

Quantitative characterization of the global electrophilicity pattern of some reagents involved in 1,3-dipolar cycloaddition reactions

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Received 6 November 2002; revised 3 February 2003; accepted 5 March 2003

Abstract—The global electrophilicity power, ω , of a series of dipoles and dipolarophiles commonly used in 1,3-dipolar cycloadditions may be conveniently classified within a unique relative scale. The effects of chemical substitution on the electrophilicity of molecules have been evaluated using a representative set of electron-withdrawing and electron-releasing groups for a series of dipoles including nitron, nitrile oxide and azide derivatives. The absolute scale of electrophilicity is used to rationalize the chemical reactivity of these species as compared to the static reactivity pattern of the reagents involved in the Diels–Alder reactions. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

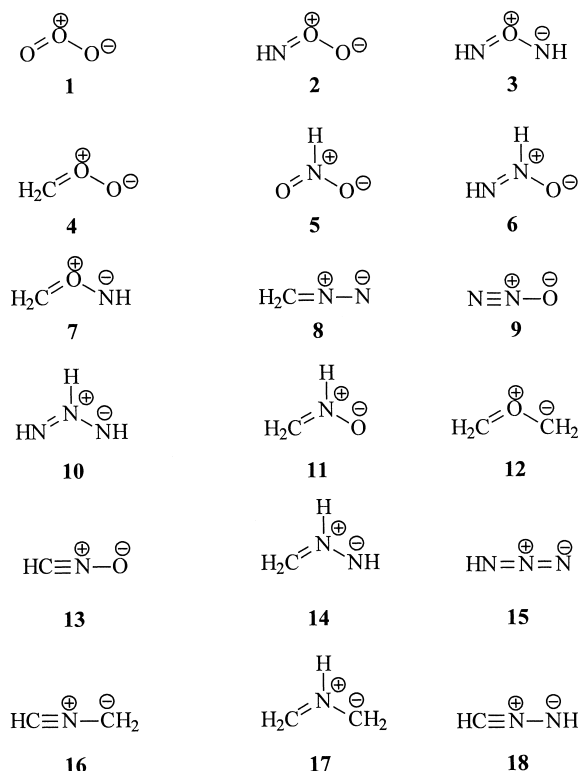
Cycloaddition reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. Current understanding of the underlying principles in the Diels–Alder (DA) reactions and the 1,3-dipolar cycloadditions (1,3-DC) has grown from a fruitful interplay between theory and experiment.^{1–3} The general concept of 1,3-DCs was introduced by Huisgen and co-workers in the early 1960s.⁴ Huisgen's work stated the basis for the understanding of the mechanism of concerted cycloaddition reactions. The development of the 1,3-DC reactions has in recent years entered a new stage as control of the stereochemistry in the addition step is now the major challenge. The stereochemistry of these reactions may be controlled either by choosing the appropriate substrates or by controlling the reaction using a metal complex acting as catalyst.⁵ A dipole is a system of three atoms over which there are distributed four π -electrons. There are a wide variety of dipoles that include a combination of carbon, oxygen and nitrogen atoms within their structures. A picture of the most common dipoles used in 1,3-DC reactions is given in Scheme 1. On the other hand, the dipolarophiles can be substituted alkenes or alkynes.

Given the importance of these reactions, a strong effort has been directed toward the characterization of the reagents in these cycloadditions as well as the elucidation of its reaction

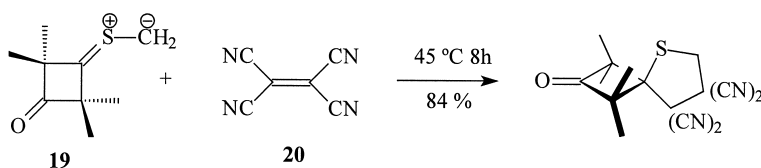
Keywords: 1,3-dipolar cycloadditions; electrophilicity power; density functional theory.

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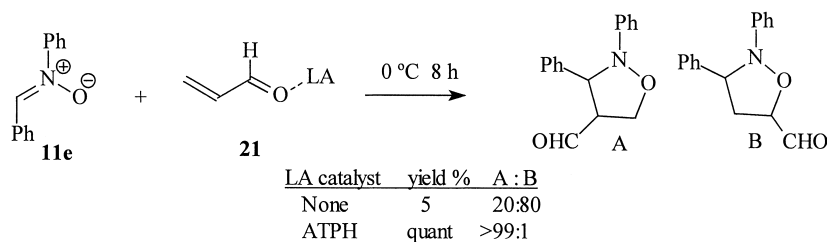
mechanisms.⁶ However, the nature of the 1,3-DC reaction mechanism is still an open problem in physical organic chemistry. For instance, the mechanism proposed primarily by Huisgen is that of a single-step, four-center



Scheme 1. Common dipoles used in 1,3-DC reactions.



Scheme 2.



Scheme 3.

cycloaddition, in which two new bonds are both partially formed at the transition state, although not necessarily to the same extent.⁷ For nitrile oxide (R_1CNO) cycloadditions, experimental data were interpreted either as being consistent with a concerted mechanism⁷ or in favor of a stepwise mechanism with diradical intermediates.⁸

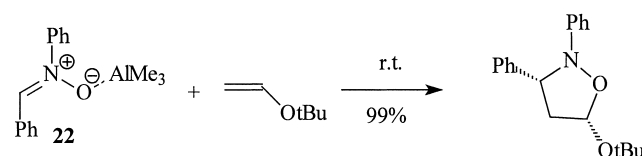
The 1,3-DCs appear to be controlled by frontier molecular orbital (FMO) interactions. In the case of an extremely large difference of the FMO energy of the cycloaddition partners, this model allows one to predict a mechanism via zwitterionic intermediates.⁹ For instance, Huisgen reported in 1986 the first experimental evidence for the two-step 1,3-dipolar cycloadditions between the thiocarbonyl ylid **19** and tetracyanoethylene (**20**) (see Scheme 2).¹⁰ Recent studies by these authors for the same 1,3-DC processes have shown that they are an example of a borderline case from a concerted to a two-step mechanism.⁹ The large HOMO energy of the thiocarbonyl ylids and the low LUMO energy of the tetracyanoethylene are responsible for the large zwitterionic character of these cycloadditions.¹⁰ Even though the presence of significant steric hindrance effects at least at one end of the dipole is an additional requirement for the Huisgen's stepwise mechanisms, Fokin and Sharpless et al. have recently reported the stepwise copper catalyzed 1,3-dipolar cycloaddition of non-hindered azides with terminal alkenes.¹¹

Within the FMO theory, Sustmann has categorized the cycloaddition processes in three different types.¹² Type I involves a dominant interaction between the highest occupied molecular orbital of the dipole ($HOMO_{dipole}$) and the lowest occupied molecular orbital of the dipolarophile ($LUMO_{dipolarophile}$). An important number of 1,3-DC reactions have been accommodated within this classification. Type II is given by the interaction between the LUMO of the dipole and the HOMO of the dipolarophile. They are named also as inverse-electron demand (IED) 1,3-DC reactions. The ozonization of alkenes may be a reaction that fits this description.¹³ Type III may be characterized by the similarity of the HOMO and LUMO energies of the dipole/dipolarophile pair. In this case both $HOMO_{dipole} - LUMO_{dipolarophile}$ and $LUMO_{dipole} - HOMO_{dipolarophile}$

interactions may be important in determining the reactivity and regiochemistry of the process.

The representative 1,3-DC reaction of a nitron with electron-withdrawing substituted alkenes belongs to the process classified as Type I class. This cycloaddition may be understood in terms of the interaction between the HOMO of the nitron and the LUMO of the alkene. This interaction may be enhanced by the presence of electron-withdrawing substituents on the dipolarophile. The activation of the alkene results in a lowering of the energy of the $LUMO_{alkene}$ and also results in an enhancement of the rate, regio-, diastereo-, and enantioselectivity of the reaction to a higher degree.⁵ Several theoretical treatments have been devoted to the study of the 1,3-DC reactions of nitrones with substituted alkenes.¹⁴ When electron-deficient alkenes such as α,β -unsaturated carbonyl compounds are activated by coordination to a Lewis acid catalyst, the C–C double bond of the alkene should be highly polarized, and the electrophilicity of the β -carbon should be increased. In 1,3-DC reactions of α,β -unsaturated carbonyl acceptors activated by a Lewis acid, the nucleophilic attack of the dipole is kinetically favored (see Scheme 3).¹⁵ As a result, it is to be expected that the bond formation at the β -carbon of dipolarophile would take place preferentially with respect to that at the α -carbon. For instance, the nitron 1,3-DC reaction of acrolein in the presence of BF_3 leads to the formation of the corresponding Michael adduct complex intermediate that cyclizes to the final cycloadduct.^{14h}

On the other hand, the IED 1,3-DC reaction of nitrones is also feasible. It requires a dominant $LUMO_{dipole} - HOMO_{dipolarophile}$ interaction.⁵ These reactions need the activation of the nitron by a Lewis acid. There exist very few examples of reactions between these activated nitrones



Scheme 4.

and electron-rich alkene.¹⁶ Jorgensen et al. have reported the IED 1,3-DC reaction of activated nitrones by chiral Lewis acids with electron-rich alkene (see Scheme 4).¹⁷ The reaction presents a total *ortho* regioselectivity, while the *exo* stereoselectivity depends on the bulky chiral Lewis acid used as catalyst.¹⁷ Later, Domingo studied the effect of the Lewis acid catalyst and solvent effects on the IED 1,3-DC reactions of nitrones with methyl vinyl ether.¹⁸ Both, the presence of the Lewis acid coordinated to the nitron and the solvent effects increase the asynchronicity of the bond formation process and the charge transfer for the *ortho* cycloadditions. This behavior may be understood by a change in the mechanism for the catalyzed IED 1,3-DC reactions: the inclusion of the Lewis acid and the solvent effects causes the nitron and methyl vinyl ether to behave as an electrophile and a nucleophile, rather than a dipole/dipolarophile pair.¹⁸

Recently, we have reported the use of the global electrophilicity index, ω , proposed by Parr et al.¹⁹ to classify the global electrophilicity of a series of dienes and dienophiles currently present in DA reactions.²⁰ The DA reagents were classified within a unique scale as strong, moderate and marginal electrophiles (nucleophiles). The difference in global electrophilicity index, $\Delta\omega$, of the diene/dienophile interacting pair may be used as an indicator of the polar and non-polar character of the mechanisms.²⁰ Concurrent studies in polar DA reactions have evidenced the reliability of $\Delta\omega$ to predict the reactivity of these processes.²¹ The model based on the global pattern electrophilicity used to characterize the DA cycloadditions may be extensible to the 1,3-DC reactions. Note that dienophiles and dipolarophiles are the same reagents. Thus, depending on the electrophilicity potential displayed by dipole/dipolarophile pairs, the mechanisms for these 1,3-DC reactions will have a more or less marked polar character. Electrophilic activation/deactivation promoted by chemical substitution is also assessed, as well as the activation induced by Lewis acid

catalyst. All this information is easily available from the properties of the ground state electron density, rather than the analysis of coefficients of the interacting reagents. It is a static reactivity picture developed around the frontier energy levels, defining the direction of the charge transfer in normal and inverse electron demand processes on one hand, and that introduces a unique absolute hierarchy of electrophilicity that it is expected to correctly predict the reactivity of a set of dipole and dipolarophiles, where one or both reagents are widely functionalised. This polarity pattern, which may be predicted from a static model based on the difference in electrophilicity of the electrophile/nucleophile interacting pair, is expected to manifest itself at the transition state structures in the 1,3-DC reactions.²⁰

2. Model equations

The global electrophilicity power has been recently defined by Parr et al.¹⁹ by:

$$\omega = \frac{\mu^2}{2\eta}, \quad (1)$$

which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. In Eq. (1) μ and η are the electronic chemical potential and the chemical hardness of the ground state (GS) of atoms and molecules, respectively. These descriptors have been defined within the context of the density functional theory of Parr, Pearson and Yang.^{22,23} While the electronic chemical potential μ describes the charge transfer pattern of the system in its ground state geometry, the chemical hardness η describes the resistance to the change. A very simple operational formula for μ , in terms of the one electron energies of FMO HOMO and LUMO, ε_H and ε_L , is given by:²²

Table 1. Global properties and global electrophilicity scale for common dipole models involved in 1,3-dipolar cycloaddition reactions

	HOMO	LUMO	μ	η	ω	ΔN_{\max}
<i>(I) Strong electrophiles</i>						
1 Ozone	-0.3352	-0.1846	-0.2599	0.1505	6.10	1.726
2 Nitrosioxide	-0.3000	-0.1415	-0.2207	0.1585	4.18	1.392
3 Nitrosimine	-0.2589	-0.1037	-0.1813	0.1552	2.88	1.168
4 Carbonyl oxide	-0.2420	-0.0889	-0.1655	0.1530	2.43	1.081
5 Nitro compound	-0.3215	-0.0852	-0.2034	0.2363	2.38	0.860
6 Azoxy compound	-0.2812	-0.0551	-0.1682	0.2261	1.70	0.744
7 Carbonyl imine	-0.2055	-0.0603	-0.1329	0.1452	1.65	0.915
<i>(II) Moderate electrophiles</i>						
8 Diazoalkane	-0.2208	-0.0471	-0.1339	0.1737	1.40	0.771
9 Nitrous oxide	-0.3422	-0.0191	-0.1807	0.3231	1.37	0.559
10 Azimine	-0.2393	-0.0329	-0.1361	0.2064	1.22	0.660
11 Nitron	-0.2279	-0.0241	-0.1260	0.2038	1.06	0.618
12 Carbonyl ylid	-0.1686	-0.0279	-0.0983	0.1407	0.93	0.699
<i>(III) Marginal electrophiles (nucleophiles)</i>						
13 Nitrile oxide	-0.2709	0.0211	-0.1249	0.2919	0.73	0.428
14 Azomethine imine	-0.1912	-0.0069	-0.0990	0.1844	0.72	0.537
15 Azide	-0.2685	0.0287	-0.1199	0.2972	0.66	0.403
16 Nitrile ylid	-0.1661	-0.0075	-0.0868	0.1586	0.65	0.547
17 Azomethine ylid	-0.1489	0.0155	-0.0667	0.1644	0.37	0.406
18 Nitrile imine	-0.2073	0.0589	-0.0742	0.2661	0.28	0.279

HOMO and LUMO energies, electronic chemical potential, μ , and chemical hardness, η , in atomic units; global electrophilicity, ω , in eV; ΔN_{\max} in electron units. See the text for definitions.

$$\mu \approx \frac{\varepsilon_H + \varepsilon_L}{2} \quad (2)$$

It is also possible to give a quantitative representation to the chemical hardness concept introduced by Pearson as:²³

$$\eta \approx \varepsilon_L - \varepsilon_H \quad (3)$$

Note that the electrophilicity index given in Eq. (1) encompasses both, the propensity of the electrophile to acquire an additional electronic charge driven by μ^2 , and the resistance of the system to exchange electronic charge with the environment described by η , simultaneously. A high value of μ and a low value of η therefore characterize a good electrophile. On the other hand, the maximum amount of electronic charge that the electrophile system may accept is given by:¹⁹

$$\Delta N_{\max} = -\frac{\mu}{\eta} \quad (4)$$

Thus, while the quantity defined by Eq. (1) describes the propensity of the system to acquire additional electronic charge from the environment, the quantity defined in Eq. (4) describes the charge capacity of the molecule.

3. Computational details

The global electrophilicity for a series of dipoles and dipolarophiles was evaluated using Eq. (1). The electronic chemical potential μ , and chemical hardness η were evaluated in terms of the one electron energies of the FMOs, HOMO and LUMO, using Eqs. (2) and (3), respectively. All the calculations were performed at the GS of the molecules using the B3LYP/6-31G* level of theory, implemented in the GAUSSIAN98 package of programs.²⁴ The maximum charge transfer ΔN_{\max} towards the electrophile was evaluated using Eq. (4).

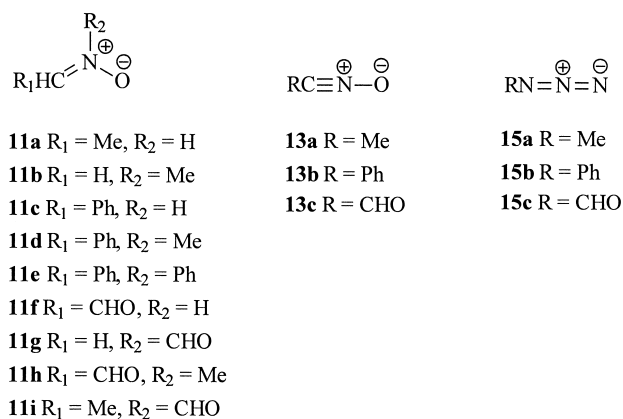
4. Results and discussion

In Table 1 a series of the simplest dipole reagents (see Scheme 1) used in the 1,3-DC reactions is summarized. They are listed in decreasing order of global electrophilicity. Also included in Table 1 are the electronic chemical potential μ , the chemical hardness η , and the maximum charge transfer ΔN_{\max} . The series of dipoles may be classified into three general groups. Group I of strong electrophiles include compounds 1–7 with an electrophilicity power larger than 1.50 eV. A second group of moderate electrophiles (group II) include compounds 8–12, with electrophilicity values comprised within the range (1.40–0.93 eV). A third group III of marginal electrophiles include compounds 13–18 with electrophilicity values less than 0.93 eV. Ozone is a well known strong and stable electrophile.³ Azomethine and nitrile ylids and imines on the other hand, that are classified as marginal electrophiles are known as reactive intermediates that have to be made in situ.³ However, suitable substitution on dipoles like azides, nitrones and nitrile oxides enhances both their stability and electrophilicity patterns. This classification is also consistent with the electronegativity pattern described by the negative of the electronic chemical potential. For instance,

the marginal electrophiles (group III) are characterized by the highest values in electronic chemical potential, thereby indicating that these compounds will more likely behave as electron donor species (i.e. as nucleophiles). Compounds classified in group I on the other hand display the lowest value in electronic chemical potential within the series, thereby suggesting that they will in general act as electron acceptors during their interaction with dipolarophiles. Note that chemical hardness presents a less clear pattern of variations within the three groups. The maximum charge that each species may accept from the environment measured by ΔN_{\max} (last column of Table 1) almost parallel the variations in electrophilicity.

Table 2 summarizes the electrophilicity pattern of a series of common dipolarophiles. These compounds are also common dienophile reagents in DA reactions.²⁰ There are three groups of strong (compounds 20–27), moderate (compounds 28 and 29) and marginal (compounds 30–34) electrophiles. In the DA reactions the dienophiles systematically act as electrophiles and the 1,3-butadienes act as nucleophiles. In the 1,3-DC reactions this static picture may be somehow similar. Note for instance that acrolein–AlMe₃ (compound 21) and nitroethylene (compound 23) display comparable electrophilicity values than fall within the range of strong electrophiles of the dipoles quoted in Table 1. Thus, these dipolarophiles should react with dipoles classified in Table 1 as marginal electrophiles (group III), and presenting normal electron demand (NED) 1,3-DC reactions. The difference in electrophilicity of the dipole–dipolarophile pair should be relatively high, consistent with a polar mechanism.²⁰ On the other hand, propene (compound 31) and methyl vinyl ether (compound 33) present the lower values of electrophilicity. These species should react with dipoles belonging to group I (strong electrophiles) of Table 1, or with dipoles belonging to groups II or III conveniently substituted, giving IED 1,3-DC reactions (see later).

The electrophilicity of the dipoles may be drastically changed by suitable substitution. In Table 3 we summarize the enhanced/diminished electrophilicity pattern induced by substituent effect for compounds 11, 13 and 15 that were classified in Table 1 as moderate, 11, and marginal electrophiles, 13 and 15 (see Scheme 5). Nitron (11) when substituted at position R1 or R2 by methyl decreases its global electrophilicity from 1.06 to 0.87 eV at the R1



Scheme 5.

Table 2. Global properties and global electrophilicity scale for some common dipolarophiles involved in 1,3-dipolar cycloaddition reactions

	HOMO	LUMO	μ	η	ω	ΔN_{\max}
<i>(I) Strong electrophiles</i>						
20 Tetracyanoethylene	-0.3351	-0.1823	-0.2587	0.1528	5.96	1.69
21 Acrolein-AlMe ₃	-0.2232	-0.1152	-0.1692	0.1080	3.61	1.567
23 Nitroethylene	-0.2958	-0.0957	-0.1958	0.2001	2.61	0.979
24 Dimethyl acetylenedicarboxylate	-0.2840	-0.0828	-0.1834	0.2011	2.28	0.912
25 Acrolein	-0.2571	-0.0650	-0.1610	0.1922	1.84	0.838
26 Methyl propiolate	-0.2807	-0.0443	-0.1625	0.2364	1.52	0.687
27 Methyl acrylate	-0.2720	-0.0452	-0.1586	0.2268	1.51	0.700
<i>(II) Moderate electrophiles</i>						
28 Phenylacetylene	-0.2310	-0.0285	-0.1297	0.2025	1.13	0.641
29 Styrene	-0.2217	-0.0305	-0.1261	0.1912	1.13	0.659
<i>(III) Marginal electrophiles (nucleophiles)</i>						
30 Ethylene	-0.2667	0.0188	-0.1239	0.2855	0.73	0.434
31 Propene	-0.2497	0.0284	-0.1107	0.2781	0.60	0.398
32 Cyclooctyne	-0.2338	0.0270	-0.1034	0.2608	0.56	0.396
33 Methyl vinyl ether	-0.2175	0.0389	-0.0893	0.2564	0.42	0.348
34 <i>N,N</i> -dimethyl-1-propyn-1-amine	-0.1989	0.0684	-0.0653	0.2673	0.22	0.244

HOMO and LUMO energies, electronic chemical potential, μ , and chemical hardness, η , in atomic units; global electrophilicity, ω , in eV; ΔN_{\max} in electron units. See the text for definitions.

position, and to 0.81 eV at the R2 position. However, substitution by a Ph group at R1 and R2 results in a slight enhancement in electrophilicity (1.45 and 1.67 eV in **11c** and **11e**, respectively). Note that substitution by the strong electron withdrawing CHO group on nitrene at R1 results in a strong electrophilic activation in compound **11f**, but substitution by CHO at R2 produces an effect even greater: the electrophilicity of nitrene is increased up to four times in compound **11g**. Substitution at R1 and R2 by CHO and Me (**11h**) or by Me and CHO (**11i**) results in a global electrophilic activation to a lesser extent.

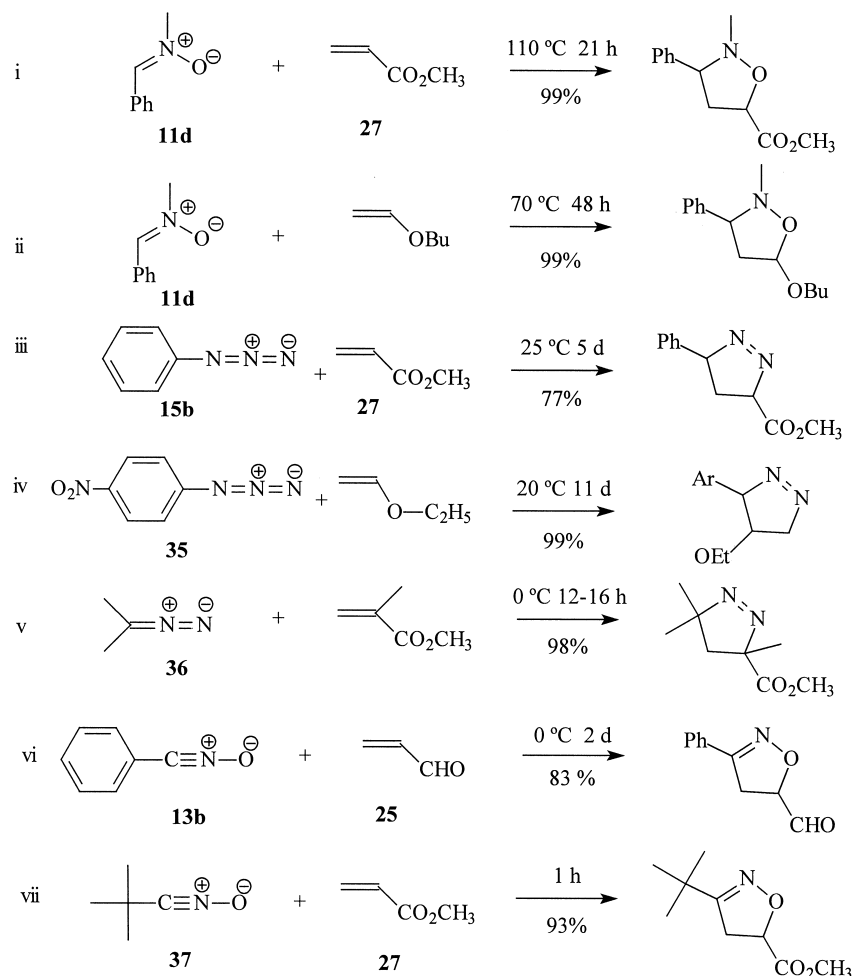
Nitrile oxide **13** which was evaluated as a marginal electrophile in Table 1 ($\omega=0.73$ eV) may be further converted into a poorer electrophile (and probably as a good nucleophile) by substitution at the carbon site by a Me group (**13a**). However, substitution at the same site by a Ph

group renders nitrile oxide as a moderate electrophile (**13b**), but substitution with a CHO group renders the nitrile oxide a strong electrophile ($\omega=2.68$ eV, **13c**). Therefore, it is expected that they will easily react with electron-rich dipolarophiles. Finally, azide (**15**) displays a quite different activation pattern induced by chemical substitution. Replacement of the hydrogen atom by Me, Ph and CHO groups always result in an electrophilic activation from $\omega=0.66$ eV in compound **15** to $\omega=1.20$, 1.21, and 1.99 eV, respectively (compounds **15a–c** in Table 3). Thus, it seems that the electrophilicity enhancement induced by the CHO group result from a cooperative effect of the enhancement in chemical softness, and the increase in the absolute value of the electronic chemical potential (compare the μ values of compounds **11**, **13** and **15** in Table 1, with their corresponding values for the CHO-derivatives in Table 3).

Table 3. Global properties and global electrophilicity for some substituted dipole models involved in 1,3-dipolar cycloaddition reactions

	R1	R2	HOMO	LUMO	μ	η	ω	ΔN_{\max}
<i>Nitrene derivatives</i>								
11a	Me	H	-0.2137	-0.0132	-0.1135	0.2005	0.87	0.566
11b	H	Me	-0.2054	-0.0106	-0.1080	0.1948	0.81	0.554
11c	Ph	H	-0.2070	-0.0508	-0.1289	0.1562	1.45	0.825
11d	Ph	Me	-0.2023	-0.0465	-0.1244	0.1558	1.35	0.798
11e	Ph	Ph	-0.2014	-0.0610	-0.1312	0.1404	1.67	0.934
11f	CHO	H	-0.2616	-0.0978	-0.1797	0.1638	2.68	1.097
11g	H	CHO	-0.2704	-0.1307	-0.2006	0.1397	3.92	1.435
11h	CHO	Me	-0.2286	-0.0859	-0.1573	0.1427	2.36	1.102
11i	Me	CHO	-0.2494	-0.0857	-0.1675	0.1637	2.33	1.024
<i>Nitrile oxide derivatives</i>								
13a	Me		-0.2472	0.0344	-0.1064	0.2816	0.55	0.378
13b	Ph		-0.2329	-0.0483	-0.1406	0.1847	1.46	0.761
13c	CHO		-0.2913	-0.0986	-0.1949	0.1927	2.68	1.012
<i>Azide derivatives</i>								
15a	Me		-0.2554	-0.0279	-0.1417	0.2275	1.20	0.623
15b	Ph		-0.2256	-0.0348	-0.1302	0.1908	1.21	0.682
15c	CHO		-0.2932	-0.0692	-0.1812	0.2240	1.99	0.809

HOMO and LUMO energies, electronic chemical potential, μ , and chemical hardness, η , in atomic units; global electrophilicity, ω , in eV; ΔN_{\max} in electron units. See the text for definitions.



Scheme 6.

These aspects introduce different mechanistic patterns expected for the 1,3-DC reactions, as compared with the DA cycloadditions (concerted vs stepwise with some zwitterionic character), as described by the electrophilicity/nucleophilicity difference of the ground states of the reacting pairs.²⁰ These results suggest that the description of the reactivity and the reaction mechanism involved in the 1,3-DC processes can be systematized as in the case of the DA cycloadditions. Such a model should be able to determine the charge transfer pattern and to decide which of the partners is acting as nucleophile/electrophile in a polar process, or anticipate a concerted pathway in those cases where the electrophilicity/nucleophilicity difference is small.

In order to test this model of reactivity some 1,3-DC reactions, which are shown in Schemes 2–4 and 6, will be analyzed. In Table 4 the electrophilicity for the series of dipoles given in these schemes are presented.

The thiocarbonyl ylid **19** has an electrophilicity value $\omega=1.44$ eV. Therefore, it may be classified as moderate electrophile. It can react with strong electrophiles like tetracyanoethylene (**20**) in a NED 1,3-DC reaction. The large $\Delta\omega$ predicted for this reaction, 4.52 eV, points to a large charge transfer at the corresponding TS,²⁰ in

agreement with Huisgen's proposal.⁹ *N*-phenyl-phenyl-nitronium (**11e**) on the other hand, with an electrophilicity value $\omega=1.67$ eV, can react with strong electrophiles like acrolein (see Scheme 3), or with marginal electrophiles (nucleophiles) like butyl vinyl ether (see Scheme 4), in NED and IED 1,3-DC reactions, respectively. The rate of these cycloadditions is clearly enhanced by the presence of a Lewis acid. Thus, coordination of acrolein to AlMe_3 , **21**, as a model of ATPH,¹⁵ increases the electrophilicity of the

Table 4. Global properties and global electrophilicity for some dipole examples

	HOMO	LUMO	μ	η	ω	ΔN_{max}
19	-0.1810	-0.053	-0.1168	0.1285	1.44	0.909
22	-0.2041	-0.0940	-0.1490	0.1102	2.74	1.353
35	-0.2550	-0.1004	-0.1775	0.1542	2.78	1.151
36	-0.1936	-0.0347	-0.1141	0.1589	1.11	0.718
37	-0.2416	0.0388	-0.1014	0.2803	0.50	0.362
38a	-0.2022	-0.1149	-0.1585	0.0874	3.91	1.814
38b	-0.1955	-0.1073	-0.1514	0.0882	3.53	1.715
38c	-0.1872	-0.0971	-0.1421	0.0901	3.05	1.577
38d	-0.1829	-0.0928	-0.1379	0.0902	2.87	1.529
38e	-0.1773	-0.0870	-0.1321	0.0903	2.63	1.464

HOMO and LUMO energies, electronic chemical potential, μ , and chemical hardness, η , in atomic units; global electrophilicity, ω , in eV; ΔN_{max} in electron units. See the text for definitions.

α,β -unsaturated carbonyl compound from 1.84 to 3.61 eV. Therefore, the large increase in $\Delta\omega$ for the catalyzed reaction (1.77 eV), accounts for the acceleration of the cycloaddition.¹⁵ Furthermore, coordination of nitrene **11e** to AlMe_3 increases the electrophilicity of this reagent from 1.67 to 2.74 eV (compound **22**). This large increase in the electrophilicity of nitrene enhances the predicted $\Delta\omega$ value for the IED 1,3-DC reaction, in agreement with the increase of the reaction rate and the charge transfer pattern observed for the process.^{17,18}

N-Methyl-phenylnitrene (**11d**) has an electrophilicity value of $\omega=1.35$ eV. Therefore it can react also with strong electrophiles like methyl acrylate (Scheme 6, entry (i)), or with marginal electrophiles (nucleophiles) like butyl vinyl ether (Scheme 6, entry (ii)), in NED and IED 1,3-DC reactions, respectively.

Arylazide (**15b**), which has an intrinsic electrophilicity value of 1.21 eV, is expected to react with electron-poor dipolarophiles as for instance methyl acrylate (**27**) (Scheme 6, entry (iii)). However, the presence of a strong electron-withdrawing group on the *para* position significantly increases the electrophilicity of azide to $\omega=2.78$ eV in compound **35**, thereby activating this molecule to react in a IED 1,3-DC reaction with ethyl vinyl ether (Scheme 6, entry (iv)). Diazomethane (**8**) on the other hand presents an intrinsic electrophilicity of 1.40 eV, and it is accordingly classified as a moderate electrophile. However, the presence of two electron-releasing methyl groups on the diazo-propane **36** decreases the electrophilicity to 1.11 eV. This compound is expected to react with electron-poor alkenes in a NED 1,3-DC (see Scheme 6, entry (v)). Finally, the nitrile oxides derivatives **13b** and **37**, which present a low value of electrophilicity, react with acrolein **25** and methyl acrylate **27** through NED 1,3-DCs also (see Scheme 6, entries (vi) and (vii)).

These examples show that nitrenes as moderate electrophiles, and azides and nitrile oxides as marginal electrophiles react with electron-poor dipolarophiles in a NED 1,3-DC. However, the presence of strong electron-withdrawing

Table 5. Rate constants for the cycloadditions of the azomethine ylids **38a–e** with the acetylenes **24**, **32** and **34** at 20°C in dioxane. Values quoted as $10^4 k_2$ ($\text{l mol}^{-1} \text{s}^{-1}$)

		24	32	34
38a	–CF ₃	7.72	2080	15300
38b	–Cl	5.11	799	5180
38c	–H	4.02	436	2140
38d	–CH ₃	3.96	240	1210
38e	–OCH ₃	2.94	122	574

See Ref. 25.

group on the dipole or coordination of the dipole with Lewis acids, results in a large increase in the global electrophilicity of the dipole, thereby activating these molecules to undergo IED 1,3-DC reactions.

The predictive power of the present model to anticipate the rates of 1,3-DC reactions has been tested by statistically comparing the rate constants of 1,3-DC reactions for a series of related azomethine ylids with substituted acetylenes and the computed electrophilicity for the corresponding dipole/dipolarophile pairs. The experimental kinetic data are those recently reported by Sauer et al.²⁵ (see Table 5). The electrophilicity index of the dipolarophiles **24**, **32** and **34** are given in Table 2, while those for the phenyl substituted azomethine ylids **38a–e** are given in Table 4.

A preliminary analysis of the kinetic results given in Table 5 shows that the largest rate corresponds to the 1,3-DC reaction between the azomethine ylid **38a** ($\text{R}=\text{CF}_3$) and the electron-rich substituted acetylene **34**. On the other hand, the reactions of the series of azomethine ylids **38a–e** with

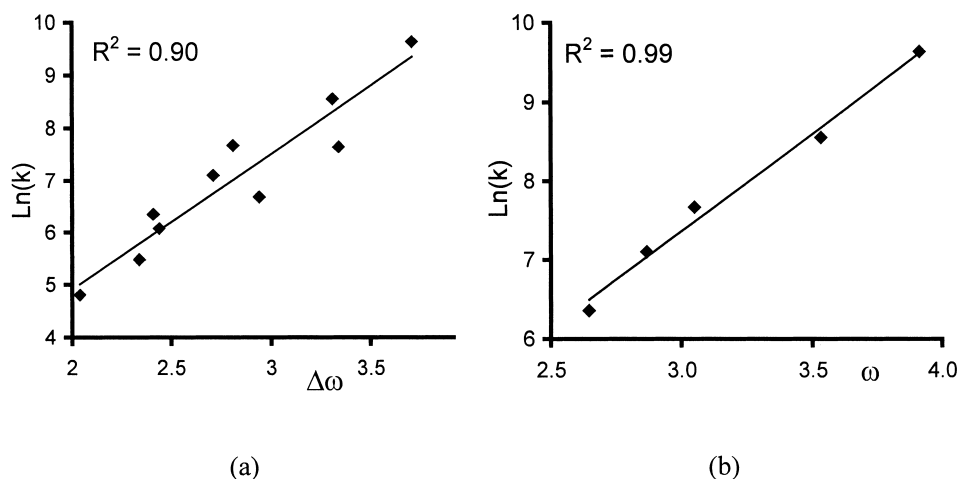


Figure 1. Statistical analysis of the logarithm of k , $\ln(k)$, for the 1,3-DC reactions of the azomethine ylids **38a–e** (a) with the acetylenes **32** and **34** versus $\Delta\omega$ for the electrophile / nucleophile pairs, and (b) with acetylene **34** versus the ω for the azomethine ylids **38a–e**.

the electron-poor acetylene **24** show the lowest rates. Note that the rate constants for this sub-series are not sensitive to the substitution on the azomethine. The computed electrophilicity for the azomethine ylids **38a–e**, which are within the range 2.63–3.91 eV, are larger than those computed for the substituted acetylene, which fall within the range 0.22–2.28 eV. Our proposal about the feasibility of the cycloaddition which can be related to the polar character of the process,²⁰ is quantitatively tested by a statistical comparison between the difference $\Delta\omega = \text{electrophilicity}_{\text{dipole}} - \text{electrophilicity}_{\text{dipolarophile}}$, and the logarithm of the rate constant k . The result is shown in Figure 1(a). It may be seen that a significant correlation between both quantities is obtained ($R^2=0.90$). The faster cycloaddition corresponds to the azomethine ylid **38a**/acetylene **34** 1,3-DC reaction, for which the largest $\Delta\omega$ values is predicted. An additional statistical comparison was performed to assess the effect of chemical substitution at the dipole on the rate constant for the 1,3-DCs. The comparison is made for the reactions involving the highly nucleophilic substituted alkyne **34**. Here again a nice correlation between $\ln k$ and ω is observed ($R^2=0.99$, see Fig. 1(b)).

5. Concluding remarks

The global electrophilicity pattern of a series of dipole and dipolarophiles commonly involved in 1,3-DC reactions has been quantitatively established in terms of the electrophilicity index. This scale conveniently accommodates the intrinsic electrophilicity pattern expected for these systems. Electrophilic activation induced by electron withdrawing groups in different positions or Lewis acids catalyst may change the reactivity pattern of these systems. For instance, moderate electrophiles like nitrones and marginal electrophiles like azides and nitrile oxides are expected to react with electron poor dipolarophiles in normal electron demand 1,3-DC processes. However, the presence of strong electron-withdrawing groups on the dipole or its coordination to a Lewis acid catalyst induce a strong electrophilic activation of the dipole towards inverse electron demand 1,3-DC reactions. The present model permits a simple systematization of the 1,3-DC reactions in terms of a unique electronic model based on the electrophilicity index. A statistical comparison between the experimental rate constants and the computed electrophilicity difference $\Delta\omega$ for the ground state dipole/dipolarophile pair correctly predict the expected charge transfer pattern for some 1,3-DC reactions, which is in turn consistent with the experimental kinetic data recorded for these processes.

Acknowledgements

This work received partial financial support from the Ministerio de Educación y Cultura of the Spanish Government by DGICYT (projects PB98-1429 and BQU2002-01032), and Fondecyt, grant N° 1020069. L. R. D. thanks the Fondecyt grant N° 7020069 for financial support and the Universidad Andrés Bello and the Universidad de Chile for the warm hospitality.

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