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On the Asynchronism of Isocyanide Addition to Dipolarophiles: Application of Local Softness

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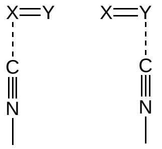
Owing to the presence of a monocoordinated carbon atom with a lone pair of electrons, isocyanides often act as 1,1-dipolar partners in diverse addition reactions. For example, isocyanides have been known to add to dipolarophiles containing double bonds such as disilenes ($R_2Si{=}SiR_2$) and silenes ($R_2Si{=}CR_2$). There are very recent theoretical studies[1,2] on the [2 + 1] cycloaddition reactions of isocyanide with different dipolarophiles. The isocyanide molecule behaves as a nucleophile in those reactions, i.e. filled n orbital interacts with the π^* orbital of the dipolarophile. For a heteronuclear dipolarophile X = Y, two distinct transition structures (TS) can be found corresponding to the attack of the carbon atom of isocyanide to the two doubly bonded atoms in the dipolarophile.

Quite often, both TS **I** and **II** have energy differences ranging from 10 to 100 kJ/mol[2].



I **II**

The predominance of one TS over the other has been referred to as the regioselectivity of the addition.[2] Nevertheless, due to the fact that there is no difference in the product, it may be more correct to regard the difference between **I** and **II** as an asynchronism in the formation of two novel bonds, one bond being formed earlier than the other. In any case, from a mechanistic viewpoint, it is important to understand the cause of such asynchronism. Atomic charges and HOMO−LUMO interactions (FMO approach) are generally used to understand the regioselective nature of a reaction.[3] Although FMO theory is fairly successful, occasionally the validity of the simple approach is questioned too. A rigorous testing of the model has therefore been recommended.[4]

In recent days, density functional theory (DFT) has gained widespread use in quantum chemistry. It could thus be expected that the concepts based on DFT[5] should provide some fruitful avenues to interpret regioselectivity. Indeed many useful and important chemical concepts such as electronegativity[6] and hardness and softness[7] appear naturally within DFT.[5] Some DFT-based local properties, e.g. Fukui functions and local softnesses,[8,9] have already been used for the reliable predictions and interpretation of the regioselectivity in various types of electrophilic and nucleophilic reactions.[10−14] Moreover, Gazquez and Mendez[15] proposed that when two molecules A and B of equal softness interact, thereby implicitly assuming one of the species is acting as a nucleophile and the other as an electrophile, then a novel bond would likely to form between an atom of A and an atom of B whose Fukui function values are close to each other. They also propose that local softness may play the same role as Fukui functions when the softnesses of two interacting molecules are different. This can be treated as a local version of the hard and soft acid base (HSAB) principle.[16] The determination of the specific sites of interaction between two chemical species is of fundamental importance to determine the products of a given reaction without actual calculations of the corresponding potential energy surface. Very recently, the HSAB principle has been applied in a local sense to rationalize the regioselectivity in Diels−Alder reactions[17] and also to understand the product distribution in photocycloaddition reactions.[14] The aim of the present communication is to use DFT-based local reactivity decriptors such as condensed Fukui functions or local softnesses to explain the asynchronism in a [2+1] addition between an isocyanide and a dipolarophile. We will thereby apply HSAB principle in a local sense to the attack of the H-N=C molecule to different types of dipolarophiles.

Let us first recall the definitions of various quantities employed. The Fukui function, $f(\mathrm{r})$, is defined by[8]

$$f(\mathrm{r}) = [\delta\mu/\delta v(\mathrm{r})]_N = [\partial\rho(\mathrm{r})/\partial N]_v \qquad (1)$$

The function f is thus a local quantity, which has different values at different points in the species, and N is the total number of electrons. Since $\rho(\mathrm{r})$ as a function of N has slope discontinuities, eq 1 provides the following three reaction indices,[8]

$$f^-(\mathrm{r}) = [\partial\rho(\mathrm{r})/\partial N]_v \text{ governing electrophilic attack,}$$

$$f^+(\mathrm{r}) = [\partial\rho(\mathrm{r})/\partial N]_v \text{ governing nucleophilic attack, and}$$

$$f^0(\mathrm{r}) = 1/2[f^+(\mathrm{r}) + f^-(\mathrm{r})] \quad \text{for radical attack.}$$

In a finite difference approximation, the condensed

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(1) Nguyen, M. T.; Vansweevelt, H.; Vanquickenborne, L. G. *J. Org. Chem.* **1991**, *56*, 5651. Nguyen, M. T.; Vansweevelt, H.; Neef, A. De; Vanquickenborne, L. G. *J. Org. Chem.* **1994**, *59*, 8015. Nguyen, M. T.; Van Keer, A.; Vanquickenborne, L. G. *J. Chem. Soc., Perkin Trans. 2* **1996**, 299.

(2) Nguyen, M. T.; Van Keer, A.; Vanquickenborne, L. G. *Chem. Ber.* **1997**, *130*, 69.

(3) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(4) Arbelot, M.; Allouche, A.; Purcell, K. F.; Chanon, M. *J. Org. Chem.* **1995**, *60*, 2330.

(5) Parr, R. G.; Yang, W. *Density-functional theory of atoms and molecules*; Oxford University Press: New York, 1989.

(6) For a comprehensive account, see *Electronegativity, Structure and Bonding*; Sen, K. D.; Jorgenson, C. K. Eds.; Springer-Verlag, New York, 1987; Vol. 66.

(7) For a comprehensive account see *Chemical Hardness, Structure and Bonding*; Sen, K. D., Ed.; Springer-Verlag, New York, 1993; Vol. 80.

(8) Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.

(9) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* ***1983****, 82, 6723.*

(10) Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct. (THEOCHEM)* **1992**, *259*, 317.

(11) Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct. (THEOCHEM},* **1991**, *234*, 329.

(12) Tielemans, M.; Areschka, V.; Colomer, J.; Promel, R.; Langenaeker, W.; Geerlings, P. *Tetrahedron* **1992**, *48*, 10575.

(13) Langenaeker, W.; Proft, F. De; Geerlings, P. *J. Phys. Chem.* **1995**, *99*, 6424.

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Fukui functions[18] of an atom, say k, in a molecule with N electrons are defined as:

$$f_k^{+} = [q_k(N + 1) - q_k(N)] \quad \text{for nucleophilic attack,}$$

$$f_k^{-} = [q_k(N) - q_k(N - 1)] \quad \text{for electrophilic attack, and} \qquad (2)$$

$$f_k^{o} = [q_k(N + 1) - q_k(N - 1)]/2 \quad \text{for radical attack}$$

where q_k is the electronic population of atom k in a molecule. In density functional theory, hardness (η) is defined as[19]

$$\eta = 1/2(\partial^2 E/\partial N^2)_{v(r)} = 1/2(\partial\mu/\partial N)_v$$

The global softness S, defined as the inverse of the global hardness η.

$$S = 1/2\eta = (\partial N/\partial\mu)_v$$

The local softness s(r) can be defined as

$$s(r) = (\partial\rho(r)/\partial\mu)_v \qquad (3)$$

Equation 3 can also be written as

$$s(r) = [\partial\rho(r)/\partial N]_v[\partial N/\partial\mu]_v = f(r)S \qquad (4)$$

Thus local softness contains the same information as the Fukui function f(r) plus additional information about the total molecular softness, which is related to the global reactivity with respect to a reaction partner, as stated in the HSAB principle. Using the finite difference approximation, S can be approximated as:

$$S = 1/(\mathrm{IE} - \mathrm{EA}) \qquad (5)$$

where IE and EA are the first vertical ionization energy and electron affinity of the molecule, respectively. Atomic softness value can easily be calculated by using eq 4, namely:

$$s_k^{+} = [q_k(N + 1) - q_k(N)]S$$

$$s_k^{-} = [q_k(N) - q_k(N - 1)]S \qquad (6)$$

$$s_k^{o} = S[q_k(N + 1) - q_k(N - 1)]/2$$

In the present study, all calculations have been carried out using density functional theory with B3LYP[20,21] exchange correlation functional and 6-31G(d,p) basis set. Geometries of all the 12 dipolarophiles given in Table 1 and the molecule HN≡C were fully optimized. Single point calculations of the cation and anion of each molecule at the geometry of the neutral molecule (demanded for constant v(r)) were also carried out to evaluate Fukui functions and global and local softnesses. The condensed Fukui functions and atomic softnesses are evaluated by using eqs 2 and 6, respectively. The gross atomic charges are evaluated by using the technique of elcetrostatic potential (ESP) driven charges. It is well known that Mulliken charges are highly basis set dependent, whereas ESP driven charges show less basis set dependence[22,23] and are better descriptors of the molecular electronic density distribution. All calculations have been carried out using Gaussian 94 program package,[24] atomic charges are calculated using the MK option.

Table 1. Global Softness, Condensed Fukui Functions, and Atomic Softnesses for Various Dipolarophiles and the Molecule HNC Calculated by DFT Using B3LYP Functional and 6-31G(d,p) Basis Functions. Data Are in Atomic Units

molecule	S	atom (Y)[a]	f^+	s^+	sd[b]
HN≡C	1.694	C	1.11[c]	1.88[c]	
$H_2C{=}SiH_2$	2.733	C	−0.11	−0.31	2.19
		Si*	0.84	2.31	0.43
$H_2C{=}PH$	2.487	C*	0.16	0.41	1.47
		P	0.69	1.72	0.16
$H_2C{=}NH$	2.049	C*	0.49	1.00	0.88
		N	0.27	0.56	1.32
$H_2C{=}O$	2.121	C*	0.61	1.30	0.58
		O	0.21	0.45	1.43
$H_2C{=}S$	2.887	C*	0.23	0.68	1.20
		S	0.61	1.75	0.13
$H_2Si{=}PH$	3.071	Si*	0.50	1.55	0.33
		P	0.44	1.36	0.52
$H_2Si{=}NH$	2.559	Si*	0.85	2.16	0.28
		N	0.08	0.22	1.66
$H_2Si{=}O$	2.481	Si*	0.94	2.34	0.46
		O	0.04	0.10	1.78
$H_2Si{=}S$	3.037	Si*	0.70	2.13	0.25
		S	0.30	0.91	0.97
HP=O	2.789	P*	0.80	2.22	0.34
		O	0.13	0.36	1.52
HP=S	3.443	P*	0.53	1.83	0.05
		S	0.42	1.44	0.44
HP=NH	2.751	P*	0.77	2.11	0.23
		N	0.18	0.48	1.40

[a] Preferred site of attack is shown by the * on the atom and is indicated on the basis of the difference in transition state energy calculations (see ref 2). [b] sd represents the absolute difference between softness of electrophilic attack of the carbon atom of HNC and softness of nucleophilic attack of the atom Y of the dipolarophile. [c] For HNC, the values correspond to f^- and s^-.

Let us now consider the addition of HN≡C to dipolarophiles. HN≡C acts as a nucleophile in such addition reactions. This can be confirmed from the IE and EA differences of the HN≡C and the dipolarophiles. For almost all the cases considered here, the transfer of electron is energetically much more favorable from HN≡C to the dipolarophile. For CH_2NH, however, the energy required to put an electron from the HN≡C is 342 kcal/mol whereas the reverse process needs 335 kcal/mol. But such a small difference may arise from the theoretical estimation of IE and EA; particularly EA is very

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(14) Sengupta, D.; Chandra, A. K.; Nguyen, M. T. *J. Org. Chem.*, in press.

(15) Jazquez, J. L.; Méndez, F. *J. Phys. Chem.* **1994**, *98*, 4591.

(16) Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson and Ross: Stroudsville, PA, 1973.

(17) Damoun, S.; Woude, G. Van de; Méndez, F.; Geerlings, P. *J. Phys. Chem.* **1997**, *101*, xxx.

(18) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

(19) Pearson, R. G.; Parr, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.

(20) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(21) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(22) Proft, F. D.; Martin, J. M. L.; Geerlings, P. *Chem. Phys. Lett.* **1996**, *250*, 393.

(23) Geerlings, P.; Proft, F. D.; Martin, J. M. L. In *Recent Developments in Density Functional Theory* (Volume 5 in *Theoretical and Computational Chemistry*) Seminario, S., Ed.; Elsevier: Amsterdam, 1996; pp 773−809.

(24) Gaussian 94, Revision C.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995.

sensitive to the methods of calculation. Therefore, we are not putting much importance to this odd case. As mentioned earlier, the initial attack can be at either of the two heteroatoms of the dipolarophile (see **I** and **II**). However, the attack on one atom is energetically favored over the other. As the HN≡C attack is nucleophilic in character, we need to consider the Fukui function (f_c^+) or local softness (s_c^+) of nucleophilic attack on the dipolarophile. First, we consider the addition of HN≡C to the dipolarophiles $H_2C{=}X$ (X = NH, O, SiH_2, PH, S). Table 1 presents the condensed Fukui function values and atomic softnesses of the dipolarophiles (f_x, s_x) and HN≡C. The preferred site of attack is also mentioned in Table 1. Previous ab initio calculations[2] showed that for all the $H_2C{=}X$ dipolarophiles, the TS corresponding to a C attack is energetically favorable except in the case of X = SiH_2, where Si attack is preferable. Considering the proposition of Gazquez and Mendez,[15] one expects that initial attack should be on that atom of the dipolarophile which has its softness value closer to that of the carbon atom of HN≡C. Table 1 depicts the difference in softness values (referred to as sd) for a nucleophilic attack on the atoms in the dipolarophile and for an electrophilic attack on the carbon of HNC. It is expected that among the two sites of attack, the one having the lower sd value will be preferred. Table 1 shows that this is indeed the case, except for CH_2PH and CH_2S. In the latter dipolarophiles, the phosphorus and sulfur atoms have larger Fukui functions for nucleophilic attack than the carbon and also have smaller sd values; the preferred site of attack corresponding to a smaller energy barrier is actually the carbon atom in both cases. It should be noted that for CH_2PH the energy difference between both TS **I** and **II** is calculated to be very small (only 3.6 kcal/mol).[2] In the case of CH_2S the discrepancy may arise from the fact that the present predictions are based only upon the isolated molecule properties and that the larger size and the presence of lone pairs of electrons in sulfur may create larger electronic repulsions to change the whole situation.

Now consider the HNC attack on the second set of dipolarophiles $H_2Si{=}X$ (X = NH, O, PH, S). Here, Si attack is always energetically favorable compared to X attack.[2] In this series, it is gratifying to see that local softness values itself and sd values predict the same asynchronism. The sd values are consistently lower for the Si attack. In all the cases mentioned above, the site with a smaller sd value also possess larger Fukui function value for nucleophilic attack, and thus it is expected that it would be more reactive toward a nucleophile.

In an attempt to establish the generality of the present approach, a final set of dipolarophiles, $HP{=}X$ (X = NH, O, S), has also been considered. It has been observed from earlier theoretical calculations[2] that for all the three dipolarophiles, P attack is energetically favorable. However, in the case of NH=PH, the transition structures corresponding to P and N attacks are almost similar in energy. One can observe from Table 1 that the sd values are lower for the P attack as compared to the N, O, and S attacks for the three $HP{=}X$ dipolarophiles.

In summary, the DFT-based reactivity descriptors such as Fukui functions and local softnesses can be useful in the interpretation of the asynchronism in the bond formation during addition reactions of isocyanides to dipolarophiles. The initial attack often takes place on that atom of the dipolarophile which possesses a softness value closer in magnitude to that of the isocyanide carbon. This is in accord with the proposal of Gazquez and Mendez[15] and tested in the case of [2 + 2] cycloadditions.[17] In addition, the sites with larger values of Fukui functions are also the preferred sites of attack. Although some exceptions can be observed where other factors such as electronic repulsions or stereoelectronic effects are likely to be predominant, it is gratifying to notice that it is possible to explain the asynchronism in [2 + 1] cycloaddition of isocyanide to different kinds of dipolarophiles by using simple DFT-based reactivity descriptors. It is more worthwhile due to the fact that predictons are made only from the individual molecular properties without doing any elaborative supermolecular calculations. In this sense, the DFT descriptors provide us with more rigorous alternatives than the classical frontier orbital analysis. It should also be mentioned that although the Fukui functions and local softnesses have their origin in DFT, the concepts can be used in any other quantum chemical theories as well, such as Hartree–Fock theory. In fact, we carried out a parallel MP2 calculation for all the systems reported here, and the observations were the same.

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