Solvent Effects on Hetero Diels–Alder Reactions of Sulfur Dioxide with 1,3-Dienes

D. Suárez,[a] **X. Assfeld,**[b] **Javier González,**[c] **M. F. Ruiz-López,**[b] **T. L. Sordo**[a] **and J. A. Sordo**[a]

[a] *Departamento de Química Física y Analítica. Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Principado de Asturias, Spain*
[b] *Laboratoire de Chimie Théorique, URA CNRS 510, Université de Nancy I, BP 239, 54506 Vandoeuvre-lès-Nancy, France*
[c] *Instituto Universitario de Química Organometálica "Enrique Moles". Universidad de Oviedo, Campus del Cristo, 33071 Oviedo, Principado de Asturias, Spain*

According to *ab initio* computations the electrostatic solvent effects are predicted to be important in the control of the selectivity of the Diels–Alder reactions of 1,3-dienes with sulfur dioxide.

Hetero Diels–Alder reactions have attracted considerable attention recently as key steps in stereoselective synthesis of natural products.[1] According to *ab initio* calculations, hetero Diels–Alder reactions are predicted to take place through concerted but slightly asynchronous transition structures in a similar way to the all-carbon version.[2]

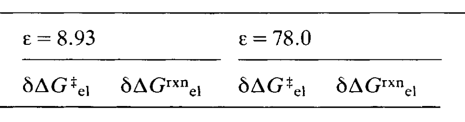
We have recently reported[3] gas-phase *ab initio* results on the stereoselectivity and regioselectivity of Lewis acid catalysed hetero-Diels–Alder addition of sulfur dioxide to isoprene, which were in good agreement with experimental evidence.[4] However, in order to make a comparison between *ab initio* results and condensed-phase experimental data, the effect of the solvent should be taken into account.[5,2d] This is especially true in the case of reactions involving species with large charge separation[6] like for example the Lewis acid catalysed reactions.[7] Here we examine solvent effects on the above mentioned cycloadditions of sulfur dioxide to 1,3-dienes (Scheme 1).

Ab initio HF/3-21G* calculations have been carried out by means of a recently proposed general algorithm for quantum-chemical computations on solvated molecules.[8] It is based on a continuum model with general cavity shape and assumes a monocentric multipolar expansion of the electrostatic solvation energy. The *ab initio* wave functions for the transition structures in a vacuum and in solution have been interpreted by means of a theoretical method based on the expansion of the molecular orbitals (MOs) of a complex system in terms of the MOs of its fragments (using the geometry each fragment has in the corresponding transition structure), and the performance of the configurational analysis.[9] This configurational analysis is performed by writing the MO wavefunction of the combined system by a combination of various fragment electronic configurations [eqn. (1)] where Ψ_0 (zero configur-

$$\Psi = C_0\,\Psi_0 + \Sigma\, C_q\,\Psi_q \qquad (1)$$

ation, ABC) is the state in which neither electron transfer nor electron excitation takes place, and Ψ_q stands for mono-transferred configurations $\Psi_{o\rightarrow u'}$, in which one electron in an occupied MO, o, in one of the fragments is transferred to an unoccupied MO, u′, of a different fragment (A^+B^-C, A^-B^+C, ... configurations), monoexcited configurations, $\Psi_{o\rightarrow u}$, in which one electron in an occupied MO, o, of one of the fragments is excited to an unoccupied MO, u, of the same fragment (A*BC, AB*C, and ABC* configurations), *etc.*[9]

Table 1 collates the reaction and activation free energies in a vacuum and in two solvents for the thermal and Lewis acid (BH_3) catalysed reactions of sulfur dioxide with buta-1,3-diene and isoprene. Relative permittivities of 8.93 and 78.0 were used to simulate deuteriated methylene chloride—the solvent for which experimental data are available[4]—and water, respectively. In a vacuum, the catalysed reactions present a greater free energy of reaction (in absolute value) than the uncatalysed ones. The electrostatic effect of the solvent increases the free energy of reaction in catalysed processes but leaves unchanged or slightly reduces that of the uncatalysed ones. Concerning the free energies of activation in a vacuum, the methyl substitution on buta-1,3-diene results in a lowering of the barrier by about 4 kcal mol^{-1} for the *meta-endo* transition structure, and the presence of the Lewis acid BH_3 coordinated to the SO_2 produces a significant catalytic effect reducing the barrier by 10–13 kcal mol^{-1} for the *endo* processes. Both effects are cooperative rendering the catalysed *meta-endo* reaction of isoprene with SO_2 the most favourable. In solution, all the uncatalysed reactions are disfavoured when electrostatic interactions with the solvent are taken into account, whereas the catalysed reactions both of buta-1,3-diene and isoprene with SO_2 present a significant diminution of the activation free energy. This diminution is greater in the case of the catalysed *meta* reactions of isoprene where the electrostatic effect of the solvent appears to



Scheme 1

Table 1 HF/3-21G* free energies of activation (ΔG‡) and reaction (ΔG^{rxn}) computed using standard procedures at 298.15 K and corresponding electrostatic solvent effects ($\delta\Delta G^{\ddagger}_{\text{el}} = \Delta G^{\ddagger}_{\text{el}} - \Delta G^{\text{reactants}}_{\text{el}}$ and $\delta\Delta G^{\text{rxn}}_{\text{el}} = \Delta G^{\text{products}}_{\text{el}} - \Delta G^{\text{reactants}}_{\text{el}}$, where ΔG^{i}_{el} is the electrostatic solvation energy of species (i). Values in kcal mol^{-1}, 1 cal = 4.184 J.[a]

Transition structures		Vacuum		Solution			
				ε = 8.93		ε = 78.0	
		$\Delta G^{\ddagger}$	ΔG^{rxn}	$\delta\Delta G^{\ddagger}_{\text{el}}$	$\delta\Delta G^{\text{rxn}}_{\text{el}}$	$\delta\Delta G^{\ddagger}_{\text{el}}$	$\delta\Delta G^{\text{rxn}}_{\text{el}}$
Buta-1,3-diene + SO_2(*endo*)	TS1	37.1	−2.6	+0.1	0.0	+0.2	+0.1
Buta-1,3-diene + SO_2(*exo*)	TS2	38.4		+0.7		+0.9	
Buta-1,3-diene + SO_2-BH_3(*endo*)	TS3	25.2	−15.7	−2.9	−2.0	−3.2	−2.0
Buta-1,3-diene + SO_2-BH_3(*exo*)	TS4	30.3		−2.8		−3.1	
Isoprene + SO_2(*meta-endo*)	TS5	33.0	−3.3	+0.1	+0.1	+0.1	+0.2
Isoprene + SO_2(*meta-exo*)	TS6	35.9		0.0		+0.3	
Isoprene + SO_2(*para-endo*)	TS7	37.3	−3.9	+0.7	0.0	+0.9	0.0
Isoprene + SO_2(*para-exo*)	TS8	38.4		+1.0		+1.3	
Isoprene + SO_2-BH_3(*meta-endo*)	TS9	20.0	−16.7	−4.4	−1.7	−4.8	−1.8
Isoprene + SO_2-BH_3(*meta-exo*)	TS10	23.2		−4.0		−4.2	
Isoprene + SO_2-BH_3(*para-endo*)	TS11	27.0	−16.5	−2.3	−2.1	−2.6	−2.3
Isoprene + SO_2-BH_3(*para-exo*)	TS12	27.2		−2.8		−2.8	

[a] Transition structures and products were fully optimised in a vacuum. Single-point SCRF calculations[8] were carried out in solution.

Table 2 Relative weights of the most important fragment electronic configurations in the transition structures TS1, TS3, TS5 and TS9, in solution and in a vacuum (the latter ones in parentheses)

	Configurations	TS1	TS5
A[a]B[b]		1.0000 (1.0000)	1.0000 (1.0000)
A^-B^+	(HOMO → LUMO)	0.3745 (0.3333)	0.4046 (0.3600)
A^+B^-	(HOMO → LUMO)	0.0440 (0.0538)	0.0342 (0.0406)
A^+B^-	(NHOMO → LUMO)	0.0389 (0.0358)	0.0335 (0.0327)
AB*	(HOMO → LUMO)	0.0905 (0.0915)	0.0807 (0.0833)
AB*	(HOMO → NLUMO)	0.0195 (0.0200)	0.0179 (0.0190)
AB*	(NHOMO → LUMO)	0.0189 (0.0181)	0.0182 (0.0174)
$A^{2-}B^{2+}$	(HOMO → LUMO/ HOMO → LUMO)	0.0322 (0.0255)	0.0371 (0.0293)

[a] A: Dienophile. [b] B: Diene.

	Configurations	TS3	TS9
ABC[a]		1.0000 (1.0000)	1.0000 (1.0000)
A^-B^+C	(HOMO → LUMO)	0.5157 (0.4184)	0.5888 (0.4617)
A^+BC^-	(NNHOMO → LUMO)	0.0380 (0.0299)	0.0418 (0.0321)
A^+B^-C	(HOMO → LUMO)	0.0185 (0.0202)	0.0106 (0.0120)
A^+B^-C	(NHOMO → LUMO)	0.0151 (0.0164)	0.0126 (0.0142)
AB*C	(HOMO → LUMO)	0.1045 (0.0940)	0.1273 (0.1153)
AB*C	(HOMO → NLUMO)	0.0261 (0.0248)	0.0277 (0.0264)
A*BC	(HOMO → LUMO)	0.0190 (0.0146)	0.0220 (0.0192)
$A^{2-}B^{2+}C$	(HOMO → LUMO/ HOMO-LUMO)	0.0609 (0.0401)	0.0776 (0.0477)

[a] C: Catalyst.

reinforce the effects of methyl substitution and catalysis. This phenomenon is more substantial the more polar the solvent is, which suggests that solvents like MeCN or DMF should be more appropriate than deuteriated methylene chloride.

From data collected in Table 1 we also learn that both stereoselectivity and regioselectivity increase with the presence of the solvent. This is especially true in the case of TS9—the transition structure leading to the experimentally observed major product[4]—where the stereoselectivity, as estimated by $\delta\Delta G^{\ddagger}_{\mathrm{el}}$ (TS10) − $\delta\Delta G^{\ddagger}_{\mathrm{el}}$ (TS9), increases 0.4–0.6 kcal mol^{-1} and the regioselectivity, as estimated by $\delta\Delta G^{\ddagger}_{\mathrm{el}}$ (TS11) − $\delta\Delta G^{\ddagger}_{\mathrm{el}}$ (TS9), increases 2.1–2.2 kcal mol^{-1}, when going from a vacuum to solution.

In order to analyse methyl substitution, catalyst and solvent effects, it is interesting to consider net charge transferences between diene and dienophile at the transition structures, and to carry out a configuration analysis of the wavefunctions.

In a vacuum, the computed Mulliken net charge transferences from diene to dienophile, for the most stable transition structures are: TS1: 0.13e; TS3: 0.28e; TS5: 0.15e; TS9: 0.33e. It can be seen that the methyl substituent and the catalyst favour charge transfer, especially the latter. Given that usually the electrostatic effect of the solvent favours charge separation, it is to be expected that the previous values would increase in solution. In effect, net charge transferences in a medium of $\varepsilon = 8.93$ are: TS1: 0.17e; TS3: 0.35e; TS5: 0.19e; TS9: 0.41e. The increase is clearly larger for the catalysed reactions (the same trend is found in a medium of $\varepsilon = 78.0$).

Table 2 shows that the most important electronic configurations of the reactants in the description of the transition structures are the zero one, AB, and the monotransference from the HOMO of the diene to the LUMO of the dienophile, A^-B^+, both in a vacuum and in solution. In a vacuum, there is a small increase in the relative mass of A^-B^+ when going from buta-1,3-diene to isoprene and a much more important one when passing to the catalysed reactions. The introduction of the solvent results in a small increase in the relative mass of A^-B^+ for the uncatalysed reactions and in a notable increase of the same configuration in the case of the catalysed reactions. These results are consistent with trends in net charge transference described above.

The stabilization of AB and A^-B^+ by solvation is expected to be greater for the reactants than for the transition structure due to cavity volume increase.[10] Thus, when the stabilisation of A^-B^+ is not important enough compared with that of AB, the solvent effect would not lead to a decrease of the energetic barrier through the interaction between the AB and A^-B^+ solvated diabatic surfaces. This is the case of the uncatalysed reactions. The much more significant stabilization of the monotransferred configuration A^-B^+ for the Lewis acid catalysed reactions in solution allows for a stronger interaction between its diabatic curve and that of the zero configuration, thus causing the important lowering in the activation energy[11] observed in Table 1. Note that there is a cooperative interaction between the solvent effect and other factors favouring charge transfer since the largest stabilisation of the A^-B^+ configuration in solution is expected for the transition structures in which this configuration has a substantial mass in the gas-phase wavefunction. Indeed, the largest coefficient of the monotransferred configuration A^-B^+ corresponds to TS9 (see Table 2), which, consequently, is the most stabilised structure in solution owing to the reinforcement of the effects of the methyl substituent and the Lewis acid catalyst by solvent (see Table 1).

The authors are grateful to the Programa de Acciones Integradas Hispano-Francesas (collaboration HF93-032) for financial support.

Received, 28th March 1994; Com. 4/01854K

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