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Electrophilicity and Nucleophilicity Index for Radicals

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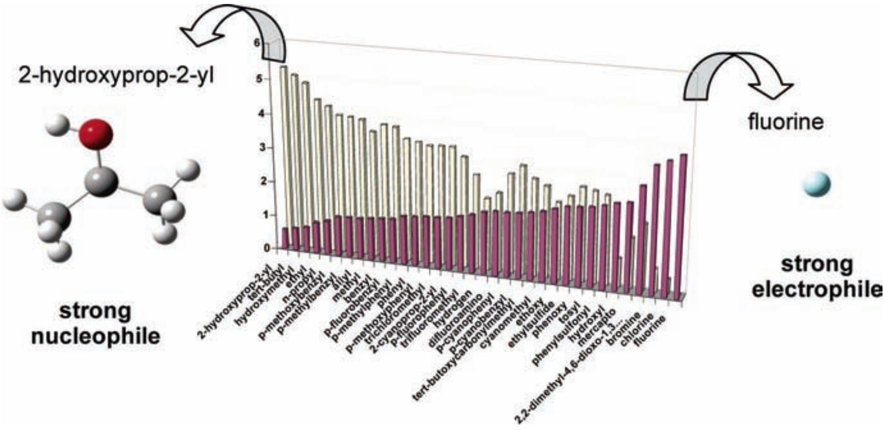
ABSTRACT



Radicals can be regarded as electrophilic/nucleophilic, depending on their tendency to attack sites of relatively higher/lower electron density. In this paper, an electrophilicity scale, global as well as local, and a nucleophilicity scale for 35 radicals is reported. The global electrophilicity scale correlates well with the nucleophilicity scale, suggesting that these concepts are inversely related.

Ever since Ingold[1] introduced the concepts “electrophile” and “nucleophile”, associated with electron-deficient and electron-rich species, respectively, there have been numerous attempts to classify atoms, molecules, and charged species within empirical scales of electrophilicity and nucleophilicity.[2−6] Although important for radical reactions, little information is found on the classification of radicals according to electrophilicity and nucleophilicity.[7,8] Nonetheless, it can be stated that the nature of the radical has an effect on which reactive sites in a substrate are more likely to be attacked, i.e., an electrophilic radical will more likely attack electron-rich sites of the substrate, while a nucleophilic radical prefers the electron-poor sites. A remarkable example is the copolymerization of vinyl acetate and methyl acrylate. The nucleophilic radical from vinyl acetate prefers to add to the electrophilic acrylate. The new radical is electrophilic and

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(1) Ingold, C. K. *Chem. Rev.* **1934**, *15*, 225.

(2) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141.

(3) (a) Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *76*, 1540. (b) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 161. (c) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

(4) (a) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348. (b) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

(5) Legon, A. C.; Millen, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 356.

(6) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(7) Heberger, K.; Lopata, A. *J. Org. Chem.* **1998**, *63*, 8646.

(8) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

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will therefore add to the nucleophilic vinyl acetate, resulting in a nucleophilic polymer radical. The new radical adds again to the acrylate. The cycle repeats endlessly, leading to the formation of an alternating copolymer.[9] In this paper, an electrophilicity scale, global as well as local, and a nucleophilicity scale for a number of radicals will be introduced.

On the basis of the work of Maynard et al.[10] and within the context of Conceptual Density Functional Theory,[11] Parr et al.[12] defined the global electrophilicity index ω as

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

where μ is the electronic chemical potential[13] and η is the chemical hardness.[14] These two quantities were calculated by using the vertical ionization energy I and electron affinity A. More information can be found in the Supporting Information. The electrophilicity index measures the energy stabilization, when an optimal electronic charge transfer from the environment to the system occurs.

To describe the electrophilic character of a reactive site within a molecule, a local electrophilicity index $\omega(\mathbf{r})$ can be proposed:[15,16]

$$\omega(\mathbf{r}) = \omega\, f^+(\mathbf{r})\ (=\omega^+(\mathbf{r})) \qquad (2)$$

with $f^+(\mathbf{r})$ the Fukui function for nucleophilic attack.[17] For the computation of $f^+(\mathbf{r})$ the Finite Differences Approximation (FDA) has been used (see the Supporting Information). This Fukui function can be condensed to atoms, using electronic population analyses. In this paper, atomic populations were obtained with the NPA method.[18] For the analysis of electrophile−nucleophile interactions, $\omega^+(\mathbf{r})$ is a better reactivity descriptor than the corresponding Fukui function, because the local electrophilicity index is a product of a global (ω) and a local index ($f^+(\mathbf{r})$).[19] The condensed-to-atom k variant is defined as:

$$\omega_k = \omega\, f_k^+\ (=\omega_k^+) \qquad (3)$$

Note that the electrophilicity index leads to absolute scales, solely dependent on the electronic characteristics of the electrophile and therefore independent of the nucleophilic partner.

Table 1. Global Electrophilicity Index ω, Local Electrophilicity Index Condensed on the Radical Center ω^+_{rc}, and Nucleophilicity Index ω^- for Our Database of 35 Radicals (B3LYP/6-311+g(d,p))[a]

radical	ω	ω^+_{rc}	ω^-
2-hydroxyprop-2-yl	0.581	0.254	0.525
***tert*-butyl**	0.651	0.376	0.505
hydroxymethyl	0.717	0.559	0.486
ethyl	0.891	0.712	0.442
n-propyl	0.980	0.693	0.425
***p*-methoxybenzyl**	1.138	0.490	0.402
***p*-methylbenzyl**	1.157	0.502	0.400
allyl	1.161	0.537	0.396
methyl	1.209	1.188	0.364
benzyl	1.239	0.546	0.388
***p*-fluorobenzyl**	1.265	0.571	0.384
p-methylphenyl	1.384	0.781	0.353
phenyl	1.405	0.811	0.348
p-methoxyphenyl	1.458	0.834	0.340
trichloromethyl	1.480	0.693	0.342
2-cyanoprop-2-yl	1.495	0.699	0.344
p-fluorophenyl	1.579	0.929	0.319
trifluoromethyl	1.672	1.183	0.271
hydrogen	1.788	1.788	0.207
difluoroamino	1.849	1.257	0.226
p-cyanophenyl	1.857	1.062	0.285
***p*-cyanobenzyl**	1.878	0.698	0.311
***tert*-butoxycarbonylmethyl**	1.930	1.208	0.278
cyanomethyl	2.003	1.286	0.261
ethoxy	2.114	1.429	0.219
ethylsulfide	2.214	1.827	0.240
phenoxy	2.236	0.649	0.269
tosyl	2.283	0.594	0.263
phenylsulfonyl	2.358	0.621	0.254
hydroxyl	2.462	2.378	0.082
mercapto	2.520	2.475	0.145
2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl	3.017	1.422	0.189
bromine	3.614	3.614	0.066
chlorine	3.772	3.772	0.042
fluorine	3.954	3.954	0.000

[a] All values are in eV. The radicals in bold have already been studied by Héberger and Lopata.[7]

Although less trivial, different definitions for a nucleophilicity index have been proposed. On the basis of the assumption that electrophilicity and nucleophilicity are inversely related to each other, Chattaraj et al.[20] suggested a multiplicative inverse of the electrophilicity index ($1/\omega$), as well as an additive inverse ($1 - \omega$).

Recently, Jaramillo et al.[21] introduced a new empirical model, depending on the electrophilic system, and suggested that the nucleophilicity index can be written as:

$$\omega^- = \frac{1}{2}\frac{(\mu_A - \mu_B)^2}{(\eta_A + \eta_B)^2}\eta_A \qquad (4)$$

assuming that A is the nucleophile and B is the electrophile. Hence, the corresponding nucleophilicity scale is of a relative nature, in contrast to the electrophilicity scale (eq 1). Defining

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(9) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, UK, 2001; pp 1045−1050.

(10) Maynard, A. T.; Huang, M.; Rice, W. G.; Covell, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 11578.

(11) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

(12) Parr, R. G.; Von Szentpaly, L.; Liu, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 1922.

(13) Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801.

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

(15) Perez, P.; Toro-Labbe, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* **2002**, *67*, 4747.

(16) Chamorro, E.; Chattaraj, P. K.; Fuentealba, P. *J. Phys. Chem. A* **2003**, *107*, 7068.

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

(18) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(19) Roy, R. K.; Usha, V.; Paulovic, J.; Hirao, K. *J. Phys. Chem. A* **2005**, *109*, 4601.

a local version of the nucleophilicity index is more complicated because of difficulties in defining a local hardness.

For this study, a database of 35 radicals has been put together, including carbon-, nitrogen-, oxygen-, and sulfur-centered radicals, as well as some halogens, thus comprising a representative set of radicals for applications in organic chemistry (see Table 1). The structures of all 35 radicals can be found in the Supporting Information. These radicals are keystones in numerous studies on radical addition reactions toward (substituted) ethenes. For 15 radicals, experimental rate constants of additions toward a set of alkenes are known; for detailed information, we refer to the work of Héberger and Lopata.[7,22] This set of 15 radicals was expanded with other radicals frequently used in free radical reactions.[23]

For the 35 radicals in our database, a theoretical global electrophilicity scale, as displayed in Figure 1, is obtained, using eq 1. The values are listed in Table 1. As expected, the electrophilicity index is the highest for the electronegative halogens (F-, Cl-, and Br-radical). The (hydroxy)alkyl-radicals are the least electrophilic radicals in the database, because of the presence of the electron-donating alkyl groups (with the exception of hydroxymethyl).[24−26] Fifteen radicals of this list have already been classified as electrophilic or nucleophilic, based on Principal Component Analysis (PCA) of experimental and theoretical reaction data.[7] The agreement with our electrophilicity scale for radicals is very good, even though our scale is absolute. Héberger and Lopata[7] divided the radicals into different groups as indicated by the vertical lines in Figure 1. Table 2 shows a detailed comparison of the 15 radicals, classified according to nucleophilicity/electrophilicity as proposed by PCA and by the (global) electrophilicity index in this work. According to the magnitude of ω, the radicals are positioned into the same groups as with PCA. This suggests that a small ω-value indicates that the radical can be designated as nucleophilic. As a first guess, the division in electrophilic/nucleophilic radicals is situated around $\omega = 2$. Note, however, that the transition from nucleophilic to electrophilic character is not very sharp. This is reflected in the differences in classification of the *tert*-butoxycarbonylmethyl and the cyanomethyl radical. Experimental studies indicate that both radicals are borderline cases.[27,28] Indeed, there is some disagreement about the character of these radicals. Fischer et al.[29] suggest that both radicals are weakly electrophilic, while Héberger and Lopata[7] found that these radicals are weakly nucleophilic, thus agreeing with the findings in this work. Note also that in this work the trifluoromethyl and the trichloromethyl radicals are designated as weakly nucleophilic, which is in contrast with earlier findings in the literature, where the radicals are found to be electrophilic.[30]

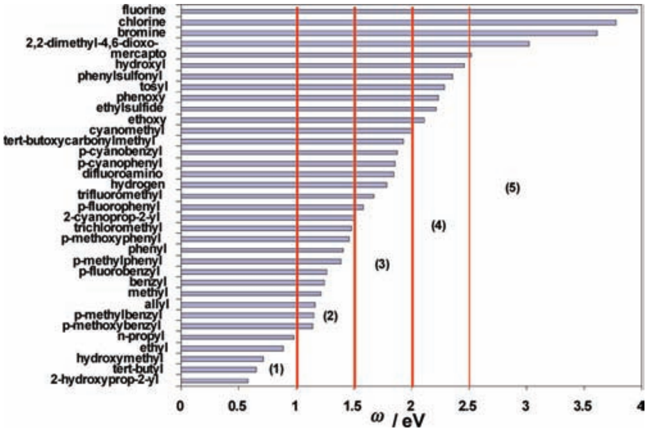

Figure 1. Electrophilicity index ω for a total of 35 radicals and their classification (see text): (1) strong nucleophile; (2) moderate nucleophile; (3) weak nucleophile; (4) weak to moderate electrophile; and (5) strong electrophile.

Table 2. Classification of 15 Radicals According to Electrophilicity/Nucleophilicity: Comparison between PCA[7,18] and the Global Electrophilicity Index ω

character	PCA	ω
strong nucleophile	2-hydroxyprop-2-yl tert-butyl hydroxymethyl	2-hydroxyprop-2-yl tert-butyl hydroxymethyl
moderate nucleophile	p-methoxybenzyl p-fluorobenzyl p-methylbenzyl benzyl methyl	p-methoxybenzyl p-methylbenzyl methyl benzyl p-fluorobenzyl
weak nucleophile	p-cyanobenzyl 2-cyanoprop-2-yl tert-butoxycarbonylmethyl cyanomethyl	2-cyanoprop-2-yl p-cyanobenzyl tert-butoxycarbonylmethyl cyanomethyl
moderate electrophile	tosyl phenylsulfonyl	tosyl phenylsulfonyl
strong electrophile	2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl	2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl

Figure 2 presents the local electrophilicity index, condensed on the radical center (eq 3). The numerical values can be found in Table 1. Note that the local electrophilicity index, condensed on the radical center, results in an *electrophilicity* scale, because the radical *center* has an electrophilic character. Comparing the local electrophilicity scale in Figure 2 with the global one (Figure 1), it is observed that the overall order remains the same but for a few radicals. Especially in the case of phenylsulfonyl, tosyl, and phenoxy,

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(20) Chattaraj, P. K.; Maiti, B. *J. Phys. Chem. A* **2001**, *105*, 169.

(21) Jaramillo, P.; Perez, P.; Contreras, R.; Tiznado, W.; Fuentealba, P. *J. Phys. Chem. A* **2006**, *110*, 8181.

(22) Héberger, K.; Lopata, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 91.

(23) Volovik, S. V.; Dyadyusha, G. G.; Staninets, V. I. *Teor. Eksp. Khim.* **1980**, *16*, 107.

(24) Münger, K.; Fischer, H. *Int. J. Chem. Kinet.* **1985**, *17*, 809.

(25) Héberger, K. Fischer, H. *Int. J. Chem. Kinet.* **1993**, *25*, 913.

(26) Wu, J. Q.; Fischer, H. *Int. J. Chem. Kinet*. **1995**, *27*, 167.

(27) Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063.

(28) Beranek, I.; Fischer, H. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Amsterdam, The Netherlands, 1989; pp 303−316.

(29) Wu, J. Q.; Beranek, I.; Fischer, H. *Helv. Chim. Acta* **1995**, *78*, 194.

(30) Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, *36*, 701.

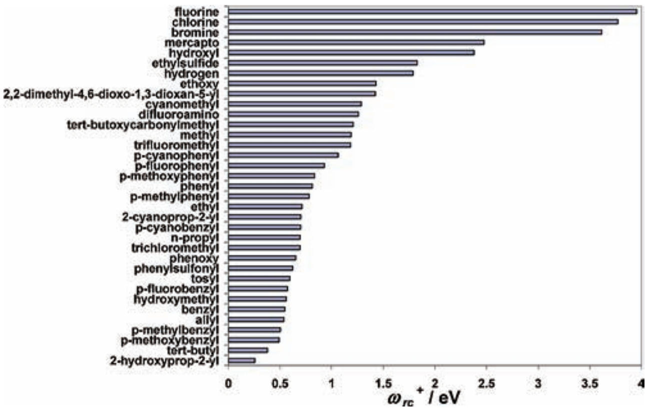

Figure 2. Local electrophilicity index for a total of 35 radicals, condensed on the radical center $\omega_{rc}{}^{+}$.

and to a lesser degree for 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl and *p*-cyanobenzyl, a large difference in value between the global and local electrophilicity index is detected. All these radicals are situated at the top of the global electrophilicity scale, but due to a low value of the Fukui function for nucleophilic attack f^{+}, the radical center is not as electrophilic as one would expect based on the ω-value of the radical. Delocalization effects have to be taken into account. In phenylsulfonyl, tosyl, and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl, the unpaired electron is delocalized over the oxygen atoms. In both phenoxy and *p*-cyanobenzyl, delocalization of the unpaired electron over the benzene ring takes place. In all these cases, the radical center is being stabilized, showing less reactivity toward substrates (low value of $f_k{}^{+}$).

Next, for the first time, a nucleophilicity scale for radicals is introduced (Table 1). Eq 4 is used to calculate the nucleophilicity index, relative to the most electrophilic radical in our database, i.e., fluorine ($\omega^{-} = 0$). Figure 3 displays the resulting nucleophilicity scale for the 35 radicals together with the global electrophilicity scale, as was depicted in Figure 1. The two scales seem to be correlated, though not perfectly: the coefficient of determination R^2 is about 0.91. Especially in the zone of weak electrophilic/nucleophilic radicals, practically no correlation is found. According to the global electrophilicity index, some radicals seem to be less electrophilic than expected, namely trifluoromethyl, difluoroamino, ethoxy, hydroxyl, and hydrogen. For these radicals a high electronic chemical potential (in absolute value) is found, i.e., a high initial attraction for electrons. This result is in line with what is generally assumed about their electrophilic character. In addition, a large value—more than 10 eV—of the chemical hardness η is observed, i.e., a low capacity to accommodate charge, resulting in a decrease of the electrophilicity index, as indicated by our electrophilicity scale.

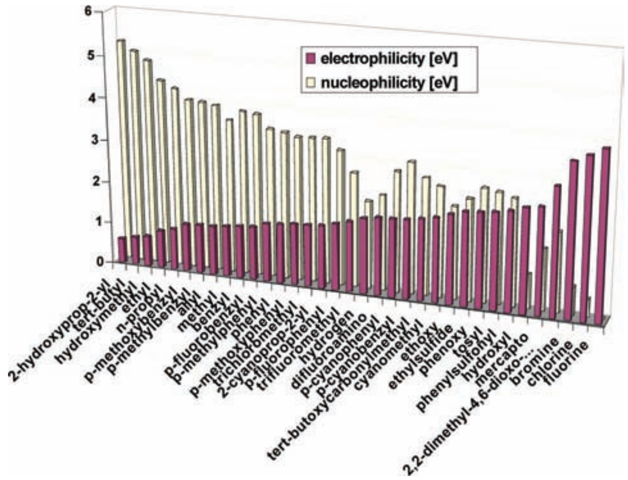

Figure 3. Electrophilicity versus nucleophilicity (value of ω^{-} times 10).

In summary, an electrophilicity scale, global and local, as well as a nucleophilicity scale for a set of important radicals for organic chemistry has been proposed. The global electrophilicity index and the nucleophilicity index correlate well, but for some weak electrophiles and nucleophiles and the hydroxyl radical, for which very large values of the chemical hardness and only intermediate to large values of the electronic chemical potential are encountered. For 15 radicals, a comparison between the classifications obtained with the global electrophilicity index and PCA was made. The agreement is astonishingly good, considering that our theoretical electrophilicity scale is absolute and free from input of reaction data (neither experimental nor theoretical).

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Supporting Information Available: Structures of all 35 radicals and computational methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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