Arylazide Cycloaddition to Methyl Propiolate: DFT-Based Quantitative Prediction of Regioselectivity

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Abstract: Several 1-(4-substituted)-phenyl-4- or 5-methoxycarbonyl-1,2,3-triazoles have been synthesized by 1,3-dipolar cycloaddition of the corresponding arylazides to methyl propiolate in carbon tetrachloride. The regioselectivity of these reactions cannot be rationalized on the basis of the electronic demands of the reactants or frontier molecular-orbital theory. Therefore, we applied to this problem a quantitative formulation of the HSAB principle to this problem developed within density functional theory. Global and local reactivity indices were computed at B3LYP/6-311 + G(d,p) level both in vacuo and in carbon tetrachloride (by the COSMO approach). The direction of charge transfer upon reactive encounter has been determined and the computed regioselectivity has been shown to be in good agreement with the experimental results. The relationship between computed and experimental data and how it

Keywords: azides • cycloaddition • density functional calculations • HSAB principle • regioselectivity

Introduction

The first example of arylazide cycloaddition to unsaturated compounds appeared over a century ago, when Arthur Michael reacted phenylazide with dimethylacetylene dicarboxylate.[1] Seventy years later, Huisgen fully investigated the mechanism, scope and limitations of azide cycloadditions,[2] which was recognized as the choice method for the direct synthesis of 1,2,3-triazoles.[3] These and other azoles[4] were the object of recent important investigation leading to the "click" chemistry approach.[5] 1,2,3-Triazoles may display a wide range of biological activity, such as anti-HIV[6] and antimicrobial[7] agents, as well as selective β_3 adrenergic receptor agonists.[8] Due to these attractive activities, new insights about the factors that influence the regiochemical output for these compounds are of interest. Following Houk's findings,[9, 10] arylazide cycloaddition to methyl propiolate can be controlled from both the HOMO and the LUMO of the 1,3-dipole, and this implies that the observed regioselectivities are difficult to rationalize on the grounds of simple FMO theory.

Recently, many important concepts and indices useful for the understanding of chemical reactivity have been rationalized within the framework of the density functional theory (DFT).[11] Well-known examples[12] 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. Within DFT, any reaction can be considered as split in two steps:[13, 14] 1) as soon as reactant molecules approach each other, they form a weakly interacting, promoted complex,[15] whereby charge is transferred between the reactants in order to equalize the electron chemical potential at constant external potential; 2) a charge reshuffling at constant electron chemical potential occurs by which the promoted complex evolves toward the product(s) or back to the reactants (see Figure 1). If one assumes that the second step can be neglected, it can be shown that the most favorable situation occurs when the reactants have equal softness. This is the DFT formulation[13, 16] of Pearson's hard–soft acid–base (HSAB) principle.[17]

However, to study regioselection a local (atomic) reactivity index is needed. The best suited is local softness $s(\mathbf{r})$,[12] which represents the sensitivity of the molecular electron density at point $\mathbf{r}$ to a change in μ. A local HSAB principle[18] can then be devised: a regioisomer is favored when the new bonds form between atoms with equal softness. The local HSAB principle has provided many reliable *qualitative* prediction of regioselectivity for 1,3-dipolar cycloadditions (1,3-DC).[19] Since in 1,3-DCs the relative energy of transition states is paralleled by the relative energy of the weakly interacting complexes forming in the early stage of the reaction[10] (cf. Figure 1), the neglect of the charge reshuffling term is reasonable.[20] Moreover, such successful predictions suggest that the early interaction energy between the reactants should be closely

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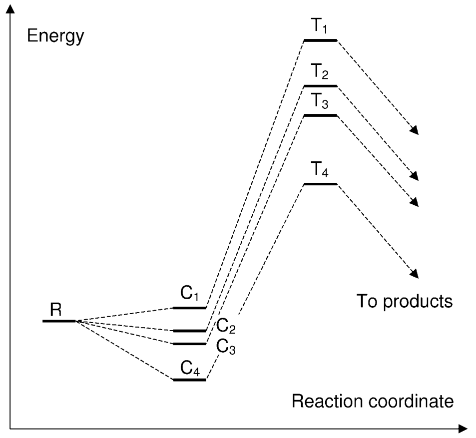


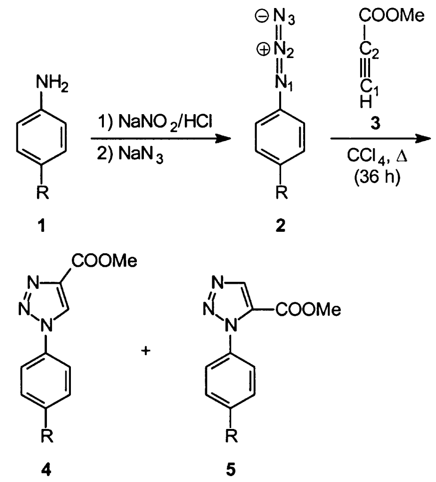
Figure 1. Energy profile of a prototypical reaction leading to several products (e.g. regioisomers). Reactants R form weakly interacting promoted complexes C_i which evolve to the corresponding transition states T_i and then to the products (not shown). If the local HSAB principle applies, the energy differences between the C_i's are proportional to the corresponding energy differences between the T_i's.

related to the transition state energy. On these grounds, a generalization of the local HSAB principle has been recently introduced,[21] which enables one to compute, from μ and s of the reactants only, the grand potential variation $\Delta\Omega$[22] due to the charge transfer occurring in the very first step of the bond-forming interaction between specific atoms of the reactants. For the above reasons, $\Delta\Omega$ is expected to be proportional to the transition state energy and to provide a *quantitative* prediction of regioselectivity without the need of locating the transition state. This method has been successfully applied by us to the 1,3-DC between nitrilimines and alkynyl- or alkenyl dipolarophiles.[23] Continuing our investigations, we present here the first quantitative prediction of the regioselectivity involved in the cycloaddition between 1-(4-substituted)phenylazides **2** and methyl propiolate **3**, which is based upon the DFT theory and the HSAB principle.

Results and Discussion

The 1,3-dipolar species **2** were prepared from the corresponding anilines by diazotization, followed by addition to sodium azide (Scheme 1). The subsequent cycloadditions were performed by refluxing **2** in dry CCl_4 in the presence of an equimolecular amount of **3**. Reaction time, product yields, and yield ratios are summarized in Table 1. The structures of regioisomeric 1-(4-substituted)phenyl-4-methoxycarbonyl-1,2,3-triazoles (**4**) and 1-(4-substituted)phenyl-5-methoxycarbonyl-1,2,3-triazoles (**5**) were unambiguously determined through analytical and spectroscopic data. In particular, as far as ^1H NMR spectra are concerned, the protons in the 4- and 5-positions of the 1,2,3-triazole ring show resonances that are in perfect agreement with literature data.[24–26]

The main results of DFT calculations at the B3LYP/6-311 + G(d,p) level both in vacuo and in CCl_4 are reported in Table 2. The electron chemical potential difference between **2** and **3** determines the direction of the overall charge flow upon interaction of the reactants, as electrons flow towards regions



Entry	a	b	c	d	e	f
R	H	Me	MeO	F	Cl	NO_2

Scheme 1.

Table 1. Experimental yields and **4**/**5** yield ratios of the cycloaddition between arylazides **2** and methyl propiolate **3** in refluxing CCl_4.

	R	Yields[a] [%] **4** + **5**	Yield ratio[b] **4**/**5**
a	H	> 96	75:25
b	Me	> 96	73:27
c	MeO	91	68:32
d	F	95	70:30
e	Cl	93	68:32
f	NO_2	> 96	55:45

[a] Isolation yields. [b] Deduced from ^1H NMR of reaction crudes.

Table 2. Results of B3LYP/6-311 + G(d,p) calculations either in vacuo or in CCl_4 (COSMO model). Electron chemical potential difference between arylazides **2** and methyl propiolate **3** along with $\delta\Delta\Omega$ difference[a] and predicted **4**/**5** yield ratio for their mutual cycloaddition.

	Vacuum			CCl_4		
R	$\mu(\mathbf{2})-\mu(\mathbf{3})$ [eV]	$\delta\Delta\Omega$ [kJ mol^{-1}]	Predicted Ratio[b] **4/5**	$\mu(\mathbf{2})-\mu(\mathbf{3})$ [eV]	$\delta\Delta\Omega$ [kJ mol^{-1}]	Predicted Ratio[b] **4/5**
H	1.04	− 1.60	74:26	1.14	− 1.81	74:26
Me[c]	1.19	− 0.79	66:34	1.28	− 1.30	69:31
MeO	1.35	− 1.14	69:31	1.46	− 1.35	69:31
F	0.97	− 1.16	70:30	1.08	− 1.31	69:31
Cl	0.97	− 1.07	69:31	1.06	− 0.55	70:30
NO_2	− 0.21	0.22	54:46	− 0.03	− 0.02	54:46

[a] Difference in grand potential variation for the pathways leading to triazoles **4** and **5**. [b] From computed $\delta\Delta\Omega$ and Equations (2) and (3) as appropriate; uncertainty ± 1%. [c] Excluded from regression.

at low electron chemical potential μ. It turns out that, both in vacuo and in CCl_4, **2a**–**e** act as nucleophiles, whereas **2f** acts as an electrophile (note, however, that the chemical potentials of **2f** and **3** are close to each other, especially in solution). The $\approx$0.1 eV increase of the $\mu(\mathbf{2})-\mu(\mathbf{3})$ difference in CCl_4 in mostly due to the decrease of $\mu(\mathbf{2})$; $\mu(\mathbf{2f})-\mu(\mathbf{3})$ is slightly larger because of a comparable decrease in $\mu(\mathbf{2f})$. Our calculations thus show that in the reaction of **3** with **2a**–**e** charge flows from the arylazide to methyl propiolate, whereas FMO theory is not able to provide a clear-cut prediction, since the two possible HOMO-LUMO interactions are comparable in size.

We now turn to regioselectivity prediction. As selectivity criterion, we used the grand potential change due to *two* bond-forming interactions between **2** and **3**, because of the general agreement about the concertedness of 1,3-DC reactions. The grand potential change for the pathway leading to 4-methoxycarbonyl-1,2,3-triazole **4** is given in Equation (1):

$$\Delta\Omega(\mathbf{4}) = -\tfrac{1}{2}[\mu(\mathbf{2}) - \mu(\mathbf{3})]^2 \{s(\mathrm{N}_1)s(\mathrm{C}_1)[s(\mathrm{N}_1)+s(\mathrm{C}_1)]^{-1} + s(\mathrm{N}_3)s(\mathrm{C}_2)[s(\mathrm{N}_3)+s(\mathrm{C}_2)]^{-1}\} \quad (1)$$

Here the atoms are numbered as in Scheme 1. The grand potential variation for $\Delta\Omega(\mathbf{5})$ can be obtained by exchanging $s(\mathrm{C}_1)$ and $s(\mathrm{C}_2)$. The difference $\delta\Delta\Omega = \Delta\Omega(\mathbf{4}) - \Delta\Omega(\mathbf{5})$ is reported in Table 2. The negative sign of $\delta\Delta\Omega$ shows that cycloadduct **4** is the major one, in line with experimental results. Note that $\delta\Delta\Omega$ of the reaction **2f** + **3** is negative only in the solution calculation, thus showing the beneficial effect of solvent inclusion. The low regioselectivity of the reaction of **2f** with **3** is due to two concurrent causes. First, $\mu(\mathbf{2f})$ and $\mu(\mathbf{3})$ are so close that $\Delta\Omega$ (and hence $\delta\Delta\Omega$) is at least one order of magnitude smaller than in the remaining cases. Besides, the grand potential change due to the formation of the N1−C1 bond is very close to that for the N3−C1 bond, so that $\delta\Delta\Omega$ is mostly due to the energy difference of a single bond, that is, that forming about C2 of **3**. Among the currently studied cycloadditions, this is the only case in which the difference in μ has a significant effect on the regioselectivity.

We now proceed one step further by demonstrating that $\delta\Delta\Omega$ is a quantitative regioselectivity index for 1,3-DC reactions. The difference in activation energy $\delta\Delta E^{\neq}$ of the two reaction paths can be obtained as $\delta\Delta E^{\neq} = -RT\log(Y)$, whereby $T = 350$ K is the reaction temperature, and Y is the experimental **4**/**5** ratio. Estimating the error in Y at ±1% and considering **2b** as an outlier (vide infra), weighted least-squares linear regression results in Equations (2) and (3):

$$\delta\Delta\Omega = (0.73 \pm 0.07)\,\delta\Delta E^{\neq} + (0.6 \pm 0.1)\ \mathrm{kJ\,mol^{-1}} \qquad \rho = 0.99\ \text{(in vacuo)} \quad (2)$$

$$\delta\Delta\Omega = (0.71 \pm 0.07)\,\delta\Delta E^{\neq} + (0.3 \pm 0.1)\ \mathrm{kJ\,mol^{-1}} \qquad \rho = 0.98\ (\text{in } \mathrm{CCl_4}) \quad (3)$$

Here ρ is the linear correlation coefficient (see Figure 2). The predicted **4**/**5** ratios (Table 2), obtained from computed $\delta\Delta\Omega$ values [Eqs (2) and (3)], are in very good agreement with the experimental values (Table 1), except for **2b**. Figure 2 and Table 2 also show that regioselectivity data cannot be rationalized only on the basis of the electron demand of R of **2**, for example, by using Hammett σ parameters. This is best illustrated by the fact that maximum regioselectivity is observed when R = H, which is the zero of the usual electron-demand scale. A satisfactory description of regioselectivity must take into account local variations of charge density due to the interaction between reactants.

The positive intercept in the above equations implies that there is a slight preference towards the major product **4**, since $\delta\Delta E^{\neq} < 0$ when $\delta\Delta\Omega = 0$. Such preference is independent of the specific interaction between the reactants. However, this constant term halves when the solvent is taken into account and comes at the border of statistical significance; the remaining 0.3 kJ mol^{-1} term might vanish on improving the solvation model. The slopes in Equations (2) and (3) are almost independent of solvation. Their values mean that the difference in transition state energy is about 30% larger than the energy difference between the promoted complexes. Although this is in line with theory, we were prompted to check the main approximation used, namely, the neglect of the constant electron potential term in Equation (1), since we previously obtained a nearly equality of $\delta\Delta\Omega$ and $\delta\Delta E^{\neq}$ in the case of 1,3-DCs involving nitrilimines. To this end, we computed the contribution of the step at constant electron chemical potential [Eq. (4)]:

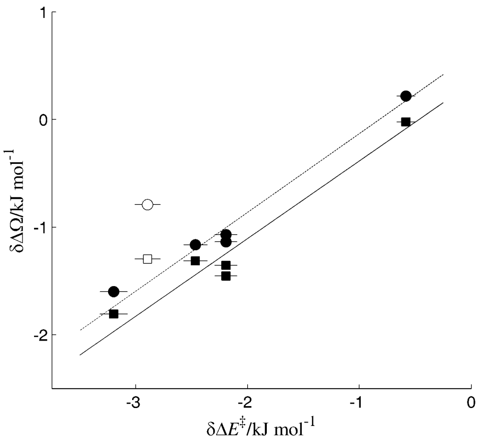


Figure 2. Linear relationship between the computed difference $\delta\Delta\Omega$ in grand potential variation for the pathways leading to cycloadducts **4** and **5** and the corresponding difference in activation energy $\delta\Delta E^{\neq}$, computed from the experimental **4**/**5** yield ratio. The error bars show the uncertainty in $\delta\Delta E^{\neq}$ due to the error in yield ratio, estimated at 1%. $\delta\Delta\Omega$ computed in vacuo: circles and dashed regression line; $\delta\Delta\Omega$ computed in $\mathrm{CCl_4}$ by the COSMO solvation model: squares and solid regression line. Open symbols denote the **2b** (R = Me) + **3** reaction which has been excluded from both regressions.

$$\Delta\Omega_\mu(\mathbf{4}) = -\tfrac{1}{2}\lambda\{[s(\mathrm{N}_1)+s(\mathrm{C}_1)]^{-1} + [s(\mathrm{N}_3)+s(\mathrm{C}_2)]^{-1}\} \quad (4)$$

Here $\Delta\Omega_\mu(\mathbf{5})$ can be obtained by exchanging $s(\mathrm{C}_1)$ and $s(\mathrm{C}_2)$, and λ is a positive parameter related to an effective number of valence electrons. As the value of λ is not precisely set by theory, we carried out a bilinear regression of $\delta\Delta E^{\neq}$ with $\delta\Delta\Omega$ and $\delta\Delta\Omega_\mu$, whereby λ was considered a parameter to be optimized. Such a regression did not show any improvement over the linear one in Equation (2). This confirms that in early transition state reactions, such as the 1,3-DCs, the relative transition-state energy depends only on the relative energy of the promoted complex formed by charge transfer in the chemical-potential equalization step at the beginning of the reactive encounter.

The experimental selectivity towards **4b** is higher than that predicted by computation. The reason for this discrepancy is a too negative value of $\Delta\Omega(\mathbf{5})$. Dissecting the latter into bond contributions, it turns out that the too large stabilization of the **5b** is caused by the particularly favorable interaction between N3 and C1. This in turn arises from a large computed softness at N3 of **2b**. Therefore, the wrong prediction of the selectivity towards **4b** is mostly due to an incorrect evaluation of the charge on the terminal nitrogen of **2b**. Figure 2, however, shows that the situation is somewhat improved when solvation is taken into account thanks to a better evaluation of the charge rearrangement about N3 of **2b** upon electrophilic attack.

We have thus shown that the combined use of DFT reactivity indices of the reactants with the local HSAB principle provides quantitative rationalization of regioselectivity for a series of 1,3-DCs not amenable to FMO and electron-demand theory. Indeed, the electron demand of the substituent R only affects the electron chemical potential μ, which cannot fully account for regioselectivity. This can be adequately rationalized only when the substituent effect on the sensitivity of the electron density at the reactive atoms is taken into account. Other advantages of the DFT-HSAB approach are that transition states need not to be located and that insight into the details of atom-atom interactions can be easily obtained. The inclusion of solvation effects leads to a tiny worsening of the correlation of $\delta\Delta E^{\neq}$ with $\delta\Delta\Omega$, but significantly improves the description of individual cases, such as **2b** + **3** and **2f** + **3**, which is less satisfactory when the systems are treated in vacuo.

Experimental Section

General methods. Melting points were determined in open tubes and are uncorrected. IR spectra were recorded with a FTIR spectrophotometer. Mass spectra were determined with a 70 eV EI apparatus. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{19}F NMR (282 MHz) spectra were taken in $CDCl_3$ at 297 K. Chemical shifts are given as ppm from tetramethylsilane (hexafluorobenzene for ^{19}F NMR), J values are given in Hz.

Compounds **4a**,[24] **4b**,[25] **4f**,[26] **5a**,[24] and **5f**[26] are known in the literature.

Cycloaddition between arylazides 2 and methyl propiolate 3: *General procedure*: A solution of **2** (5.0 mmol) and **3** (0.43 g, 5.0 mmol) in dry carbon tetrachloride (25 mL) was refluxed for the time indicated in Table 1. Evaporation of the solvent in vacuo gave a residue which was separated by chromatography on a silica gel column with ethyl acetate/hexane 1:2. Major 4-methoxycarbonyl-1,2,3-triazole **4** was eluted first, followed by minor 5-methoxycarbonyl-1,2,3-triazole **5**. Crystallization from diisopropyl ether gave analytically pure **4** and **5**.

Compound 4c: Pale yellow solid, m.p. 93–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.84$ (3H, s), 3.88 (3H, s), 7.00–7.60 (4H, m), 8.42 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.20$ (q), 55.51 (q), 114.23 (d), 126.86 (d), 138.02 (d), 127.13 (s), 158.22 (s), 160.67 ppm (s); IR (Nujol): $\tilde{\nu} = 1730$ cm^{-1}; MS: m/z: 233 [M^+]; elemental analysis calcd (%) for $C_{11}H_{12}N_3O_3$: C 56.65, H 4.75, N 18.02; found: C 56.70, H 4.77, N 17.94.

Compound 4d: White solid, m.p. 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.99$ (3H, s), 7.20–7.60 (4H, m), 8.49 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 50.71$ (q), 114.41 (d), 126.64 (d), 136.63 (d), 127.36 (s), 160.18 (s), 163.32 ppm (s); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -111.11$ ppm; IR (Nujol): $\tilde{\nu} = 1730$ cm^{-1}; MS: m/z: 221 [M^+]; elemental analysis calcd (%) for $C_{10}H_8FN_3O_2$: C 54.30, H 3.65, N 19.00; found: C 54.34, H 3.69, N 19.06.

Compound 4e: Pale yellow solid, m.p. 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.00$ (3H, s), 7.00–7.20 (4H, m), 8.49 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.37$ (q), 114.09 (d), 126.14 (d), 128.12 (s), 138.39 (d), 159.36 (s), 162.2 ppm (s); IR (Nujol): $\tilde{\nu} = 1730$ cm^{-1}; MS: m/z: 249 [M^+]; elemental analysis calcd (%) for $C_{10}H_8ClN_3O_2$: C 52.92, H 3.23, N 16.83; found: C 52.97, H 3.26, N 16.78.

Compound 5b: White solid, m.p. 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.41$ (3H, s), 3.84 (3H, s), 7.30–7.70 (4H, m), 8.24 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.82$ (q), 52.09 (q), 120.58 (d), 125.33 (d), 129.93 (d), 133.76 (s), 139.46 (d), 158.01 (s), 160.71 ppm (s); IR (Nujol): $\tilde{\nu} = 1740$ cm^{-1}; MS: m/z: 217 [M^+]; elemental analysis calcd (%) for $C_{11}H_{11}N_3O_2$: C 60.82, H 5.10, N 19.34; found: C 60.88, H 5.14, N 19.28.

Compound 5c: Pale yellow solid, m.p. 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.88$ (3H, s), 3.99 (3H, s), 6.90–7.40 (4H, m), 8.24 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.40$ (q), 55.60 (q), 113.71 (d), 122.37 (d), 127.13 (d), 129.16 (s), 157.81 (s), 160.32 ppm (s); IR (Nujol): $\tilde{\nu} = 1735$ cm^{-1}; MS: m/z: 233 [M^+]; elemental analysis calcd (%) for $C_{11}H_{12}N_3O_3$: C 56.65, H 4.75, N 18.02; found: C 56.68, H 4.78, N 17.92.

Compound 5d: White solid, m.p. 79–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.86$ (3H, s), 7.20–7.70 (4H, m), 8.26 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.22$ (q), 115.60 (d), 121.48 (d), 125.41 (d), 127.31 (s), 159.45 (s), 162.76 ppm (s); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -110.51$ ppm; IR (Nujol): $\tilde{\nu} = 1740$ cm^{-1}; MS: m/z: 221 [M^+]; elemental analysis calcd (%) for $C_{10}H_8FN_3O_2$: C 54.30, H 3.65, N 19.00; found: C 54.36, H 3.67, N 19.07.

Compound 5e: Pale yellow solid, m.p. 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.87$ (3H, s), 7.50–7.70 (4H, m), 8.27 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.07$ (q), 121.96 (d), 125.46 (d), 129.92 (d), 132.21 (s), 140.17 (s), 157.68 (s), 161.28 ppm (s); IR (Nujol): $\tilde{\nu} = 1735$ cm^{-1}; MS: m/z: 249 [M^+]; elemental analysis calcd (%) for $C_{10}H_8ClN_3O_2$: C 52.92, H 3.23, N 16.83; found: C 52.88, H 3.19, N 16.87.

Computational methods: DFT calculations were performed with the Gaussian 98[27] program suite by means of a Beowulf PC cluster. The hybrid B3LYP functional was employed with the standard 6-311 + G(d,p) basis set. The geometry of **2a–f** and **3** in vacuo was fully optimized and characterized with vibrational analysis at the same level of theory. The anion and cation of **2a–f** and **3** were treated at the UB3LYP/6-311 + G(d,p) level by using the geometry of the neutral systems. Calculations of the solvated systems were carried out by the COSMO model[28] with dielectric constant $\varepsilon = 2.228$ at the in vacuo geometry. The COSMO approach describes the solvent reaction field by means of apparent polarization charges distributed on the surface of the cavity in which the solute molecule is embedded. Atomic electron populations were evaluated following the Merz–Kollman scheme[29] (including fitting of atom-centered dipoles). This scheme, which already proved to be reliable,[30] has been used in most DFT calculations of regiochemistry of 1,3-DCs, so that our results can be directly compared with existing literature. It has also been recently considered as an appropriate local descriptor of charge.[31] Reactivity indices were computed within the finite difference approximation:[11] $\mu = -(\mathrm{IP} + \mathrm{EA})/2$ and $S = (\mathrm{IP}\text{-}\mathrm{EA})^{-1}$, whereby IP and EA are the (vertical) ionization potential and electron affinity, respectively. The local softness s (condensed to each individual atom[32]) 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, whereby $p(N)$, $N = N_0 - 1$, N_0, $N_0 + 1$, was the atomic electron population of the cationic, neutral, and anionic system, respectively.

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[1] A. J. Michael, *Prakt. Chem.* **1893**, *48*, 94.

[2] R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, Wiley-Interscience, New York, **1984**, pp. 1–176.

[3] E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297; W. Lwowsky, in *1,3-Dipolar Cycloaddition Chemistry, Vol. 1*, Wiley-Interscience, New York, **1984**, pp. 621–627; *The Chemistry of the Azido Group* (Ed.: S. Patai), Wiley, London, **1971**.

[4] Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2001**, *3*, 4091; Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2002**, *4*, 2525; Z. P. Demko, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2214; *Angew. Chem. Int. Ed.* **2002**, *41*, 2110; Z. P. Demko, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2217; *Angew. Chem. Int. Ed.* **2002**, *41*, 2113; F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2002**, *124*, 12210.

[5] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

[6] S. Velazquez, R. Alvarez, C. Perez, F. Gago, C. De, J. Balzarini, M. J. Camarasa, *Antiviral Chem. Chemother.* **1998**, *9*, 481; R. Alvarez, S.

Velazquez, F. San, S. Aquaro, C. De, C. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185.

[7] M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, Y. B. H., *J. Med. Chem.* **2000**, *43*, 953.

[8] L. L. Brockunier, E. R. Parmee, H. O. Ok, M. R. Candelore, M. A. Cascieri, L. F. Colwell, L. Deng, W. P. Feeney, M. J. Forrest, G. Hom, J., D. E. MacIntyre, L. Tota, M. J. Wywratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111.

[9] K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, J. K. George, *J. Am. Chem. Soc.* **1973**, *95*, 7287.

[10] K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[11] R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, **1989**.

[12] H. Chermette, *J. Comput. Chem.* **1999**, *20*, 129.

[13] P. K. Chattaraj, H. Lee, R. G. Parr, *J. Am. Chem. Soc.* **1991**, *113*, 1855.

[14] A. Toro-Labbé, *J. Phys. Chem. A* **1999**, *103*, 4398.

[15] J. L. Gazquez, *J. Phys. Chem. A* **1997**, *101*, 9464.

[16] A. Cedillo, P. K. Chattaraj, R. G. Parr, *Int. J. Quant. Chem.* **2000**, *77*, 403.

[17] R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533.

[18] J. L. Gázquez, F. Méndez, *J. Phys. Chem.* **1994**, *98*, 4591.

[19] A. K. Chandra, M. T. Nguyen, *J. Comput. Chem.* **1998**, *19*, 195; A. K. Chandra, M. T. Nguyen, *J. Phys. Chem. A* **1998**, *102*, 6181; F. Mendez, J. Tamariz, P. Geerlings, *J. Phys. Chem. A* **1998**, *102*, 6292; T. N. Le, L. T. Nguyen, A. K. Chandra, F. De Proft, P. Geerlings, M. T. Nguyen, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1249; A. K. Chandra, T. Uchimaru, M. T. Nguyen, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2117; P. Geerlings, F. De Proft, *Int. J. Quant. Chem.* **2000**, *80*, 227; L. T. Nguyen, F. De Proft, A. K. Chandra, T. Uchimaru, M. T. Nguyen, P. Geerlings, *J. Org. Chem.* **2001**, *66*, 6096.

[20] Of course, the reshuffling term may be needed in other reactions where the transition state is not early. For instance see: S. Damoun, G. Van de Woude, K. Choho, P. Geerlings, *J. Phys. Chem.* **1999**, *103*, 7861; S. Pal, K. R. S. Chandrakumar, *J. Am. Chem. Soc.* **2000**, *122*, 4145.

[21] A. Ponti, *J. Phys. Chem. A* **2000**, *104*, 8843.

[22] 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.

[23] A. Ponti, G. Molteni, *J. Org. Chem.* **2001**, *66*, 5252; G. Molteni, A. Ponti, M. Orlandi, *New J. Chem.* **2002**, *26*, 1340; A. Ponti, G. Molteni, *New J. Chem.* **2002**, *26*, 1346.

[24] R. K. Huisgen, L. Möbius, G. Szeimies, *Chem. Ber.* **1965**, *98*, 4014.

[25] C. Wentrup, V. V. Ramana Rao, W. Frank, B. E. Fulloon, D. W. Moloney, T. Mosandl, *J. Org. Chem.* **1999**, *64*, 3608.

[26] R. Fusco, G. Bianchetti, D. Pocar, R. Ugo, *Gazz. Chim. Ital.* **1962**, *92*, 1040.

[27] Gaussian 98 (Revision A.11.3), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, **2002**.

[28] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.

[29] U. C. Singh, P. A. Kollman, *J. Comput. Chem.* **1984**, *5*, 129; B. H. Besler, K. M. Merz, Jr., P. A. Kollman, *J. Comput. Chem.* **1990**, *11*, 431.

[30] F. De Proft, J. M. L. Martin, P. Geerlings, *Chem. Phys. Lett.* **1996**, *256*, 400.

[31] P. K. Chattaraj, *J. Phys. Chem. A* **2001**, *105*, 511.

[32] W. Yang, W. J. Mortier, *J. Am. Chem. Soc.* **1986**, *108*, 5708.

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