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Substituent effect on the allyl vinyl sulfide rearrangement (thio-Claisen rearrangement) and the vinylthioethanimine rearrangement. A theoretical study

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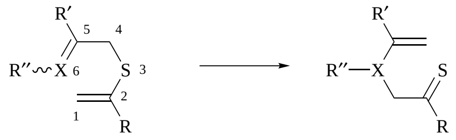
The transition structures for the [3,3] sigmatropic rearrangements of a variety of substituted allyl vinyl sulfides (X=CH) and vinylthioethanimines (X=N) $H_2C{=}CR{-}S{-}CH_2{-}CR'{=}XR''$ (R = NH_2; R′ = BH_2, CN; R″ = CF_3) have been located using *ab initio* and DFT (B3LYP) calculations and the 6-31G* basis set. Relative energies have been estimated using post-HF calculations up to the QCISD(T)/6-31G*//B3LYP/6-31G* level. Solvent effects on these processes have been simulated by means of SCRF computations associated with a continuum model. The results show that combined donor–acceptor disubstitutions (R = NH_2, R′ = BH_2 or CN) improve considerably the reactivity of the allyl vinyl sulfide (vinylthioethanimine). Thus, 2-amino-5-cyano disubstitution lowers the enthalpy of activation by 6.6 kcal mol^{-1} (9.3 kcal mol^{-1}) (1 cal = 4.184 J) and increases the exothermicity of the rearrangement by 13.0 kcal mol^{-1} (19.1 kcal mol^{-1}). In addition, as the corresponding saddle points are highly polar in nature, an additional transition state stabilization, even in moderately polar solvents, is predicted by the SCRF calculations.

Introduction

Thio-Claisen rearrangements are important [3,3] sigmatropic shifts widely used in synthetic organic chemistry.[1] The simplest allyl vinyl sulfide (Scheme 1, X = CH_2, R = R′ = R″ = H) easily leads to an unstable thioaldehyde, pentenethial. In the thioketone series (Scheme 1, X = CH, R = alkyl, R′ = R″ = H), these sigmatropic processes have been shown to be reversible.[2] This synthetic limitation was not observed for dithioesters (X = CH_2, R = SR, R′ = R″ = H)[3] and for *O*-substituted thioesters (X = CH_2, R = OR, R′ = R″ = H).[4]



X = CH **1**   **1′**
X = N (*Z*)-**2**   **2′**
(*E*)-**2**

a: R = NH_2, R′ = R″ = H
b: R = NH_2, R′ = BH_2, R″ = H
c: R = NH_2, R′ = CN, R″ = H
d: R = NH_2, R′ = H, R″ = CF_3

Scheme 1

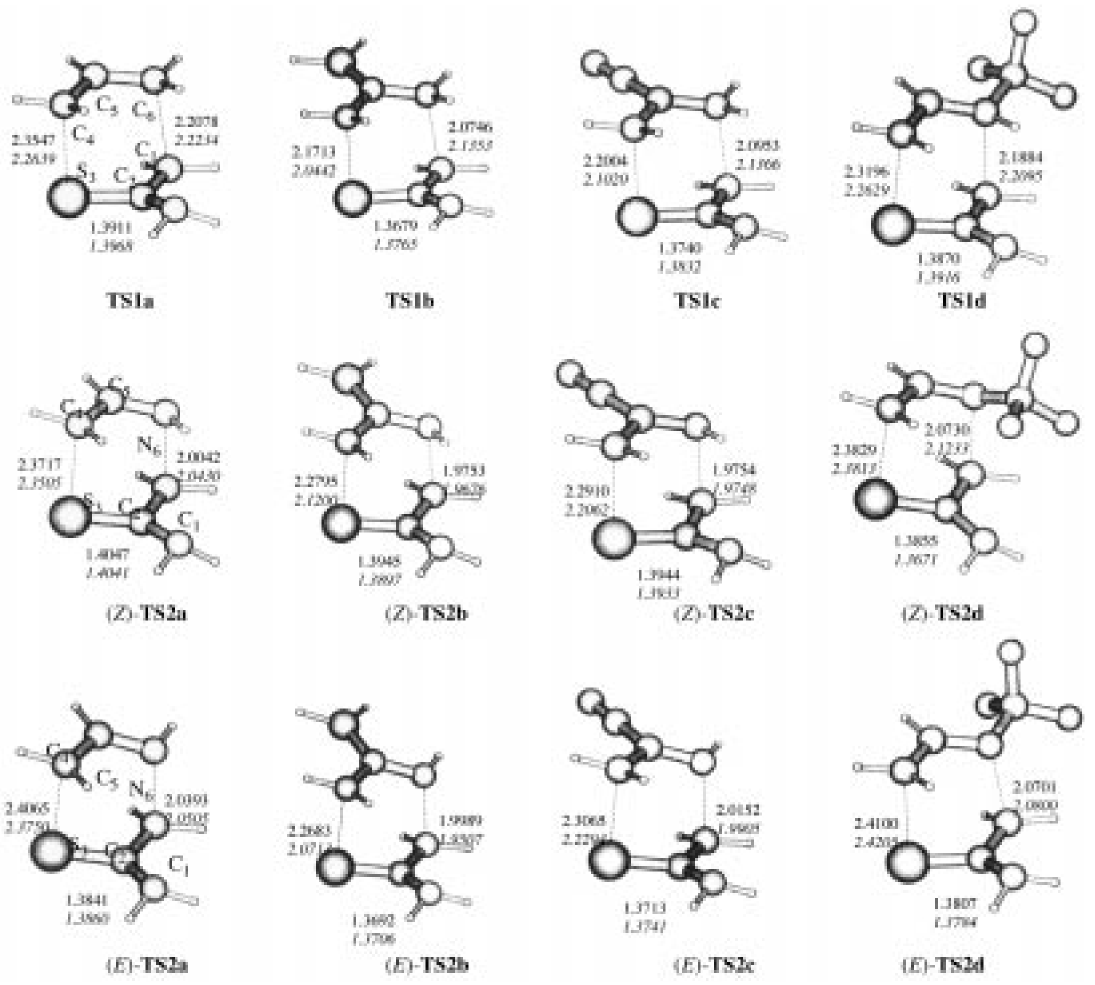
We previously reported a theoretical study of the thio-Claisen rearrangement of the unsubstituted allyl vinyl sulfide and of one of its aza analogues, vinylthioethanimine (Scheme 1, XR″ = NH *Z* and *E*, R = R′ = H).[5] We proposed that those rearrangements proceed *via* chair-like transition states; at the QCISD(T)/6-311+G(2df,2p)//MP2/6-31G(d) level, the activation enthalpy of the former rearrangement is equal to 21.1 kcal mol^{-1} (1 cal = 4.184 J); the corresponding values for the vinylthioethanimine rearrangement are 25.6 (*Z*) and 31.4 (*E*) kcal mol^{-1}. In addition, the thio-Claisen rearrangement was calculated to be slightly exothermic (Δ_rH −1.5 kcal mol^{-1}) while the second is predicted to be endothermic [$\Delta_rH(Z)$ 7.0 kcal mol^{-1}; $\Delta_rH(E)$ 9.1 kcal mol^{-1}]. These positive Δ_rH values suggest an easily reversible rearrangement **2′** $\longrightarrow$ **2** and strong synthetic limitations. In the same study, on the basis of a natural bond orbital (NBO) analysis, we expected that substitution at the C^2 atom by a π-donor group (and especially an amino group) should stabilize the products **1′** and **2′**.

The main goal of this paper is to check if these assumptions are supported by a high-level *ab initio* computational study. In addition, given the polar character of the species considered, the effect of solvation has been included. We have selected the starting compounds depicted in Scheme 1; the choice of CF_3 substituent at X^6 will be discussed afterwards.

Computational methods

In our preceding study,[5] we reviewed recent calculations of the parent Cope and Claisen rearrangements; in the light of the work of Borden[6] and Davidson,[7] it seems well established that the former [3,3] sigmatropic shift is concerted and does not involve the formation of a diradical intermediate. On the basis of this result, we assumed that the reaction studied here occurs along a concerted reaction pathway and thus we decided to employ single reference techniques.

All the results presented in this work have been obtained using *ab initio* and DFT calculations, by means of GAUSSIAN94[8] and a modified version with additional code needed for the SCRF computations, with the standard 6-31G* basis set.[9] For DFT calculations, the hybrid functional B3LYP[10] which contains gradient corrections for both exchange and correlation has been chosen. This non-local DFT method has been successfully used for the study of Cope and Claisen rearrangements[11] as well as the study of substituent effects on this latter reaction.[12] Geometry optimizations have been carried out at the HF and B3LYP levels. Transition structures have been located and characterized by frequency calculations[13] at the RHF/6-31G* theory level. HF geometries are used as starting points for B3LYP optimizations. Symmetry-broken UHF calculations with the same basis set gave transition structures and energies identical to those obtained by RHF calculations. Thus, these rearrangements are classified as closed-shell reactions. Reactant and product conformers were those obtained by the IRC procedure;[14] IRCs were calculated at the HF/6-31G* level in a mass-weighted internal coordinate system using the Gonzalez–Schlegel method[15] available in the GAUSSIAN94 program. In many cases, single-point energies were computed up to



TS1a **TS1b** **TS1c** **TS1d**

(*Z*)-**TS2a** (*Z*)-**TS2b** (*Z*)-**TS2c** (*Z*)-**TS2d**

(*E*)-**TS2a** (*E*)-**TS2b** (*E*)-**TS2c** (*E*)-**TS2d**

Fig. 1 Optimized geometries of the transition structures on the [3,3] sigmatropic rearrangements calculated at the HF and B3LYP (italicised) levels

MP4SDTQ and QCISD(T) levels using B3LYP optimized geometries. Zero-point vibrational energies (ZPE) were scaled by 0.9135.[16] NBO[17] calculations were also performed to analyse the delocalization interactions in the transition states (TSs) by means of the NBO version 3.1 which was built into link 607 on the GAUSSIAN program.[18]

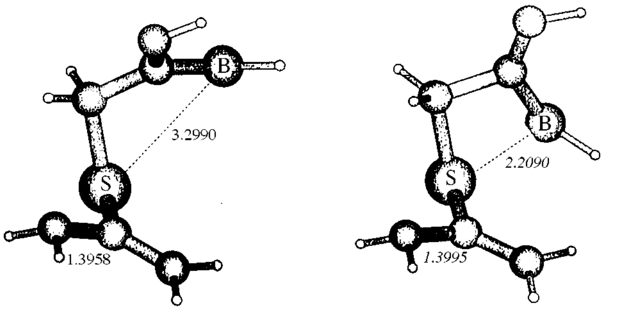
To simulate nonspecific solvent effects on these processes, SCRF computations associated with a continuum model have been performed for relative permittivity taken equal to 2.0 and 10.0, this interval encompassing the range of solvents used for this kind of reaction. This model is based on a multipolar development of the charge distribution of the solute, in which the solute is assumed to be isolated from the solvent by a hypothetical cavity of any shape.[19] As shown in recent work,[20] this approach is an effective method for studying reaction processes in solution.

Results and discussion

Structures and energies

The transition structures of [3,3] sigmatropic rearrangements depicted in Scheme 1 are shown in Fig. 1. Calculated activation parameters and thermodynamic quantities for these twelve reactions are collected in Table 1.

As shown in Fig. 2 HF and B3LYP optimized geometries of the (*E*)-**2b** isomer differ notably in their S–B distance which is equal to 3.299 and 2.209 Å at HF and B3LYP levels, respectively. For the latter geometry, the best Lewis structure obtained by an NBO search possesses a bond between the S and B atoms. Insofar as BH_2 substitution creates specific interactions likely to bias the analysis of the effects of the substituent, another model of π-acceptor substituent (CN) has been considered.



(*E*)-**2b** (HF) (*E*)-**2b** (B3LYP)

Fig. 2 HF and B3LYP optimized geometries of (*E*)-**2b**

As seen from Fig. 1 the length of the breaking S^3–C^4 bond calculated by the B3LYP/6-31G* method is systematically shorter than the one obtained from RHF calculations; concerning the length of the forming C^1–C^6 bond, the two methods give comparable results. All TSs present the same features, *i.e.* chair-like, aromatic type transition structures. However, substituents induce sizeable changes in the geometry. In the thio-Claisen series, as compared to the unsubstituted system, the presence of an amino group on C^2 (**TS1a**) induces a small shortening of the breaking bond [0.07 (HF) or 0.06 Å (B3LYP)] and a lengthening of the forming bond [0.07 (HF) or 0.1 Å (B3LYP)]. Similar trends have been reported by Gao and colleagues[21] in their study of the Claisen rearrangement; a MeO group at C^2 lengthens the C^1–C^6 bond by 0.064 Å and shortens the O^3–C^4 bond by 0.045 Å (HF/6-31G* calculations). The addition of an electron-attracting group at C^5 (**TS1b** and **TS1c**) results in a noticeable shortening of both S^3–C^4 and C^1–C^6 bonds. If the substitution

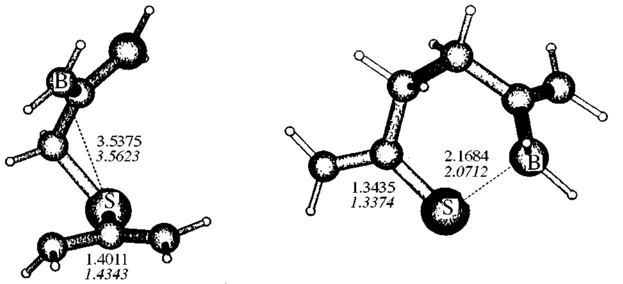
Table 1 Barrier height $\Delta E^{\ddagger}$, zero point vibrational energy differences Δ(ZPE), activation energy $\Delta H^{\ddagger}$, reaction energy $\Delta_r E$ and reaction enthalpy $\Delta_r H$(298 K) in kcal mol^{-1} for the various rearrangements. Relative values with respect to unsubstituted processes are given in parentheses.

		$\mathbf{1} \longrightarrow \mathbf{1'}$				(Z)-$\mathbf{2} \longrightarrow \mathbf{2'}$				(E)-$\mathbf{2} \longrightarrow \mathbf{2'}$			
		a	b	c	d	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**
	HF	35.9 (−4.2)	30.6 (−9.5)	32.5 (−7.6)	38.6 (−1.5)	47.3 (−0.8)	42.6 (−5.5)	44.0 (−4.1)	53.8 (5.7)	51.2 (−2.6)	44.1 (−9.7)	46.0 (−7.8)	53.1 (−0.7)
$\Delta E^{\ddagger}$/	B3LYP	16.7 (−4.1)	11.0 (−9.8)	13.4 (−7.4)	17.4 (−3.3)	23.3 (−1.7)	17.0 (−8.0)	20.0 (−5.0)	26.7 (1.7)	25.7 (−5.0)	19.5 (−11.2)	20.9 (−9.8)	26.2 (−4.5)
kcal mol^{-1}	MP4SDTQ	18.5 (−3.2)	12.7 (−9.0)	15.2 (−6.5)	—	24.5 (−1.2)	18.1 (−7.6)	21.4 (−4.3)	—	27.8 (−4.6)	21.3 (−11.1)	23.0 (−9.4)	—
	QCISD(T)	20.7 (−3.6)	15.0 (−9.3)	—	—	27.6 (−1.1)	21.4 (−7.3)	—	—	30.6 (−4.6)	23.4 (−11.8)	—	—
ΔZPE/		−0.3	−0.2	−0.4	−0.5	−0.2	−0.3	−0.4	−0.7	−0.5	−0.3	−0.6	−0.8
kcal mol^{-1}	HF	35.0 (−4.3)	29.8 (−9.5)	31.6 (−7.7)	37.5 (−1.8)	46.3 (−1.1)	42.0 (−5.4)	43.1 (−4.4)	52.6 (5.1)	50.1 (−2.8)	43.2 (−9.8)	45.2 (−7.7)	51.8 (−1.2)
	B3LYP	15.8 (−4.4)	10.2 (−9.8)	12.5 (−7.5)	16.3 (−3.6)	22.3 (−2.0)	16.4 (−7.9)	19.1 (−5.3)	25.5 (1.1)	24.6 (−5.2)	18.4 (−11.3)	20.1 (−9.7)	24.9 (−5.0)
$\Delta H^{\ddagger}$/	MP4SDTQ	17.6 (−3.3)	11.9 (−9.0)	14.3 (−6.6)	—	23.5 (−1.5)	17.5 (−7.5)	20.5 (−4.6)	—	26.7 (−4.8)	20.4 (−11.2)	22.2 (−9.3)	—
kcal mol^{-1}	QCISD(T)	19.8 (−3.7)	14.2 (−9.3)	—	—	26.6 (−1.4)	20.8 (−7.2)	—	—	29.5 (−4.8)	22.5 (−11.9)	—	—
	HF	−21.5 (−16.4)	−25.5 (−20.4)	−20.7 (−15.6)	−19.3 (−14.2)	−14.9 (−19.6)	−20.1 (−24.8)	−15.9 (−20.6)	−14.4 (−19.1)	−16.0 (−22.4)	−20.0 (−26.4)	−16.3 (−22.7)	−9.8 (−16.2)
$\Delta_r E$/	B3LYP	−20.4 (−15.7)	−29.8 (−25.1)	−19.9 (−15.2)	−18.3 (−13.6)	−16.9 (−19.3)	−23.0 (−25.4)	−17.7 (−20.1)	−15.4 (−17.8)	−17.2 (−21.8)	−19.6 (−24.2)	−17.5 (−22.1)	−11.4 (−16.0)
kcal mol^{-1}	MP4SDTQ	−20.4 (−13.2)	−32.6 (−25.4)	−20.6 (−13.4)	—	−12.2 (−15.9)	−18.1 (−22.1)	−12.3 (−16.0)	—	−13.3 (−19.4)	−14.4 (−20.5)	−13.2 (−19.3)	—
	QCISD(T)	−19.6 (−13.2)	−31.9 (−25.5)	—	—	−11.5 (−16.0)	−17.5 (−22.0)	—	—	−12.7 (−19.4)	−14.1 (−20.8)	—	—
Δ_rZPE/		1.2	1.5	1.2	1.1	1.6	1.8	1.2	1.3	1.4	1.7	1.5	1.3
kcal mol^{-1}	HF	−20.5 (−16.1)	−25.2 (−20.7)	−19.7 (−15.2)	−18.5 (−14.0)	−13.8 (−19.4)	−18.9 (−24.5)	−15.0 (−20.6)	−13.4 (−19.0)	−14.9 (−22.6)	−18.8 (−26.5)	−14.8 (−22.5)	−8.8 (−16.5)
	B3LYP	−19.4 (−15.4)	−29.5 (−25.4)	−18.9 (−14.8)	−17.5 (−13.4)	−15.8 (−19.1)	−21.8 (−25.1)	−16.8 (−20.1)	−14.4 (−17.7)	−16.1 (−22.0)	−18.4 (−24.3)	−16.0 (−21.9)	−10.4 (−16.3)
$\Delta_r H$/	MP4SDTQ	−19.4 (−12.9)	−32.3 (−25.7)	−19.6 (−13.0)	—	−11.1 (−15.7)	−16.9 (−21.8)	−11.4 (−16.0)	—	−12.2 (−19.6)	−13.2 (−20.6)	−11.7 (−19.1)	—
kcal mol^{-1}	QCISD(T)	−18.6 (−12.9)	−31.6 (−25.8)	—	—	−10.4 (−15.8)	−15.3 (−21.7)	—	—	−11.6 (−19.6)	−12.9 (−20.9)	—	—

Table 2 Some structural and electronic properties of the transition structures in the gas phase

	n_P (1–6)		$1 - n_P$ (3–4)		q_{C1}[a]	q_{X6}[a]	Δq[a,b]	μD
	HF	B3LYP	HF	B3LYP	HF	HF	HF	HF
TS1[c]	0.369	0.376	0.606	0.546	−0.431	−0.364	−0.232	3.37
TS1a	0.330	0.326	0.583	0.488	−0.500	−0.319	−0.135	2.87
TS1b	0.413	0.379	0.432	0.303	−0.544	−0.247	0.016	4.49
TS1c	0.399	0.401	0.464	0.373	−0.527	−0.283	0.017	5.88
TS1d	0.343	0.336	0.560	0.489	−0.459	−0.336	−0.209	2.48
(*Z*)-**TS2**[c]	0.459	0.453	0.577	0.552	−0.259	−0.675	−0.086	1.64
(*Z*)-**TS2a**	0.389	0.373	0.598	0.571	−0.335	−0.637	0.018	1.78
(*Z*)-**TS2b**	0.416	0.429	0.530	0.358	−0.360	−0.557	0.059	3.16
(*Z*)-**TS2c**	0.422	0.431	0.541	0.445	−0.342	−0.575	0.112	6.41
(*Z*)-**TS2d**	0.361	0.342	0.610	0.590	−0.326	−0.612	0.060	1.97
(*E*)-**TS2**[c]	0.452	0.492	0.609	0.577	−0.285	−0.693	−0.056	2.49
(*E*)-**TS2a**	0.374	0.375	0.622	0.583	−0.378	−0.640	0.022	1.96
(*E*)-**TS2b**	0.400	0.442	0.520	0.285	−0.409	−0.560	0.090	2.62
(*E*)-**TS2c**	0.395	0.420	0.554	0.468	−0.390	−0.581	0.121	5.28
(*E*)-**TS2d**	0.363	0.365	0.625	0.613	−0.336	−0.610	−0.040	2.29

[a] NPA analysis. [b] Change [$\Delta q = q(\mathrm{TS}) - q(\mathrm{reactant})$] in NPA charges for the vinylthio moiety; a positive value indicates a charge transfer from $H_2C{=}CR{-}S$ to $R''X{=}CR'{-}CH_2$. [c] Unsubstituted TSs.



1b **1′b**

Fig. 3 Optimized geometries of the starting compound and the product of the **1b** ⟶ **1′b** rearrangement; B3LYP values are italicised

by an acceptor group occurs at C^6 instead of C^5, the resulting transition structure **TS1d** is close to **TS1a**; we conclude that the CF_3 substituent at C^6 has little effect on the TS geometry. The much tighter transition structures predicted for **TS1b** and **TS1c** correspond to a smaller cleavage of the $S^3{-}C^4$ bond but also to a more advanced formation of the $C^1{-}C^6$ bond. A better description of the extent of bond forming and bond breaking is given by the Pauling bond order n_P;[22,23] from Table 2, one can see a large decrease of $1 - n_P(3–4)$ values from **TS1a** to **TS1c** as well as a moderate increase of $n_P(1–6)$ values. With respect to the unsubstituted **TS1**, **TS1b** and **TS1c** are reached for more synchronous bond breaking and bond forming.

Similar trends are observed in the aza series; the only noticeable difference concerns the effect of donor substitution at C^2 [(*Z*)- and (*E*)-**TS2a**] which induces an elongation of both $S^3{-}C^4$ and $C^1{-}N^6$ bonds. Another point of interest is the variation of the NH_2 linkage to the vinyl sulfide moiety along the reaction path. In the starting compounds, NH_2 is significantly pyramidalized and the $C^2{-}N(H_2)$ bond lies in the range 1.400–1.405 Å (HF) or 1.403–1.408 Å (B3LYP) (an illustration is given in Figs. 2 and 3). In the TSs, the amino group is less pyramidalized and the $C^2{-}N(H_2)$ bond is shortened. This shortening is modest in the case of monosubstitution at C^2 or 2,6-disubstitutions (0.01–0.015 Å); it is enhanced by combined 2,5-donor–acceptor substitutions [for example, **TS1b**: 0.033 (HF) or 0.028 (B3LYP); **TS1c**: 0.029 (HF) or 0.024 Å (B3LYP)]; a less important $C^2{-}N(H_2)$ bond shortening is calculated for the corresponding (*Z*)-**TS2** transition structures which could be tentatively attributed to a *Z* effect. In the products resulting from these rearrangements, the amino group lies in the $S^3C^2C^1$ plane and the $C^2{-}N(H_2)$ is shorter than in the starting material; an illustration is given in Fig. 3. This shortening of the $C^2{-}N$ bond is in line with our preceding analysis of the role played by the increasing delocalization interaction between the N lone pair and the π^*_{C2S3} orbital along with the progress of the reaction and is in agreement with the partial π character of the C–N bond in thioamides.[24]

Let us consider the energetics of these rearrangements. In our previous study of the parent unsubstituted compounds,[5] single-point post-HF calculations have been made, using MP2/6-31G* optimized geometries. For the purposes of comparison and consistency, it was necessary to ensure how the choice of the geometries affects the calculated barriers and reaction energies for these rearrangements. The variation in $\Delta E^\ddagger$ and $\Delta_r E$ for the two geometries is very small and only B3LYP geometries will be used in post-HF calculations in this work. Similar observations have been made in the case of cycloaddition reactions.[25]

We discuss first the changes in reaction energy upon substitution. Inspection of Table 1 shows that π-donor substitution at C^2 results in a considerable increase in the exothermicity of these sigmatropic rearrangements. This increase varies in the range 13–16 kcal mol^{-1} for the **1a** ⟶ **1′a** process and 16–19 kcal mol^{-1} (*Z*) or 19–22 kcal mol^{-1} (*E*) for the **2a** ⟶ **2′a** processes according to the level of calculations. In a general way, the $\Delta(\Delta_r E)$ obtained by MP4SDTQ or QCISD(T) methods are less negative by *ca.* 3 kcal mol^{-1} than the RHF one. In our opinion, this lowering of $\Delta_r E$ resulting from an NH_2 substitution at C^2 may be representative of the difference between the $LP_N \longrightarrow \pi^*_{C1C2}$ and $LP_N \longrightarrow \pi^*_{C2S3}$ delocalization energies. As mentioned in the Introduction in the case of the **2** ⟶ **2′** process, a synergetic effect resulting from coupling the donor group at C^2 and the acceptor group at C^5 is also expected. It is true for the strong π-acceptor BH_2 with a supplementary lowering of $\Delta_r E$ by about 6 kcal mol^{-1} for the *Z* reaction and 1.4 [QCISD(T)] to 4 kcal mol^{-1} (HF) for the *E* one. We return briefly to n_P Pauling bond orders values collected in Table 2. An unexpected common feature appears for **b** and **c** substitutions: the lesser degree of $C^3{-}C^4$ bond breaking is accompanied by a greater degree of $C^1{-}X^6$ bond formation; thus, the more exothermic processes correspond to the tighter transition structures. On the other hand, no noticeable synergetic effect can be calculated for the cyano derivatives. This synergetic effect is not operative for the **1** ⟶ **1′** process; however, close examination of Table 1 indicates a more negative $\Delta_r E$ value for the **1b** ⟶ **1′b** rearrangement (especially when correlation energy is taken into account). This increase in exothermicity should be attributed to a strong $LP_S \longrightarrow LP^*_B$ interaction in **1′b**; as a result, the S–B distance is strongly shortened as shown in Fig. 2(b).

A CF_3 group at the 6-position does not improve the exothermicity of these processes and more precisely the (*E*)-**2d** $\longrightarrow$ **2′d** reaction which is 6 kcal mol^{-1} less exothermic than the (*E*)-**2a** $\longrightarrow$ **2′a** one.

We consider now the effect of substituents on the energy barriers of these sigmatropic shifts. The RHF method overestimates the energy barriers; taking the QCISD(T)/6-31G* results as references, on the other hand, the B3LYP method underestimates the energy barriers. Inclusion of ZPE and thermal corrections results in $\Delta H^\ddagger$ values slightly lower than $\Delta E^\ddagger$. For the thio-Claisen reaction, a π-donor substituent in the 2-position (**1a**) lowers the energy barrier by about 4 kcal mol^{-1} in good agreement with experimental trends.[3,4] In the aza reaction, the amino group stabilizes (*Z*)-**TS2a** less than (*E*)-**TS2a** (1 *vs.* 4.5 kcal mol^{-1}). It is noteworthy that this lower stabilization corresponds to a small change in the C^2–NH_2 bond. The combined 2-NH_2, 5-BH_2 substitution results in a very large stabilization of the transition states in the order (*Z*)-**TS2b** (*ca.* 7 kcal mol^{-1}), **TS1b** (*ca.* 9 kcal mol^{-1}) and (*E*)-**TS2b** (*ca.* 11.5 kcal mol^{-1}). If the weaker electron-withdrawing but more synthetically realistic cyano group is substituted for the borane group, the stabilization effect decreases by 2–3 kcal mol^{-1} but remains substantial. Arrhenius and thermodynamics parameters of the (*Z*)- and (*E*)-**2c** $\longrightarrow$ **2′c** reactions are nearly the same; the comparison of these parameters with that calculated for the unsubstituted thio-Claisen rearrangement suggests that **2c** would stand as a relatively good candidate for undergoing a [3,3] sigmatropic shift. 6-CF_3 instead of 5-BH_2 or 5-CN does not improve the reactivity of **1d** or **2d** species. **TS1d** lies higher in energy than **TS1a** and the **1d** $\longrightarrow$ **1′d** step is less exothermic than the **1a** $\longrightarrow$ **1′a** one. In the same way, with respect to **2a**, the presence of CF_3 at N^6 raises the activation energy by 3.4–5.5 kcal mol^{-1} (*Z*) or 0.5–1.9 kcal mol^{-1} (*E*) according to the method of calculation and reduces the exothermicity of the reaction by 0.4–1.4 kcal mol^{-1} (*Z*) or 5.7–6.1 kcal mol^{-1} (*E*). In our earlier study,[5] we tentatively explained the lower reactivity of the vinylthioethanimine by a large electrostatic repulsion between negative charges carried by C^1 and N^6 centres. Because of the anionic character of the N^6 atom, we expected that the presence of a π-acceptor at the 6-position should stabilize the corresponding transition structure. The CF_3 group which is generally regarded as a strong π-acceptor has been chosen as a model. Our calculations show not only that the expected stabilization does not occur, but also that a steric penalty may arise for such a substitution [judging by the larger difference between the activation energies of (*Z*)-**TS2d** and (*Z*)-**TS2a** than between the activation energies of (*E*)-**TS2d** and (*E*)-**TS2a**].

Electronic structure and mechanistic considerations

In addition to Pauling bond orders, Table 2 contains information derived from a natural population analysis (NPA)[17,26] based on an HF/6-31G* wavefunction. Included are the C^1 and X^6 atomic charges as well as dipole moments and charge transferred from $H_2C{=}CR{-}S$ to $R''X{=}CR'{-}CH_2$ moieties in various TSs. 2- and 2,5-substitutions lead to a depletion of the electronic density at the X^6 centre, while the electron density at C^1 increases. It appears that the efficiency of 2,5-substitution in lowering the energy barriers of **TS2b** and **TS2c** originates for the main part from the stabilizing effect of the substituents but also from a slight decrease of the coulombic repulsion between C^1 and N^6 centres. On the other hand, the expected charge transfer from N^6 to CF_3 does not notably occur. As expected, also seen from Table 2 the combined 2,5 donor–acceptor substitution favours the charge transfer from the $H_2C{=}CR{-}S$ fragment to the $R''X{=}CR'{-}CH_2$ one. Table 3 gives the delocalization interactions obtained by means of the NBO deletion procedure[18] which depicts C^1–X^6 bond formation and S^3–C^4 bond breaking. The amount of charge transferred, Δq, can be understood by observing the increase of the $\pi_{C1C2} \longrightarrow \pi^*_{C5X6}$ stabilizing interaction when 2,5-substitution takes place. This large increase in stabilization can be ascribed, in part, to the decrease of the C^1–X^6 distance with successive substitutions and also to the increase of the donor (acceptor) properties of $C^1{=}C^2{-}R$ ($R'C^5{=}X^6$) π-systems. This is concluded from the ratio 1/2 [for example, ratios are 1.5 (**TS1**),[5] 2.6 (**TS1a**), 5.3 (**TS1b**) and 4.6 (**TS1c**)].

Table 3 Delocalization interactions (*E*/kcal mol^{-1}) in representative TSs (HF calculations)

	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]
TS1a	−21.8	−7.3	−8.1	−17.1	−25.2	−16.5
TS1b	−41.1	−7.8	−4.2	−14.2	−21.4	−6.8
TS1c	−37.4	−8.2	−5.4	−14.2	−24.6	−8.8
TS1d	−22.7	−9.1	−7.5	−16.0	−26.1	−13.5
(*E*)-**TS2a**	−18.3	−15.4	−10.6	−15.3	−19.0	−19.7
(*E*)-**TS2b**	−28.3	−13.4	−7.1	−14.6	−17.0	−13.2
(*E*)-**TS2c**	−23.6	−13.7	−9.1	−14.2	−17.6	−16.2
(*E*)-**TS2d**	−13.8	−16.4	−12.2	−13.9	−15.2	−24.0

[a] 1: $\pi_{C1C2} \longrightarrow \pi^*_{C5X6}$; 2: $\pi_{C5X6} \longrightarrow \pi^*_{C1C2}$; 3: $\pi_{C1C2} \longrightarrow \sigma^*_{S3C4}$; 4: $\sigma_{S3C4} \longrightarrow \pi^*_{C1C2}$; 5: $\pi_{C5X6} \longrightarrow \sigma^*_{S3C4}$; 6: $\sigma_{S3C4} \longrightarrow \pi^*_{C5X6}$.

Table 4 Key geometrical parameters (*d*/Å) of the optimized transition structures, and changes in charge transfer Δq (electron unit) and in dipole moment $\Delta\mu$ upon solvation

	ε	$d_{1\text{–}6}$/Å	$d_{3\text{–}4}$/Å	$\Delta(\Delta q)$[a]	$\Delta\mu$/D[b]
TS1a	2	2.227	2.367	−0.199	0.4
	10	2.260	2.391	−0.244	1.1
TS1b	2	2.060	2.124	0.020	0.9
	10	2.042	2.014	0.134	2.5
TS1c	2	2.078	2.148	0.030	2.3
	10	2.081	2.131	0.054	3.1
TS1d	2	2.198	2.323	−0.091	0.3
	10	2.210	2.327	−0.107	0.4
(*Z*)-**TS2a**	2	2.012	2.376	−0.010	0.2
	10	2.026	2.384	−0.020	0.5
(*Z*)-**TS2b**	2	1.980	2.273	0.004	0.5
	10	1.985	2.260	0.016	1.0
(*Z*)-**TS2c**	2	1.985	2.283	0.108	1.0
	10	1.989	2.266	0.121	1.6
(*Z*)-**TS2d**	2	2.079	2.385	0.001	0.1
	10	2.088	2.389	0.007	0.3
(*E*)-**TS2a**	2	2.051	2.415	−0.012	0.3
	10	2.059	2.417	−0.023	0.6
(*E*)-**TS2b**	2	2.007	2.266	0.004	0.3
	10	2.013	2.258	0.009	0.5
(*E*)-**TS2c**	2	2.019	2.290	0.001	0.6
	10	2.024	2.283	0.014	0.9
(*E*)-**TS2d**	2	2.086	2.422	0.001	0.21
	10	2.099	2.419	0.005	0.3

[a] $\Delta(\Delta q) = \Delta q(\text{solvent}) - \Delta q(\text{gas phase})$. [b] $\Delta\mu = \mu_{TS}(\text{solvent}) - \mu_{TS}(\text{gas phase})$.

The tighter character of **TS1b**, **TS1c** and **TS2b**, **TS2c** mentioned above can be related to the magnitude of the delocalization interactions. The interactions 3 and 6 which involve either σ_{S3C4} or σ^*_{S3C4} orbitals weaken the S^3–C^4 bond; 3 and 6 are less stabilizing in these TSs and thus the S^3–C^4 bond breaking is less advanced than in the other transition structures.

Close examination of Table 3 shows that the most important decrease in stabilization energy affects essentially the contributions 3 and 6; this fact can probably be attributed to a small $\langle \pi_{C1C2} | \sigma^*_{S3C4} \rangle$ and $\langle \sigma_{S3C4} | \pi^*_{C5X6} \rangle$ overlap consequent on 2-NH_2 and 5-BH_2 (or 5-CN) substitutions. Conversely, the interaction between the π_{C1C2} and π^*_{C5X6} leads to an in-phase interaction between C^1 and X^6; an enhancement of interaction 1 by substitution gives rise to a strengthening and a shortening of the C^1–X^6 distance.

The last indication given in Table 2 concerns TSs dipole moments; in both cases, 2,5 donor–acceptor substitutions result in highly polar transition states and, therefore, even moderately polar solvents should accelerate the reaction. This point is now examined.

Table 5 Solvation energy $E^{\ddagger}_{\mathrm{sol}}$ of TSs, changes in barrier height $\Delta\,(\Delta E^{\ddagger})$ and reaction energy $\Delta\,(\Delta_{\mathrm{r}}E)$ upon solvation; energies are in kcal mol^{-1}

		$E^{\ddagger}_{\mathrm{sol}}$/kcal mol^{-1}		$\Delta\,(\Delta E^{\ddagger})$/kcal mol^{-1}		$\Delta\,(\Delta_{\mathrm{r}}E)$/kcal mol^{-1}	
		$\varepsilon = 2$	$\varepsilon = 10$	$\varepsilon = 2$	$\varepsilon = 10$	$\varepsilon = 2$	$\varepsilon = 10$
1 $\longrightarrow$ **1′**	**a**	−2.0	−4.5	−0.5	−2.0	−2.0	−5.3
	b	−2.2	−4.8	−0.9	−2.0	−3.3	−6.3
	c	−4.4	−8.1	−1.2	−4.1	−1.9	−4.0
	d	−1.9	−4.0	1.7	0.5	−0.1	−2.9
(*Z*)-**2** $\longrightarrow$ **2′**	**a**	−2.1	−4.6	0.5	0.0	−0.8	−5.6
	b	−2.1	−4.7	0.3	−0.5	−1.0	−3.2
	c	−4.1	−7.6	−0.2	−2.5	−0.5	−3.3
	d	−1.9	−4.4	−1.9	−4.5	−2.5	−6.3
(*E*)-**2** $\longrightarrow$ **2′**	**a**	−2.7	−5.6	1.5	−1.8	0.7	−4.9
	b	−2.2	−5.2	0.9	−1.9	−0.3	−4.0
	c	−4.0	−8.2	−0.5	−3.3	−1.1	−2.1
	d	−2.1	−4.3	−2.1	−4.5	−2.5	−6.4

[a] $E^{\ddagger}_{\mathrm{sol}} = E^{\ddagger}(\mathrm{solvent}) - E^{\ddagger}(\mathrm{gas\ phase})$. [b] $\Delta\,(\Delta E) = \Delta E(\mathrm{solvent}) - \Delta E(\mathrm{gas\ phase})$.

SCRF results

The key geometrical parameters, charge separation and dipole moment of the transition structures for two relative permittivities ($\varepsilon = 2$ and 10) are listed in Table 4 and the energetics in solution are shown in Table 5. Generally, the effect of solvation on the lengths of breaking and forming bonds is weak. For 2- and 2,6-substitutions, looser transition structures are obtained with respect to gas phase results. However, solvation effects act in the opposite way in the case of **TS1b** and **TS1c**: the tighter feature of these TSs, already mentioned above, is increased with both C^1–C^6 and S^3–C^4 bonds being shortened compared to the gas phase values.

For **TS2b** and **TS2c** (*Z* and *E*) an intermediate situation is observed since SCRF calculations indicate a slight increase of the C^1–N^6 distance and a slight decrease of the S^3–C^4 one, thus predicting an earlier transition state in solution than in the gas phase. A parallel between the variations of the C^1–X^6 distance and the change in negative charge borne by the C^1 and X^6 centres can be stressed; for example, Mulliken analysis shows that, in (*Z*)-**TS2b**, solvation results in an increase of both negative charges [C^1: −0.327 ($\varepsilon = 1$) and −0.346 ($\varepsilon = 10$); N^6: −0.634 ($\varepsilon = 1$) and −0.658 ($\varepsilon = 10$)] while in **TS1b** only the electronic density at C^1 is increased upon solvation [C^1: −0.485 ($\varepsilon = 1$) and −0.503 ($\varepsilon = 10$); C^6: −0.336 ($\varepsilon = 1$) and −0.324 ($\varepsilon = 10$)]. However, the magnitude of the charge variations remains weak. It is interesting to notice that, in a recent study of the hydration, modelled by the continuum approach, of the Claisen rearrangement, Hillier *et al.*[27] report a lengthening of both forming and breaking bonds from gas phase to solution.

As far as charge transfer is concerned, two different trends appear: for **TS1a** and **TS2a** (*Z* and *E*), solvation enhances the charge transfer from the $R''X{=}CR'{-}CH_2$ fragment to the $H_2C{=}CR{-}S$ one; regarding the 2,5-disubstituted transition structures, solvation induces a charge transfer from the vinylthio moiety to the allyl or ethanimine moiety; this flow of charge is significant in the thio-Claisen rearrangements (**TS1b** and **TS1c**). No trends may be inferred when one compares changes in charge transfer $\Delta(\Delta q)$ and changes in dipole moments, $\Delta\mu$, upon solvation. Clearly, the less important changes in dipole moments are obtained for derivatives **a** and **d**.

From Table 5, it appears that all TSs are stabilized by solvation, the greater lowering being calculated for **c** derivatives in line with the greater change in dipole moment from gas phase to solution. This lowering is substantial, *ca.* 4 kcal mol^{-1} for $\varepsilon = 2$ and 8 kcal mol^{-1} for $\varepsilon = 10$. If the solvation energies of the starting compounds are taken into account, the resulting changes in barrier heights $\Delta(\Delta E)^{\ddagger}$ are more erratic. Fortunately, for the more reactive systems in the gas phase (*i.e.* 2,5-disubstituted compounds), our calculations suggest that even moderately polar solvents lead to a lowering of the energy barrier (in the range 0.5–4.1 kcal mol^{-1}). It is generally admitted that continuum models at the SCRF level underestimate the barrier lowering[27b,28] while the lowering due to solvation is greater at the RHF than at a correlated level.[27a] Assuming that these two effects cancel each other, ‘synthetically reasonable’ energy barriers of 19 kcal mol^{-1} [(*Z*)-**TS2c**] and 19.7 kcal mol^{-1} [(*E*)-**TS2c**] can be estimated in moderately polar solvents. It should be noted that Gao *et al.*,[21] in their study of substituent effects on the aqueous Claisen rearrangement, obtained a considerable rate acceleration for an opposite disubstitution, *i.e.* an acceptor group (CN) at C^2 and a donor group (OMe) at C^5 on an allyl vinyl ether. A surprising result is obtained for **TS2d** (*Z* and *E*) for which a large lowering of the energy barriers has been calculated; the reason for this is the positive solvation energy E_{sol} of the starting material (*Z*)- and (*E*)-**2d**.

Finally, we examine the changes in reaction energy $\Delta(\Delta_{\mathrm{r}}E)$ upon solvation; in both cases, our results predict an increase in the exothermicity of these rearrangements from gas phase to solution. Thus, one expects that the **2c** $\longrightarrow$ **2′c** (*Z* and *E*) process will be exothermic by about 15 kcal mol^{-1} in a moderately polar medium, a value which would prevent a reverse rearrangement.

Conclusions

The present study examines substituent and solvent effects on the energetics of the thio-Claisen rearrangement and one of its potential aza analogue rearrangements, using *ab initio* and non-local DFT methods. We have found that 2,5-disubstitution leads to tighter transition structures and to substantial lowering of the barrier height. In addition, while allyl vinyl sulfide and vinylthioethanimine rearrangements are respectively slightly exothermic or endothermic, the [3,3] sigmatropic shift of their 2,5-donor–acceptor derivatives are predicted to be exothermic. Furthermore, the saddle points which connect these substrates and products are highly polar in nature and an additional transition state stabilization, even in moderately polar solvents, is predicted by SCRF calculations. SCRF results also indicate that solvation enhances the exothermicity of these processes. Thus, according to these calculations, 2,5-donor–acceptor substituted vinylthioethanimine would be reactive in a [3,3] sigmatropic rearrangement. Experimental verification of these predictions would be interesting and will provide a test of the computational results.†

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† Supplementary material. Tables giving total energies and zero-point vibrational energies of the reactants and energetics of unsubstituted rearrangements for MP2 and B3LYP geometries have been deposited at the British Library (SUPPL. No. 57298, pp. 3). For details of the Supplementary Publications Scheme, see ‘Instructions for Authors’, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, Issue 1.

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