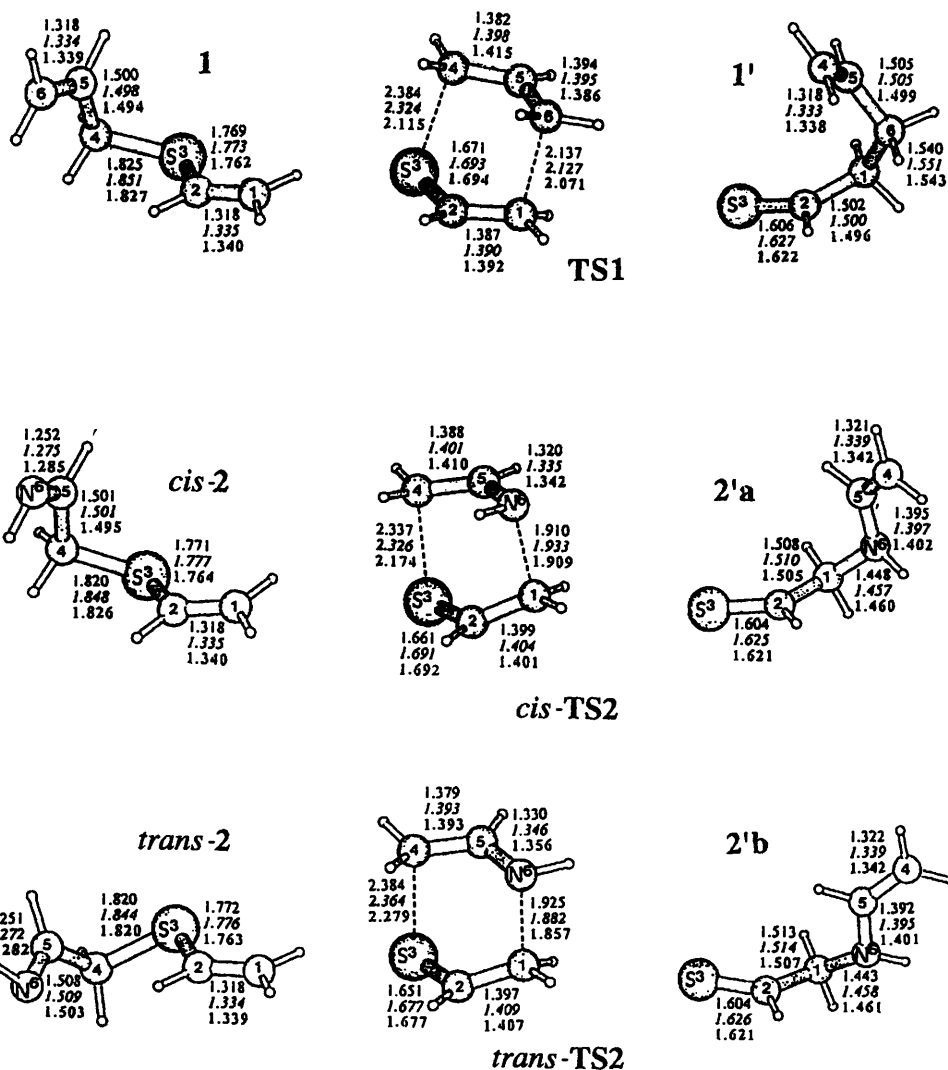


Fig. 1 Optimized geometries of stationary points on the [3,3]-sigmatropic rearrangements calculated at the HF, B3LYP and MP2(fc) levels (from top to bottom)

reactions (1) and (2) (Scheme 1) using *ab initio* molecular orbital and density functional theories. An analysis of the delocalization interactions and charge transfer along the intrinsic reaction coordinate (IRC) has been performed in order to better understand the mechanism of these processes. Finally, an estimate of the effect of solvation on those same processes has been obtained using a polarizable continuum model and self consistent reaction field formalism. Our aim is to examine theoretically the feasibility of process (2) and to suggest, if necessary, conditions that would induce a rate acceleration. On the basis of the results obtained for the Cope and Claisen rearrangements, we assumed that the thio-Claisen rearrangement occurs along a concerted reaction pathway and thus we decided to employ single reference techniques.

### Computational methods

*Ab initio* molecular orbital and DFT calculations were carried out using the GAUSSIAN 94<sup>22</sup> and a modified version with additional code needed for the SCRF computations. For DFT calculations the hybrid functional B3LYP<sup>23</sup> which contains gradient corrections for both exchange and correlation has been chosen. The geometries of reactants, products and transition structures were fully optimized at the HF, MP2(fc) and B3LYP levels with the 6-31G\* basis set.<sup>24</sup> The calculated stationary points (local minima and saddle points) were characterized by harmonic vibrational frequency calculations at both HF/6-31G\* and B3LYP/6-31G\* levels. For reactants and products,

there are many stable conformers with similar energies due to the flexibility of these molecules. A thorough search of all possible conformers was not carried out here, insofar as the goal of this study is the thio-Claisen rearrangement. Thus, the reactant and product conformers were those obtained by the intrinsic reaction coordinates (IRC)<sup>25</sup> procedure: the IRC has proved to be a very useful tool for following a reaction from a stationary point having one imaginary frequency to local minima on each side of this point, *i.e.* to reactants and products. In the following, for Figs. 2 and 3 the (net) reaction coordinate is equal to 0.0 for the transition states (TSs) and increases along the step TS→reactant. IRC were calculated at the HF/6-31G\* level. B3LYP optimizations gave the same conformations. Single-point energies were calculated at various levels up to ~QCISD(T)(fc)/6-311 + G(2df,2p)//MP2(fc)/6-31G\* according to the additivity approximation:

$$E[\text{QCISD(T)/6-311 + G(2df,2p)}] \sim E(\text{QCISD(T)/6-31G}^*) + E[\text{MP2/6-311 + G(2df,2p)}] - E(\text{MP2/6-31G}^*) \quad (1)$$

In order to correct for electron correlation, the zero-point vibrational energies (ZPEs) taken from the frequency analyses were scaled by factors of 0.9135<sup>26</sup> and 0.9827<sup>27</sup> for the HF and B3LYP frequencies, respectively. Natural bond orbital (NBO)<sup>28</sup> calculations were also performed to analyse the delocalization interactions along the reaction paths. NBO analyses were performed with the program NBO version 3.1, which was built into link 607 on the GAUSSIAN program.<sup>29</sup>

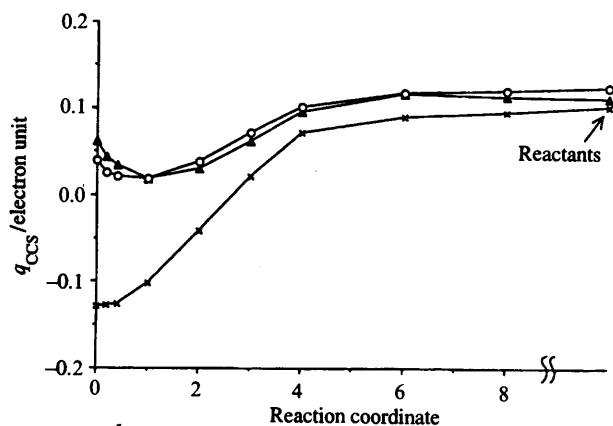


Fig. 2 Variation of the net charge  $q_{\text{CCS}}$  of the vinylthio fragment along the reaction coordinate (6-31G\* natural population analysis);  $\times$ , 1 $\rightarrow$ TS1;  $\blacktriangle$ , 2 $\text{trans}\rightarrow$ TS2 $\text{trans}$ ;  $\circ$ , 2 $\text{cis}\rightarrow$ TS2 $\text{cis}$

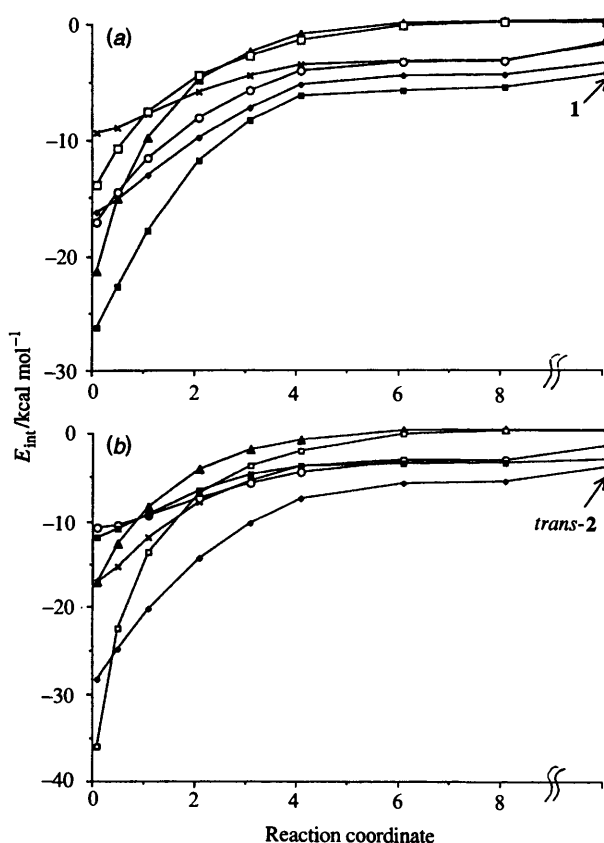


Fig. 3 Variation of the delocalization interactions along the reaction coordinate; (a) reactant 1 $\rightarrow$ TS1 step; (b) reactant 2 $\text{trans}\rightarrow$ TS2 $\text{trans}$  step. Similar results are obtained for 2 $\text{cis}\rightarrow$ TS2 $\text{cis}$  pathway and thus are not given here.  $\times$ ,  $\pi_{\text{C1C2}}\rightarrow\sigma_{\text{S3C4}}^*$ ;  $\blacktriangle$ ,  $\pi_{\text{C1C2}}\rightarrow\pi_{\text{C5X6}}^*$ ;  $\circ$ ,  $\sigma_{\text{S3C4}}\rightarrow\pi_{\text{C1C2}}^*$ ;  $\diamond$ ,  $\sigma_{\text{S3C4}}\rightarrow\pi_{\text{C5X6}}^*$ ;  $\square$ ,  $\pi_{\text{C5X6}}\rightarrow\pi_{\text{C1C2}}^*$ ;  $\blacksquare$ ,  $\pi_{\text{C5C6}}\rightarrow\sigma_{\text{S3C4}}^*$

To simulate solvent effects on the two chemical processes, SCRf (self consistent reaction field) computations associated to a continuum model have been performed for various solvents with relative permittivity varying from  $\epsilon = 2.0$  to 78.8. The used model is based on a multipolar development of the charge distribution of the solute, which solute is assumed to be isolated from the environment (*i.e.* the solvent) by a hypothetical cavity of any shape.<sup>30</sup> As shown in recent work<sup>31</sup> this approach seems to constitute a good way for studying reaction processes in solution.

## Results and discussion

### Energies

The equilibrium structures corresponding to the stationary points on the potential energy surfaces for the three

rearrangements (from 1, *cis*-2 and *trans*-2) are depicted in Fig. 1. The total energies and ZPE energies of these calculated structures are shown in Table 1. As mentioned in the computational section, reactant structures 1, *cis*-2 and *trans*-2 and product structures 1', 2'a and 2'b have been identified by IRC calculations (minima on both sides of the TS) and do not correspond to the lowest energy conformers. Nevertheless, in the case of the thio-Claisen process, we have located the absolute minima of allyl vinyl sulfide. It lies 0.4, 0.6, 0.5 and 0.6 kcal mol<sup>-1</sup> below the conformation shown at the HF, MP2, QCISD(T) (6-31G\* basis set) and B3LYP levels, respectively. Whatever the level of calculations may be, *cis*-2 is calculated to be less stable than *trans*-2 by about 2 kcal mol<sup>-1</sup>. Concerning the product 2', the energy difference between the two conformers 2'a and 2'b (obtained respectively from *cis*-2 and *trans*-2) is weak; it is noticed, however, that only HF/6-31 calculations predict the 2'b form to be more stable.

Calculated activation parameters and thermodynamic quantities for the three reactions are given in Table 2. As expected in processes involving bond breaking and bond forming, HF barrier heights  $\Delta E^\ddagger$  are overestimated. Correlated barrier heights are about 20 kcal mol<sup>-1</sup> lower than those obtained by the HF method. In both cases, an increase of the size of the basis set from 6-31G(d) to 6-311 + G(2df,2p) tends to decrease the barrier heights as the description of the transition structures are improved. It is worth noting that B3LYP hybrid functional, which is less expensive in computational time gives  $\Delta E^\ddagger$  values close to those computed at our highest level of theory. Non-potential (ZPE and thermal) energy contributions result also in a slight lowering of the energy barrier. A ( $\Delta E^\ddagger + \text{ZPE}$ ) value of 26.8 kcal mol<sup>-1</sup> has been computed by Houk and co-workers<sup>13</sup> for the Claisen rearrangement at the B3LYP/6-31G\* level. The corresponding value for the thio-Claisen rearrangement is equal only to 21.0 kcal mol<sup>-1</sup>. This calculated trend is in accordance with experimental findings which indicate that the sulfur version of the Claisen rearrangement occurs at lower temperature than the oxygen version.<sup>32</sup>

Inspection of Table 2 shows clearly that rearrangement (2) occurs with a higher activation energy than the thio-Claisen shift. Relative values (in parentheses) seem to be overestimated at the HF/6-31G\* level, while it is pleasant to notice that  $\sim$ QCISD(T)/6-311 + G(2df,2p) and B3LYP/6-31G\* relative values are very close. At our best estimate, the activation energies for reaction through *cis*-TS2 and through *trans*-TS2 are respectively 4.5 and 10.3 kcal mol<sup>-1</sup> higher than through TS1. In addition, the entropic term is more unfavourable for the process from *cis*-2. Thus, on the basis of these calculations, more difficult rearrangements are expected for compounds *cis*-2 and especially *trans*-2.

Another point of interest in this comparative study is the reaction enthalpy. Indeed, it has been shown experimentally that the thio-Claisen rearrangement is a reversible reaction<sup>32</sup> and this equilibration causes synthetic limitation. For the thio-Claisen sigmatropic shift, our calculations indicate a low negative value of the reaction enthalpy which lies in the range  $-1.5$  to  $-6.4$  kcal mol<sup>-1</sup>. 2 $\text{cis}$  and 2 $\text{trans}$  reactions are predicted to be endothermic, weakly at the B3LYP level (+3.0 and +5.1 kcal mol<sup>-1</sup> respectively), more at the QCISD(T)/6-311 + G(2df,2p) level (+7.0 and +9.1 kcal mol<sup>-1</sup> respectively). The difference  $\Delta(\Delta_r H)$  between reaction (1) and (2) given in parentheses in Table 2 can be compared to the bond energy difference of C-C, C=C, C-N and C=N. According to the values recommended by Leroy *et al.*,<sup>33</sup> [2E(C-C)-E(C=C)] is equal to +33.65 kcal mol<sup>-1</sup> and the quantity [2E(C-N)-E(C=N)] to +23.53 kcal mol<sup>-1</sup>. This gives an energy difference of 10.12 kcal mol<sup>-1</sup>. It is interesting to note that the use of larger basis sets leads to an increase of  $\Delta_r H$ . These higher  $\Delta_r H$  values suggest an easier reverse rearrangement 2' $\rightarrow$ 2 and strongest synthetic limitations.

**Table 1** Total energies (au) and zero-point vibrational energies (kcal mol<sup>-1</sup>) of the reactants, transition structures and products for the rearrangements 1 and 2<sup>a</sup>

	G-31G*					6-311 + G(2df,2p)		ZPVE <sup>c</sup>	
	HF <sup>b</sup>	MP2 <sup>b</sup>	MP4(SDTQ) <sup>c</sup>	QCISD(T) <sup>c</sup>	B3LYP <sup>c</sup>	MP2 <sup>c</sup>	QCISD(T) <sup>d</sup>	HF	B3LYP
<b>1</b>	-591.454 88	-592.213 37	-592.306 10	-592.309 62	-593.483 85	-592.532 75	-592.629 01	77.4	-72.0
<b>TS1</b>	-591.390 96	-592.186 47	-592.271 96	-592.271 33	-593.450 79	-592.509 12	-592.593 98	77.4	72.3
<b>1'</b>	-591.462 94	-592.224 30	-592.317 24	-592.319 43	-593.491 38	-592.537 18	-592.632 31	78.3	73.0
<i>cis</i> - <b>2</b>	-607.454 51	-608.245 52	-608.334 34	-608.336 68	-609.526 30	-608.577 36	-608.666 52	70.2	65.0
<i>cis</i> - <b>TS2</b>	-607.377 95	-608.212 42	-608.293 58	-608.291 25	-609.486 44	-608.545 97	-608.624 80	70.6	65.6
<i>cis</i> - <b>2'</b>	-607.447 04	-608.239 57	-608.328 02	-608.329 38	-609.522 44	-608.567 07	-608.656 88	70.8	66.2
<i>trans</i> - <b>2</b>	-607.457 41	-608.249 13	-608.337 68	-608.339 80	-609.529 11	-608.578 20	-608.668 87	70.3	65.2
<i>trans</i> - <b>TS2</b>	-607.371 60	-608.204 65	-608.285 63	-608.283 62	-609.480 18	-608.538 36	-608.617 33	70.1	65.2
<i>trans</i> - <b>2'</b>	-607.447 24	-608.239 09	-608.327 46	-608.329 09	-609.521 90	-608.566 55	-608.656 55	70.8	65.7

<sup>a</sup> For nomenclature, see Fig. 1. <sup>b</sup> Optimized at the same level of theory. <sup>c</sup> Single point calculation at the MP2/6-31G\* geometry. <sup>d</sup> Calculated from relation (1). <sup>e</sup> Unscaled values.

**Table 2** Barrier heights  $\Delta E^\ddagger$ , activation energies  $\Delta H^\ddagger$ , energies  $\Delta_r E$ , enthalpies (kcal mol<sup>-1</sup>) and activation entropies (cal mol<sup>-1</sup> K<sup>-1</sup>) of the rearrangement (1). Relative values with respect to **1** are in parentheses

Reaction	Level of calculation	$\Delta E^\ddagger$	$\Delta H^\ddagger$ (298 K)	$\Delta_r E$	$\Delta_r H$ (298 K)	$\Delta_r S$ (298 K)
<b>1</b>	HF <sup>a</sup>	40.11	39.26	-5.06	-4.47	-7.9
	HP2 <sup>a</sup>	16.88	16.03	-6.86	-6.27	
	MP4 (SDTQ) <sup>a</sup>	21.42	20.57	-6.99	-6.40	
	QCISD(T) <sup>a</sup>	24.03	23.18	-6.15	-5.56	
	B3LYP <sup>a</sup>	20.75	20.16	-4.73	-4.00	-8.3
	QCISD(T) <sup>b</sup>	21.97	21.12	-2.07	-1.48	
<i>cis</i> - <b>2</b>	HF <sup>a</sup>	48.04	47.46 (8.2)	4.69	5.62 (10.1)	-9.2
	MP2 <sup>a</sup>	20.77	20.19 (4.2)	3.74	4.67 (10.9)	
	MP4 (SDTQ) <sup>a</sup>	25.57	24.99 (4.4)	3.96	4.89 (11.3)	
	QCISD(T) <sup>a</sup>	28.50	27.93 (4.8)	4.58	5.51 (11.1)	
	B3LYP <sup>a</sup>	25.01	24.64 (4.5)	2.42	3.03 (7.0)	-10.3
	QCISD(T) <sup>b</sup>	26.17	25.59 (4.4)	6.04	6.97 (8.4)	
<i>trans</i> - <b>2</b>	HF <sup>a</sup>	53.84	52.91 (13.6)	6.38	7.71 (12.2)	-7.9
	HP2 <sup>a</sup>	27.91	26.98 (11.0)	6.30	7.63 (13.9)	
	MP4 (SDTQ) <sup>a</sup>	32.66	31.73 (11.1)	6.41	7.74 (14.1)	
	QCISD(T) <sup>a</sup>	35.25	34.32 (11.1)	6.72	8.05 (13.6)	
	B3LYP <sup>a</sup>	30.70	29.97 (9.8)	4.65	5.06 (9.1)	
	QCISD(T) <sup>b</sup>	32.34	31.41 (10.3)	7.73	9.06 (10.5)	

<sup>a</sup> 6-31G\* Basis set. <sup>b</sup> Calculated from relation (1).

In summary, kinetic and thermodynamic parameters indicate that the conversion **2**→**2'** is more difficult than the conversion **1**→**1'**. A thorough knowledge of the geometry and electronic structure of the transition states is the key to the understanding of the reaction and to how it can be accelerated.

### Geometries and electronic structures

Depicted in Fig. 1 are the equilibrium structures corresponding to the stationary points of the three rearrangements. The reactants issued from IRC calculations adopt similar conformations with dihedral angles <C-1C-2C-3C-4, <C-1S-3C-4C-5 and <S-3C-4C-5X-6 (see Fig. 1 for numerotation) in the order of 220°, 65° and 240° respectively. For this conformation, the terminal atoms C-1 and X-6 are properly located to form the C-1X-6 bond. A rotation around the C-2S-3 bond leads to the more stable rotamer which is obtained for a <C-1C-2S-3C-4 dihedral angle of about 140°. Optimizations at the MP2 and B3LYP level also lead to the same conformer, except in the case of compound *trans*-**2**: at the B3LYP/6-31G\* level, this conformer is not a minimum on the potential surface and a stable conformation has been located for a <C-1C-2S-3C-4 dihedral angle equal to 158°. As shown in Fig. 1, all three methods predict chair like, aromatic-type transition states for the three processes investigated here. The calculated length of the breaking C-S bond ranges from 2.11 to 2.38 Å and the lengths of the forming C-C and C-N bonds range from 2.07 to 2.14 Å and 1.86 to 1.93 Å respectively. The bond lengths calculated by the MP2/6-31G\* method are systematically shorter than the ones from RHF or B3LYP calculations. We

discuss first the geometry changes upon substitution of the oxygen (Claisen) by a sulfur atom (thio-Claisen). On the basis of the length of the forming C-C bond, **TS1** is much more compact than the transition structure of the parent Claisen rearrangement for which C-C bond lengths equal to 2.266 Å (RHF/6-31G\*)<sup>15</sup> and to 2.312 Å (B3LYP/6-31G\*)<sup>13</sup> have been computed. A better description of the extent of bond-forming and bond-breaking is given by Pauling order  $n_p$ .<sup>34</sup>  $n_p$  values are consigned in Table 3. Calculated C-C bond order lies in the range 0.37–0.41 and C-S bond order varies between 0.40 and 0.62. MSCCF/6-31G\* results<sup>15</sup> for the Claisen chair transition structure give bond orders of 0.18 for the C-C bond and 0.31 for the C-O bond. The looser character of this later transition structure can be related to the higher exothermicity of the Claisen reaction [ $\Delta_r E = -21.3$  kcal mol<sup>-1</sup> (HF/6-31G\*) and  $-23.2$  kcal mol<sup>-1</sup> (MP2/6-31G\*)].<sup>14</sup>

Now, we compare transition structures **TS1**, *cis*-**TS2** and *trans*-**TS2**. As expected, the C<sub>1</sub>-N<sub>6</sub> forming bond is shorter than the C-1-C-6 bond. At the same time, **TS1** and **TS2** (*cis* and *trans*) are reached for about the same S-3-C-4 distances. Consequently, for **TS2** *cis* and *trans*,  $n_p$  (1-6) is larger than  $n_p$  (3-4) while the opposite inequality is obtained for **TS1**, [see Table 3; close examination of  $n_p$  values shows that only for the *cis*-**TS2** MP2 transition structure  $n_p$  (1-6) is lower than  $n_p$  (3-4)]. In addition, Fig. 1 indicates, at both levels of calculation, that the C-1-C-2 bond is shorter and the C-2-S-3 bond larger in **TS1**. These trends suggest that **TS1** is a more reactant-like transition structure than **TS2** (and particularly *trans*-**TS2**). This analysis is

**Table 3** Some structural and electronic properties of the transition structures

Level of calculation		TS1	cis-TS2	trans-TS2
$n_p$ (1-6) <sup>a</sup>	HF	0.369	0.459	0.452
	MP2	0.414	0.474	0.516
	B3LYP	0.376	0.453	0.492
$n_p$ (3-4) <sup>a</sup>	HF	0.394	0.423	0.391
	MP2	0.618	0.554	0.470
	B3LYP	0.454	0.448	0.423
Non-Lewis electron (electron unit)	I <sup>b</sup>	1.199 85	1.437 89	1.597 22
	II	1.265 18	1.242 42	1.143 24
Dipole moment (D) <sup>c</sup>		3.37 (1.58)	1.64 (1.68)	2.49 (1.42)
$\Delta q$ (electron unit) <sup>d</sup>		-0.232 (-0.143)	-0.086 (0.032)	-0.056 (0.045)

<sup>a</sup> Pauling bond order. <sup>b</sup> Lewis structures are defined as structures I and II. <sup>c</sup> The dipole moments of reactant molecules are in parentheses. <sup>d</sup> Change [ $\Delta q = q(\text{TS}) - q(\text{reactant})$ ] in NPA charges between the ground state and the transition state for vinylthio moiety; a positive value indicates a charge transfer from  $\text{H}_2\text{C} = \text{CH} - \text{S}$  to  $\text{X} = \text{CH} - \text{CH}_2$ ; in parentheses, change in Mulliken charges.

**Table 4** Delocalization interactions (kcal mol<sup>-1</sup>) in various TS

Interactions <sup>a</sup>	TS1	cis-TS2	trans-TS2
1 $\pi_{\text{C1C2}} \rightarrow \sigma_{\text{S3C4}}^*$	-9.7	-18.4	-17.6
2 $\pi_{\text{C1C2}} \rightarrow \pi_{\text{C5X6}}^*$	-21.7	-17.6	-17.7
3 $\sigma_{\text{S3C4}} \rightarrow \pi_{\text{C1C2}}^*$	-17.5	-9.2	-11.3
4 $\sigma_{\text{S3C4}} \rightarrow \pi_{\text{C5X6}}^*$	-16.6	-30.3	-28.8
5 $\pi_{\text{C5X6}} \rightarrow \pi_{\text{C1C2}}^*$	-14.3	-35.0	-36.3
6 $\pi_{\text{C5X6}} \rightarrow \sigma_{\text{S3C4}}^*$	-26.7	-11.9	-12.4
$\Sigma$ (1) + (2) + (4) ( $\Sigma_1$ )	-48.0	-66.3	-64.1
$\Sigma$ (3) + (5) + (6) ( $\Sigma_2$ )	-58.5	-56.1	-60.3

<sup>a</sup> Atomic numbering as in Fig. 1.

supported by the NBO search of the Lewis structures of TS1 and TS2.

The non-Lewis occupancies are reported in Table 3 (the lower the non-Lewis density, the better the corresponding structure). When comparing these values, it can be concluded that the participation of the resonance structure I to the description of TS1 is preponderant while II is the principal resonance structure for cis-TS2 and trans-TS2. These differences in transition state geometries should have importance in the effect of substituents on  $\Delta E^\ddagger$  and  $\Delta_r E$  of reactions (1) and (2) (*vide infra*).



### Mechanistic considerations

In this part, we report, in the framework of the NBO model, a population analysis and we discuss the nature and the magnitude of the delocalization interactions along the 1(2)→TS1(TS2) step. As shown in Table 3, a charge analysis shows the differences between the character of the transition structures during the shifts (1) and (2). There is a charge transfer of 0.232 electron from the allyl fragment to the vinylthio fragment during this step; this charge transfer is less important (0.06 and 0.09) when the ethanimine fragment replaces the allyl fragment. The amount of charge transfer is not correlated to the variation of the dipole moment between ground and transition states. It should be noted as shown in Fig. 2, that the amount of atomic charge  $q$  borne by the vinylthio moiety, remains always positive along the 2→TS2 pathway and that the maximum of charge transfer is obtained before TS2 has been reached. These trends suggest that the allyl fragment is a better electron donor than the ethanimine one.

More detailed informations on the electron delocalization process can be obtained by means of the NBO deletion procedure.<sup>28</sup> A semi-quantitative second-order perturbation

analysis reveals that the main delocalization interactions in the transition states occur between NBOs indicated in the first column of Table 4. Among these interactions, 1, 3, 4 and 6 participate in weakening the S-3-C-4 bond while 2 and 5 participate in strengthening the C-1-X-6 bond. The magnitude of the delocalization energies is subordinated to the length of the forming and breaking bonds in the transition states; as a matter of fact, larger stabilizing interactions 5 are calculated for cis-TS2 and trans-TS2 (shorter C-1-C-6 bond in TS2). However, the knowledge of the relative weights of the interactions can be of interest in a better understanding of the mechanism. The examination of Table 4 denotes some trends following the substitution of the N-6-H group for the C-6-H<sub>2</sub> group:

(i) the interaction 6 which is the main delocalization in TS1 is dramatically reduced in cis-TS2 and trans-TS2; this decrease can be rationalized by means of second-order perturbation theory, eqn. (2)

$$E_{\text{int}} = -2 < \pi_{\text{C5X6}} | F | \sigma_{\text{S3C4}}^* > / (\epsilon \sigma_{\text{S3C4}}^* - \epsilon \pi_{\text{C5X6}}) \quad (2)$$

The energy difference between  $\sigma^*$  acceptor orbital and  $\pi$  donor orbital in the denominator of eqn. (2) is larger in TS2 (the  $\pi_{\text{C5N6}}$  orbital lies lower than the  $\pi_{\text{C5C6}}$  one) and the Fock matrix element between the interacting orbitals is smaller (N is more electronegative than C and thus  $\pi_{\text{C5N6}}$  is more concentrated on the N-6 atom).

(ii) The same argument holds to explain the variation of the ratio 2:5 which is equal to 1.52 in TS1 and only equal, respectively, to 0.50 and 0.48 in cis-TS2 and trans-TS2;  $\pi_{\text{C5N6}}$  is more concentrated on the C-5 atom, allowing a better overlap with  $\pi_{\text{C1C2}}$ ; in the same way,  $\pi_{\text{C5N6}}$ , which is more concentrated on the N-6 atom interacts better with  $\pi_{\text{C1C2}}^*$ . Furthermore, it is noteworthy that the ratio 3:4 in TS1 is three times lower in TS2.

The question is now: is it possible to stabilize TS2 by substituent effects? Assuming that the larger effect will be obtained by the perturbation of the main contribution, we focused on the  $\pi \rightarrow \pi^*$  interaction 5; an increased stabilization is expected when introducing a  $\pi$  donor on C-5 and a  $\pi$  acceptor on C-2 (one can notice that the same reasoning, when applied to TS1, will lead to the introduction of a  $\pi$  donor substituent on C-2 and a  $\pi$  acceptor on C-5), but the presence of a  $\pi$  donor at C-5 would reduce the magnitude of 2 (which is the second main contribution) and 4; a  $\pi$  acceptor on C-2 would also increase the magnitude of 3 but reduces 1 and 2. Thus, at this point, the temporary conclusion might be that the idea to enhance some of the stabilizing contributions in order to increase the reactivity of compound 2 cannot be a guideline in our search.

We return briefly to the charge transfer described in Fig. 2. The given indications seem to be inconsistent with the data collected in Table 4 insofar as the main contribution in TS2 corresponds to a charge transfer from the nitrogen to the vinyl carbon. In order to provide additional insight into the charge

**Table 5** NBO energetic analysis of delocalization interactions (kcal mol<sup>-1</sup>) in YCH = X

X	CH <sub>2</sub>				S		NH	
	NH <sub>2</sub>	SH	BH <sub>2</sub>	CN	NH <sub>2</sub>	SH	BH <sub>2</sub>	CN
$n_Y \rightarrow \pi^*_{CX}$	-26.8	-18.2			-67.9	-31.7		
$\pi_{CX} \rightarrow n^*_{Y(\sigma^*CX)}$			-21.5	-17.2			-13.2	-11.4

**Table 6** Key geometrical parameters (Å) of the optimized transition structures and charge transfer  $\Delta q$  charges upon solvation

	$\epsilon$	R(C-1-X-6)	R(S-3-C-4)	$\Delta q^a$	$\mu(D)$
<b>TS1</b>	2	2.154	2.409	-0.179	4.0
	5	2.175	2.437	-0.220	4.6
	10	2.187	2.453	-0.240	4.9
	32.6	2.197	2.467	-0.258	5.2
	78.3	2.201	2.471	-0.263	5.3
<i>cis</i> - <b>TS2</b>	2	1.913	2.345	0.018	1.9
	5	1.916	2.352	0.004	2.1
	10	1.918	2.356	-0.003	2.2
	32.6	1.919	2.358	-0.008	2.3
	78.3	1.919	2.358	-0.010	2.3
<i>trans</i> - <b>TS2</b>	2	1.925	2.396	0.031	2.8
	5	1.932	2.407	0.016	3.1
	10	1.939	2.413	0.010	3.2
	32.6	1.942	2.417	0.005	3.4
	78.3	1.944	2.419	0.004	3.4

<sup>a</sup> See Table 3 for definition.

transfer the two moieties (vinylthio and ethanimine), we have computed the interactions 1–6 for different values of the reaction coordinate. The results are shown in Fig. 3. First, crossing curves are numerous, especially for the 2→TS2 step. Thus, an analysis of the interactions in the early times of the process cannot be extended to the TSs. Fig. 3(a) shows that the main variations concern the  $\pi_{C1C2} \rightarrow \pi^*_{C5C6}$  and  $\pi_{C5C6} \rightarrow \sigma^*_{S3C4}$  interactions for the 1→TS1 pathway while Fig. 3(b) clearly show that for the 2→TS2 step,  $\sigma_{S3C4} \rightarrow \pi^*_{C5N6}$  and especially  $\pi_{C5N6} \rightarrow \pi^*_{C1C2}$  interactions are the most modified. If we compare Fig. 2 with Fig. 3(b), the increase of the positive charge born by the vinylthio part takes place when the increase of the stabilizing interaction 5 is very substantial. Insofar as  $\pi_{C6N6} \rightarrow \pi^*_{C1C2}$  corresponds a charge transfer from the aza moiety to the vinylthio moiety, it is clear that any relation occurs between the charge  $q$  of the vinylthio moiety and the relative magnitudes of  $\pi_{C5N6} \rightarrow \pi^*_{C1C2}$  and  $\sigma_{S3C4} \rightarrow \pi^*_{C5N6}$  interactions. In Table 4 are given the sums of the interactions 1 + 2 + 4 and 3 + 5 + 6; interaction energy and amount of charge transferred are closely related.<sup>28</sup> If we assume that contributions 1, 2 and 4 lead to a vinylthio→ethanimine net charge transfer, and that the others lead to the corresponding back charge transfer, we note a relationship between  $q_{CCS}$  and the ratio  $\Sigma_1/\Sigma_2$ : a ratio value lower than one corresponds to a negative value of  $q_{CCS}$  and a ratio value greater than one is associated to a positive value of  $q_{CCS}$ .

There is also a difference of atomic charge on the X-6 centre in rearrangements (1) and (2); this charge is more negative for X-6 = N-6 than for X-6 = C-6. The C-1 atom bears also a negative charge. One expects a greater electrostatic repulsion during the aza-rearrangement.

At this point of the study, we tentatively make some proposals to improve the reactivity of 2 in reaction (2). The rearrangement of the unsubstituted starting material 2 is an endothermic process; one proposal is the search of substituents which stabilize 2' (and hence to less extend TS2). In a preceding study of the reactivity of the C=S bond,<sup>35</sup> we have pointed out a strong stabilizing interaction between the lone pair of  $\pi$  donor heteroatomic substituents such as NH<sub>2</sub> and the  $\pi^*_{CS}$  orbital [in HC(S)NH<sub>2</sub>]; the interaction is dramatically reduced when the

ethylenic  $\pi^*_{CC}$  orbital is involved (for instance in ethenamine). Consequently, substitution on the C-2 carbon by a  $\pi$  donor group will stabilize 1' and 2' more than 1 and 2 and negative values of the reaction enthalpy can then be expected.<sup>36</sup> In this connection, NBO deletion procedure is a tool in the choice of the substituents. For instance, the values given in Table 5 reveal that NH<sub>2</sub> can be chosen in preference to SH, the differences in stabilization being larger for the former substituent.

Using the same argument, another substitution may be considered on the C-5 carbon of compound 2. As shown in Table 5, the  $\pi$  acceptor group stabilizes more the C=C bond than the C=N bond and thus this stabilizing effect should be added to the former to enhance the thermodynamic driving force of rearrangement (2). Furthermore, it is expected that the  $\pi$  acceptor group will draw a part of the negative charge of the nitrogen atom and thus, will reduce the electrostatic repulsion previously mentioned. Substituent effect studies are under investigation.

#### Solvent effect

Table 6 lists key geometrical variables, charge separation and dipole moment of the three transition structures for various relative permittivities. Relative solvation energies are summarized in Table 7. Recently, Storer *et al.* observed that pronounced solvent effects are accompanied by loose transition structures.<sup>37</sup> Our results agree with this observation: the larger variations of C-1–C-6 and S-3–C-4 distances correspond to the most important change in energy barrier (TS1, see Table 7); with respect to gas phase values, the elongation of C-1–C-6 and S-3–C-4 bonds are equal respectively to 0.064 and 0.087 Å in TS1 ( $\epsilon = 78.3$ ); smaller elongations are calculated for *trans*-TS2 (0.019 and 0.035 Å respectively) and particularly for *cis*-TS2 (0.010 and 0.021 Å respectively). At the same time, the ionic character of TS1 is enhanced. Increases in the amount of charge transferred from the vinylthio fragment to the allyl fragment as well as in dipole moments are noticed. In contrast, very weak variations upon solvation are observed for *cis*-TS2 and *trans*-TS2. However, in both cases, solvation increases the donor character of the vinylthio moiety.

For TS1 the solvation model yields a barrier lowering in all media, weak (0.3 kcal mol<sup>-1</sup>) in alkanes, substantial (2.5 kcal mol<sup>-1</sup>) in methanol or water. Furthermore, except for alkanes, solvation effects increase moderately the reaction exothermicity. Unfortunately, for TS2 the polarizable continuum approach predicts a weaker solvent effect: the barrier height corresponding to the *cis* transition state increases for  $\epsilon < 10$  and remains nearly the same as in gas phase for higher relative permittivity; the only pleasant result is the increase of the exothermicity of reaction (2) in polar media. For the *trans*-TS2, the barrier height is slightly lowered from  $\epsilon > 4$  but, in return, a weak decrease of the reaction exothermicity is predicted. All these results show that the solvent has a weak influence on the rearrangements of *cis*-2 and *trans*-2.

#### Conclusions

This article describes an *ab initio* comparative study of the thio-Claisen rearrangement and of one of its potential aza analogue. The main results can be summarized as follows.

(i) Whatever the level of calculation is, vinylthioethanimine

**Table 7** Solvation energy  $E_{\text{sol}}$  of starting compound and changes in barrier height  $\Delta(\Delta E^\ddagger)$  and reaction energy  $\Delta(\Delta_r E)$  upon solvation; energies are in kcal mol<sup>-1</sup>

Process	$\epsilon$	2	5	10	32.6	78.3
1→1'	$E_{\text{sol}}^a$	-1.7	-1.9	-2.1	-2.3	-2.4
	$\Delta(\Delta E^\ddagger)^b$	-0.3	-1.7	-2.2	-2.5	-2.6
	$\Delta(\Delta_r E)^b$	+0.2	-0.9	-1.2	-1.4	-1.4
<i>cis</i> -2→ <i>cis</i> -2'	$E_{\text{sol}}^a$	-2.6	-3.5	-3.8	-4.3	-4.3
	$\Delta(\Delta E^\ddagger)^b$	+0.8	+0.3	0.0	-0.1	-0.1
	$\Delta(\Delta_r E)^b$	+0.7	-0.3	-0.8	-1.3	-1.2
<i>trans</i> -2→ <i>trans</i> -2'	$E_{\text{sol}}^a$	-2.1	-3.2	-3.7	-4.2	-4.3
	$\Delta(\Delta E^\ddagger)^b$	+0.3	-0.2	-0.4	-0.5	-0.5
	$\Delta(\Delta_r E)^b$	+0.5	+0.3	+0.3	+0.3	+0.4

<sup>a</sup>  $E_{\text{sol}} = E_{\text{T}}(\text{SOLVENT}) - E_{\text{T}}(\text{GAS PHASE})$ . <sup>b</sup>  $\Delta(\Delta_r E) = \Delta E(\text{solvent}) - \Delta E(\text{gas phase})$ .

is predicted to be less reactive than allyl vinyl sulfide in sigmatropic rearrangement; the barrier heights differences are found to be substantial (4.5 kcal mol<sup>-1</sup> for *cis*-2 and 10.0 kcal mol<sup>-1</sup> for *trans*-2), due probably to a large electrostatic repulsion between the centres involved in the forming bond.

(ii) Rearrangement (2) is an endothermic process, even in solution.

(iii) B3LYP/6-31G\* predictions are in agreement with our height level [QCISDT/6-311 + G(2df,2p)] results. It is a pleasant result insofar as the study of sigmatropic [3,3]-rearrangements of large substituted derivatives is in the process of being investigated.

(iv) The results obtained considering the polarizable continuum approach show that solvation has no major influence on rearrangement (2). Thus and unlike the thio-Claisen shift, no significant rate enhancement of this reaction can be expected on going from the gas phase into solution.

(v) Mechanistic considerations based on NBO analysis reveal that the charge transfer during the first stage of the reaction involves many delocalization interactions of almost the same importance.

(vi) According to us, an improvement of the feasibility of rearrangement (2) would be obtained by appropriate substitutions in order to yield an exothermic process. Studies in this field are in progress.

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