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Assessment of mechanistic hypotheses of 1,3-dipolar cycloaddition of (arylsulfonyl)allene to nitrilimines by DFT reactivity indices

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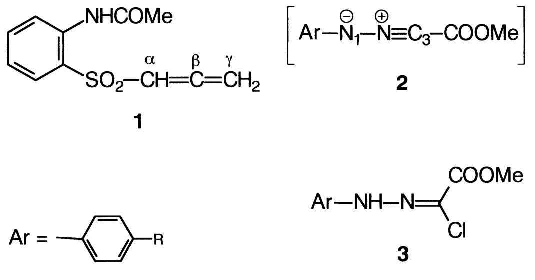
Abstract—The mechanism of 1,3-dipolar cycloaddition between 1-[2-(acetylamino)phenylsulfonyl]-1,2-propadiene **1** and a series of *N*-(4-substituted)phenyl-*C*-methoxycarbonylnitrilimines **2** has been reinvestigated on the basis of DFT calculations and a quantitative formulation of the HSAB principle. Comparison of the new computational results with experimental findings led to the formulation of a mechanistic scheme involving both 1,3-prototropic and 1,3-arylsulfonyl shifts. The role of silver cation is also pointed out. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the last two decades, the behaviour of allenes[1–4] towards a number of 1,3-dipolar species has been studied in great detail[5] due to both synthetic and mechanistic implications. Synthetic advantages are concerned with the array of functionalities presented by the resulting cycloadducts, which can be used as versatile starting materials for further transformations.[6–9] On the other hand, the presence of two cumulated unsaturations make allenes interesting dipolarophiles from the mechanistic point of view. In fact, both C=C bonds are suitable positions for dipolar attack which can proceed with two opposite orientations; hence, both site- and regioselectivity phenomena can be involved in their cycloadditions.

Owing to the known high reactivity of arylsulfonylallenes,[10] their cycloadditions on nitrilium betaines have been extensively investigated in the field of nitrile oxide cycloadditions,[10–12] while nitrile imines were only the object of occasional reports.[10,13,14] Recently, we examined the reaction between 1-[2-(acetylamino)phenylsulfonyl]-1,2-propadiene **1**[12] and a series of *N*-(4-substituted)phenyl-*C*-methoxycarbonylnitrilimines **2**, which were generated in situ by silver carbonate treatment of the corresponding hydrazonoyl chlorides **3** (Scheme 1).[14] Although pyrazole cycloadducts **4** and **5** and 4-hydroxymethylpyrazole **6** were obtained (Scheme 2), their formation and yield ratio do not harmonise with the predictions based upon the FMO theory.[14,15]

Recently, many important concepts and indices useful to understand chemical reactivity have been rationalized within the framework of the density functional theory (DFT).[16] Well-known examples[17] are the electron chemical potential μ, which represents the escaping tendency of molecular electrons, and the molecular softness S, which is the sensitivity of the total number of electrons to a change in μ. However, to study site- and regio-selection a local (atomic) reactivity index is needed. The best suited is local softness $s(\mathbf{r})$,[17] which represents the sensitivity of the molecular electron density at point $\mathbf{r}$ to a change in μ. Local softness is closely related to the Fukui function $f(\mathbf{r})=s(\mathbf{r})/S$, and therefore it is an extension of the FMO concept which takes into account the relaxation of the electron density upon charge transfer between molecules and (at least approximately) electron correlation. Within DFT, a local formulation[18–20] of Pearson's hard–soft acid–base (HSAB) principle[21] has been developed, which has



Entry	a	b	c	d	e
R	H	Me	MeO	Cl	NO$_2$

Scheme 1.

Keywords: allenes; nitrilimines; 1,3-dipolar cycloadditions; density functional theory; local softness; hard–soft acid–base principle.

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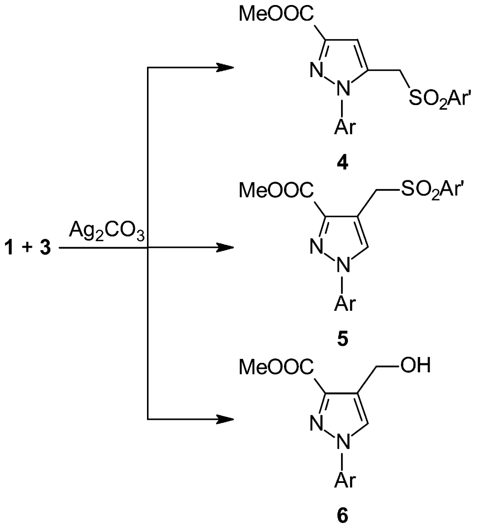

Scheme 2.

provided many reliable prediction of the preferred regioisomer for 1,3-dipolar cycloadditions (1,3-DC),[22–28] since in 1,3-DCs the relative energy of transition states is paralleled by the relative energy of the weakly interacting pre-activation complexes forming in the early stage of the reaction.[29] On these grounds, a generalization of the local HSAB principle has been recently introduced,[30] which enables one to compute, from μ and s of the reactants only, the grand potential[†] variation $\Delta\Omega$ due to the charge transfer occurring in the very first step of the bond-forming interaction between specific atoms of the reactants. This method, which permits reliable reactivity predictions without locating transition states, has been successfully applied by us to the 1,3-DC between nitrilimines and alkynyl- or alkenyl dipolarophiles,[31–33] and between arylazides and methyl propiolate.[34]

Continuing our investigations, we present here an assessment of the mechanistic hypotheses proposed to explain the experimental results of a previous study[14] of the cycloaddition between 1-arylsulfonyl-1,2-propadiene **1** and nitrilimines **2**, which is based upon the site- and regioselectivity computed by the DFT and the HSAB principle.

2. Results and discussion

The FMO description of the 1,3-DC of nitrilimines to arylsulfonylallenes involves interaction between the dipole HOMO and the allene LUMOs.[14] The PM3 unoccupied FMOs of **1** are shown in Figure 1. Owing to the presence of the arylsulfonyl group, and the consequent low molecular symmetry (C_1), at least three unoccupied FMOs must be considered, which lie within a 1 eV range. The lowest and highest of these FMOs resemble those of allene $H_2C{=}C{=}CH_2$ in that they are almost confined to the α,β and β,γ positions, respectively. The intermediate FMO has significant atomic-orbital coefficients on α, β, and γ positions and a peculiar, twisted shape since both p_x and p_y orbitals are comprised in this FMO. Notwithstanding the FMO picture is far from being clear-cut due to the presence of the intermediate FMO, it seems that the energetic proximity of the three unoccupied FMOs and the similarity of the atomic coefficients would allow all the four possible adducts **A**–**D** (see Scheme 3) to form in appreciable amounts. However, reliable conclusions must be drawn on the basis of higher-level calculations and on a better reactivity model such that afforded by the reactivity indices of DFT obtained from calculations based on the dependable[35] B3LYP hybrid functional and on an augmented, polarized, triple-ζ basis set.

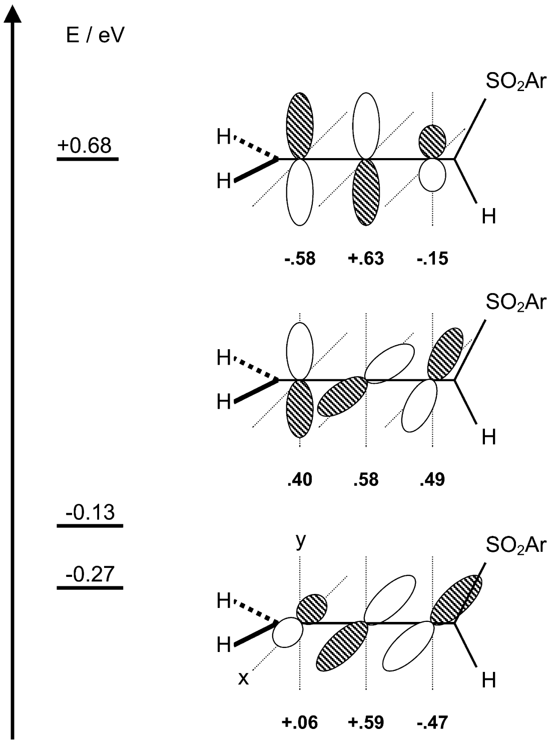

Figure 1. Unoccupied allenic frontier molecular orbitals of **1** computed by the PM3 method. For the lowest and highest molecular orbital, the atomic coefficients refer to the p_x and p_y atomic orbitals, respectively. For the intermediate molecular orbital, which comprises both p_x and p_y atomic orbitals, the root-mean-square of the x and y coefficients on each allenic carbon is reported.

The main results of DFT calculations at the B3LYP/6-311+G(d,p) level are reported in Table 1. The electron chemical potential difference between **1** and **2** determines the direction of the overall charge flow upon interaction of the reactants, as electrons flow towards regions at low electron chemical potential μ. Our calculations thus show that **2a**–**d** act as nucleophiles whereas **2e** acts as electrophile when reacting with allene **1**. Note, however, that the chemical potentials of **2a**–**e** and **1** differ less than 1 eV, so that charge transfer is expected to be rather small.

We now turn to site and regio-selectivity prediction. As selectivity criterion, we used the grand potential change due to two bond-forming interactions between **1** and **2**, because of the general agreement about the concertedness of 1,3-DC reactions. The grand potential change for the pathway leading to adduct **A** is

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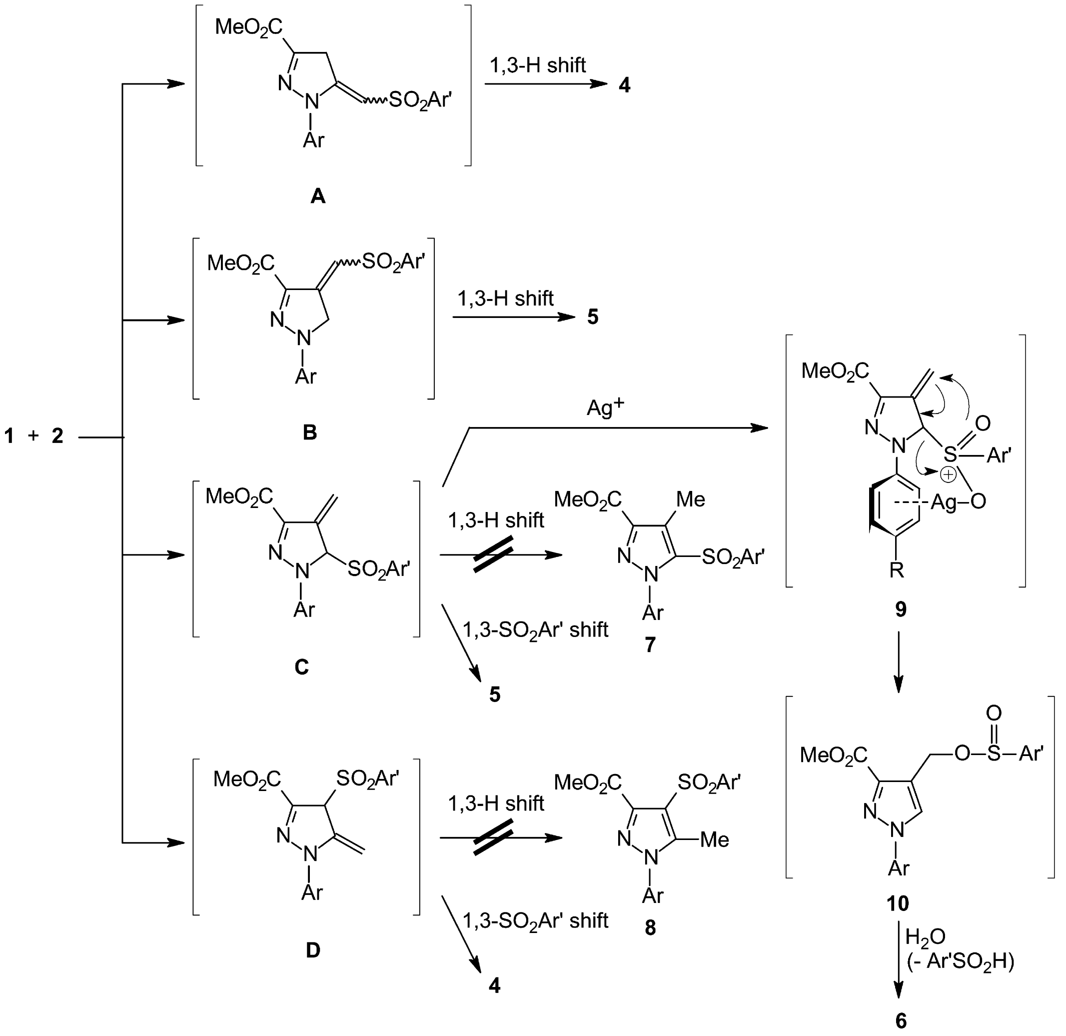
[†] The grand potential is the natural thermodynamic quantity to describe the behavior of the reactants' atoms, which are open subsystems freely exchanging energy and electrons.



Scheme 3.

$$\Delta\Omega(\mathbf{A}) = -(1/2)[\mu(\mathbf{2}) - \mu(\mathbf{1})]^2\{s(\mathrm{N}_1)s(\mathrm{C}_\beta)[s(\mathrm{N}_1) + s(\mathrm{C}_\beta)]^{-1} + s(\mathrm{C}_3)s(\mathrm{C}_\gamma)[s(\mathrm{N}_3) + s(\mathrm{C}_\gamma)]^{-1}\} \quad (1)$$

where atoms are indexed as in Scheme 1 and new bonds form between C_β of **1** and N_1 of **2**, and between C_γ of **1** and C_3 of **2**. The grand potential change for adducts **B**, **C**, and **D** can be similarly obtained. From the $\Delta\Omega$ values reported in Table 1, one can see that there is a certain site-selectivity since in the reactions leading to compounds **A** and **B**, which involve addition to the α,β allene double bond, a stabilization upon reactive encounter occurs whereas the stabilization of the complex leading to compounds **C** and **D** (addition to β,γ bond) is about two orders of magnitude smaller and even negative (i.e. a destabilization) in the case of reaction of **2e** with **1**. The reason for this behaviour is due to the unfavourable interaction of the allenic C_α with both termini of the nitrilimine moiety, which almost exactly cancels the favourable interaction of the latter ones with the C_β of **1**. Conversely, regioselectivity is poor since $\Delta\Omega(\mathbf{A})-\Delta\Omega(\mathbf{B})$ and $\Delta\Omega(\mathbf{C})-\Delta\Omega(\mathbf{D})$ are very small in any case.

Table 1. Results of B3LYP/6-311+G(d,p) calculations. Electron chemical potential difference between sulfonylallene **1** and nitrilimines **2** and grand potential stabilization $\Delta\Omega$ of the four possible adducts. See Scheme 3 for product notation

R	$\mu(\mathbf{2})-\mu(\mathbf{1})$ (eV)	$\Delta\Omega$ (kJ mol^{-1})			
		A	**B**	**C**	**D**
H	0.24	−0.0435	−0.0411	−0.0013	−0.0011
Me	0.55	−0.2125	−0.1981	−0.0023	−0.0018
MeO	0.38	−0.1063	−0.0999	−0.0027	−0.0021
Cl	0.14	−0.0133	−0.0125	−0.0003	−0.0002
NO_2	−0.58	−0.1337	−0.1280	0.0279	0.0234

From our previous work,[31–34] it is known that in 1,3-DC the proportionality factor between computed stabilization energy differences and transition-state energy differences is of order unity. Therefore, although the $\Delta\Omega$ values are largely different relative to each other, they are small compared to the thermal energy $k_\mathrm{B}T$=2.5 kJ mol^{-1} at room temperature. This behaviour can be traced back to the similarity of electron chemical potential between the nitrilimine dipole and the allenic dipolarophile which makes all $\Delta\Omega$ values small notwithstanding the significant differences in local softness between the involved atoms. Since the maximum $\Delta\Omega$ difference related to site-selectivity amounts to about 0.2 kJ mol^{-1}, it can be estimated that the maximum site-selectivity amounts to about 10% product yield. In the same way, regioselectivity can be estimated to be negligible in any case.

These computational results enable us to state that (i) all four primary cycloadducts **A**–**D** are formed in approximately equal amounts, (ii) addition to the α,β allene double bond is slightly favoured over addition to the β,γ double bond, (iii) regioselectivity is negligible in all cases. These indications are fully consistent with our previous experimentally-derived mechanistic statements concerning the 1,3-DC between **1** and 2,4,6-trimethyl-3,5-dichlorobenzonitrile oxide.[12]

We now turn to a brief summary of our experimental results,[14] which were recently obtained from the 1,3-DC of **1** to **2a**–**e**, followed by a discussion of the mechanistic hypotheses in the light of the new high-level computational results.

Cycloadditions between **1** and **2** were carried out by using different proportions of the reactants, which are summarized in Table 2 along with reaction times, products and product yields. When using a 2:1 molar ratio between hydrazonoyl chloride and allene, shorter reaction times and enhancement of the overall yield **4**+**5**+**6** were observed. The latter pyrazoles must arise from primary cycloadducts **A**–**D** via 1,3-hydrogen shift and/or 1,3-arylsulfonyl shift.

These experimental results are accounted for by the mechanistic picture outlined in Scheme 3 which is based on the finding that **A**–**D** are formed in approximately equal amounts. Therefore, competitive cycloadditions of nitrilimines **2** across the α,β and the β,γ positions of **1** are involved, in close analogy with the behaviour of **1** towards 2,4,6-trimethyl-3,5-dichlorobenzonitrile oxide,[12] giving the elusive primary cycloadducts **A**–**D**. According to this picture, pyrazoles **4** and **5** arises from **A** and **B**, respectively, via 1,3-prototropic shift, and from **C** and **D** via 1,3-allylic shift of the sulfonyl group. 1,3-Prototropic shift onto intermediates **C** and **D** should give pyrazoles **7** and **8** which however were not isolated from the reaction mixture within experimental accuracy. Therefore, the 1,3-arylsulfonyl shift should be faster than the 1,3-prototropic shift.

It remains to explain the formation of the 4-hydroxymethylpyrazole **6**. Due to the known complexing ability of the silver ion towards arenes[36,37] we suggest the intermediacy of the metalated specie **9** arising from **C**. This 18-electron complex cannot form from **D** because of the large distance between the SO_2 and the Ar groups. Thus, we can also explain the enhanced formation of **9** at the expense of **5** when using a 1:1 molar ratio between hydrazonoyl chloride and allene, because of the higher concentration of free silver ion. Further rearrangement of **9** gives sulfinic ester **10**, whose intermediacy was proven unequivocally in our previous work,[14] via a sulphur-to-oxygen bond migration.[38]

Table 2. Reaction between allene **1** and nitrilimines **2** in the presence of 2 mol equiv. of Ag_2CO_3

Entry	**3** (mol equiv.)	*t* (*h*)	Products and yields (%)			
			1[a]	**4**	**5**	**6**
a	1	67	44	18	8	20
	2	28	30	22	23	8
b	1	120	54	16	7	12
	2	48	32	26	20	–
c	1	140	47	18	11	18
	2	48	27	26	12	15
d	1	96	70	8	1	3
e	1	170	80	–	–	–

[a] Recovered starting material.

3. Computational methods

All calculations were performed with the Gaussian98[39] program suite by means of a Beowulf PC cluster. For DFT calculations the hybrid B3LYP functional was employed with the standard 6-311+G(d,p) basis set. The geometry of **1** and **2a**–**e** in vacuo was fully optimised and characterized with vibrational analysis at the same level of theory. The anion and cation of **1** and **2a**–**e** were treated at the UB3LYP/6-311+G(d,p) level using the geometry of the neutral systems. Atomic electron populations were evaluated following the Merz-Kollman scheme[40,41] (including fitting of atom-centred dipoles). This scheme, which already proved to be reliable,[42] has been used in most DFT calculations of regiochemistry of 1,3-DCs, and it has also been recently considered as an appropriate local descriptor of charge.[43] Reactivity indices were computed within the finite difference approximation:[16] $\mu=-(\mathrm{IP}+\mathrm{EA})/2$ and $S=(\mathrm{IP}-\mathrm{EA})^{-1}$, where IP and EA are the (vertical) ionisation potential and electron affinity, respectively. The local softness s (condensed to each individual atom[44]) was computed as $s^{+}=S[p(N_0+1)-p(N_0)]$ for electrophiles, and as $s^{-}=S[p(N_0)-p(N_0-1)]$ for nucleophiles, where $p(N)$, $N=N_0-1$, N_0, N_0+1, is the atomic electron population of the cationic, neutral, and anionic system, respectively. Semiempirical PM3 calculations were also performed with the Gaussian 98 program suite. The geometry of **1** was fully optimised and characterized with vibrational analysis. The FMOs involved in the reaction have been carefully identified from their shape since the allenic π^* MO are not the LUMO and NLUMO.

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