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Theoretical Evaluation of the Global and Local Electrophilicity Patterns of Singlet Carbenes

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The global electrophilicity pattern of singlet carbenes has been evaluated using an absolute scale based on reactivity indexes and an extension of it to describe the local electrophilicity power of molecules. The predicted electrophilicity values agree well with the relative experimental scale, based on kinetic data proposed by Moss [*Acc. Chem. Res.* **1989**, *22*, 15]. A good qualitative comparison is found between the theoretical and experimental carbene-*philicity*. The theoretical model is able to accommodate within a unique scale those carbenes evaluated as electrophilic, ambiphilic, and nucleophilic species. The local analysis provides additional information about electrophilic activation/deactivation patterns induced by substituent groups in the molecule.

1. Introduction

Carbenes belong to a class of highly reactive carbon intermediates where the carbon atom has two nonbonding electrons. Methylene (:CH_2) is the reference structure giving rise to the general nomenclature that characterize divalent carbon species. These structures are simply named as substituted derivatives of methylene. They include the important family of phenylcarbenes PhCR, and halocarbenes (X_2C) species. Also included in this series are the $H_2C{=}C$: structures that incorporate vinylidenes. These are species including a double bonded divalent carbon. This last series of compounds encompasses both carbon monoxide (:C = O), and isonitriles (RN=C:) structures[1].

Carbenes are usually thought of as being sp^2-hybrized structures, yet their spin multiplicity may correspond to a singlet or triplet ground state (GS). The singlet GS leaves a vacant p-orbital thereby conferring a high electrophilic character to this structure. The triplet GS on the other hand has two nonbonding sp^2 and p-orbitals containing one electron each.[1] Triplet carbenes are therefore characterized by biradical rather than ionic properties. The reactivity pattern of carbenes is rather wide and includes cycloaddition reactions to alkenes, cycloaddition to 1,3 dienes, cycloaddition to arenes and alkynes and insertion to C−H and X−H bonds.[2,3]

Singlet carbenes being highly electron deficient react with nucleophiles including tertiary amines, phosphines, ethers, sulfides, and sulfoxides.[4,5] The nature of the substituents has an important effect on the electronic properties of carbenes. For example, as the carbene substituents R in :CR_2 become a better π-donor, the ground state changes from triplet to singlet state. Halogen substitution results in singlet GS. For instance, dichlorocarbene is a singlet ground state due to electron donation from chlorine to the vacant p-orbital of carbon that stabilizes the singlet state through dipolar resonance structures, although because of the relative electronegativities there is a strong σ-polarization in the opposite direction.[1,2] Therefore, singlet carbenes are in general highly electrophilic species.[1−4]

Electrophilicity of carbenes was first experimentally evaluated by Moss et al., using a kinetic model based on the addition reaction of carbenes to simple alkenes to yield cyclopropanes.[6−8] The proposed classification incorporates within a unique scale, species having electrophilic, ambiphilic, and nucleophilic properties generically named *philicity*.[6−11] The *philicity* scale is defined by a unique empirical index m_{CXY}, where CXY are the carbene species, measured from the least-squares slope of $\log(k_i/k_o)_{CXY}$ vs $\log(k_i/k_o)_{CCl2}$ plot. The quantity k_i is the rate constant for the reaction toward a particular alkene pair, measuring the relative response, or selectivity of carbene CXY, to changes in the alkene structure. The quantity k_o is the rate constant adjusted to a standard alkene. This model has been used by other authors to evaluate an increasing number of singlet carbenes,[12,13] so that a significant amount of information has accumulated over the past decades. The experimental scale has been the subject of successive modifications, despite the predictive semiquantitave theory involved and the significant body of congruent experimental data. This data base is an excellent source for the validation of theoretical models of electrophilicity based on reactivity indexes.

From a theoretical point of view, the usefulness of having a hierarchy of electrophilicity, built up from electronic structure information, is advantageous for several reasons: first of all, although the experimental scale has a relative character and normally applies to families of molecules, the theoretical scales based on the electronic structure of molecules have a more universal character, as they can be applied to a larger body of molecules presenting wide structure and bonding properties. Another relevant advantage of a theoretical scale based on global reactivity indexes is that their local counterpart permits the prediction of how the global property is distributed in the different sites of the molecules. This is of particular importance at the active site(s) of a molecule. Consider for instance the variations in the local properties induced by field effects including substituent, solvent, and catalysts, which may be used as a reliable model for electrophilic activation (super-electrophilicity). All of these arguments are of course valid once the theoretical scale has been validated against the experimental one.

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TABLE 1: Global Theoretical and Experimental Philicity Values of Singlet Carbenes

	I_{theo} (eV)	A_{theo} (eV)	μ (eV)	η (eV)	ω(eV)	ω (eV)[a]	m_{CXY}	observed *philicity*	predicted *philicity*	ΔN_{max}
Group I. Electrophilic Carbenes										
CH_2-T	10.45	0.23	−5.34	10.22	1.40	1.56			E	0.523
MeCF	9.71	0.00	−4.85	9.71	1.21				E	0.500
MeCCl	9.16	0.68	−4.92	8.49	1.43		0.58[6,8]	E[7]	E	0.580
CF_2	12.31	−0.02	−6.15	12.34	1.53	1.49	1.47[6,8]	E[7]	E	0.498
CHF	10.70	0.47	−5.59	10.22	1.53	1.47			E	0.546
MeCBr	8.99	0.91	−4.95	8.08	1.52				E	0.612
PhCF	8.59	1.11	−4.85	7.47	1.57		0.96[6,8]	E[7]	E	0.649
PhCCl	8.18	1.51	−4.85	6.66	1.76		0.71[7]	E[7]	E	0.727
PhCBr	8.06	1.67	−4.86	6.40	1.85		0.64[7]	E[7]	E	0.760
CCl_2	10.16	1.46	−5.81	8.70	1.94	1.93	1.00[7]	E[7]	E	0.668
MeCCN	9.44	2.12	−5.78	7.33	2.28				E	0.789
PhCCN	8.28	2.37	−5.33	5.92	2.40				E	0.900
Group II. Ambiphilic Carbenes										
MeCOMe	8.34	−0.67	−3.84	9.01	0.82		1.21[6,7]	A[6]	N	0.426
MeOCF	10.38	−0.56	−4.91	10.94	1.10		1.85[7,8]		A	0.449
PhCOMe	7.80	0.33	−4.07	7.47	1.11		1.34[7]	A[7]	A	0.544
MeOCCl	9.60	−0.18	−4.71	9.78	1.13		1.59[7,8,11]	A[7]	A	0.481
MeOCBr	9.32	−0.08	−4.62	9.41	1.13				A	0.491
PhOCF	9.38	−0.09	−4.64	9.47	1.14		1.74[7,11]	A[7]	A	0.490
PhOCCl	9.10	0.44	−4.77	8.66	1.31		1.49[7,10,11]	A[7]	A	0.550
PhOCBr	8.96	0.60	−4.78	8.36	1.36				A	0.571
Group III. Nucleophilic Carbenes										
$PhCNMe_2$	6.98	−0.37	−3.31	7.35	0.74				N	0.450
MeOCOPh	8.53	−0.44	−4.04	8.97	0.91		2.11[8,9]	N[7]	N	0.451
$C(OMe)_2$	8.98	−0.52	−4.23	9.50	0.94		2.22[7]	N[7]	N	0.446
$MeCNMe_2$	7.40	−0.45	−3.47	7.85	0.77		2.91[8]	N[7]	N	0.442
$C(OH)_2$	9.85	−0.61	−4.62	10.46	1.02		2.71[8]	N[7]	N	0.441

[a] Experimental values of I and A from ref 22. See the text for details. Subscripts in columns 8 and 9 refer to the experimental sources of *philicity*.

2. Model Equations

The global electrophilicity, ω, of atoms and molecules has been recently defined by Parr et al. as[14]

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

in terms of the electronic chemical potential μ (the negative of electronegativity) and the chemical hardness η. This definition introduces in a balanced way the propensity of the system to acquire an additional amount of electronic charge ΔN_{max} , measured by the square of the electronegativity and at the same time the resistance of the system to exchange electronic charge with the environment measured by the chemical softness S (the inverse of the chemical hardness).[15]

The amount of additional electronic charge ΔN_{max} that stabilizes the electrophile is given by[14]

$$\Delta N_{max} = -\frac{\mu}{\eta} \tag{2}$$

The electrophilicity concept has been recently generalized to define a local electrophilicity, ω_k, condensed on the atom k in the molecule, which may be either defined by[16,17]

$$\omega_k = \frac{\mu^2}{2} s_k^{+} \tag{3}$$

in terms of the electrophilic local softness s_k^+.[15] An alternative expression for the local electrophilicity is

$$\omega_k = \omega\, f_k^{+} \tag{4}$$

where the exact relationship $s_k^+ = f_k^+ S$, relating the local softness s_k^+ with the electrophilic Fukui function f_k^+ and the global softness S, has been used.[15] Although eq 3 implies that the more electrophilic site in the molecule will coincide with the softest site, eq 4 implies that the global electrophilicity ω will be distributed following the electrophilic Fukui function (i.e., the Fukui function for nucleophilic attacks $f_k^+(\mathbf{r})$). Equation 4 also shows that the more electrophilic site will be the one presenting the highest value of the Fukui function, i.e., the active site of the molecule.

3. Results and Discussion

To evaluate how the global electrophilicity index ω compares with the classification of the global *philicity* pattern of carbenes according to Moss's scale defined by the m_{CXY} empirical index, we evaluated this property using eq 1. The electronic chemical potential μ and chemical hardness η, have been approached by $\mu = -(I + A)/2$ and $\eta = (I - A)$, in terms of the vertical ionization potential I and electron affinity A, for the singlet ground state of the carbenes included in Table 1, at the B3LYP/6-311++G(d,p) level of theory using the Gaussian 98 suite of programs.[18] To validate the predicted pattern of *philicity* of carbenes, as described by the ω index, we first evaluated the vertical ionization potential and electron affinity that determines the values of μ, η and ω via eq 1. They are shown in Table 1. Also included in Table 1 is a comparison between theoretical and experimental I and A quantities for some electrophilic carbenes for which this information is available. Comparison of columns six and seven, shows that the estimated I and A quantities produce reliable values of the ω index for CF_2, CHF, and CCl_2.

According to the experimental classification of Moss et al., the carbenes having m_{CXY} values lower than 1.50 were classified as electrophilic carbenes (E); those having m_{CXY} values greater than 2.2 were classified as nucleophilic carbenes (N); and those having m_{CXY} values between 1.5 and 2.2 were classified as ambiphilic (A) species. Note that the theoretical scale ω follows an inverse order with respect to the experimental scale. Here, a high value of ω means a high electrophilicity. Within the theoretical scale, the electrophilic carbenes are characterized by an electrophilicity ω value ranging from 1.21 eV for MeCF to 2.40 eV for PhCCN. Ambiphilic species on the other hand, show ω values around unity. Nucleophilic carbenes are characterized within the theoretical classification by ω values lower than 1.02 eV. Note that the MeCOMe species that was classified as ambiphilic by Moss[6−11] appears within the theoretical scale in the frontier of the ambiphilic/nucleophilic carbenes. The comparison of the global electrophilicity pattern in both scales is excellent. It is also interesting to note that the carbenes predicted as electrophilic species show in general values of μ close or greater than −5.0 eV, the highest values of electronegativity within the series. These species quoted as group **I** in Table 1 are classified as electrophilic carbenes, in agreement with the scale of Moss et al.[6]

The ambiphilic species (group **II** in Table 1) on the other hand are less electronegative than the first group of electrophilic carbenes and more electronegative than the carbenes classified as nucleophiles (group **III** in Table 1). The variation in chemical hardness η is not regular within the whole series of carbenes. However, PhCCN, the most electrophilic species evaluated in the theoretical scale, has a relative high value of electronegativity and at the same time the lowest value in chemical hardness. The $MeCNMe_2$ species on the other hand, which is predicted in both scales as the most nucleophilic carbene, has the lowest value of electronegativity and a moderately high value in chemical hardness. The comparison between the experimental and theoretical scales of electrophilicity is however not quantitative, a result probably traced to the problems in predicting electron affinity values that determine both the electronegativity and hardness patterns according to to Parr's model of electrophilicity. Note also that the electrophilic carbenes have a charge capacity ranging from 0.5 and 0.9 e, whereas the ambiphilic and nucleophilic carbenes consistently have a lower charge capacity as measured by ΔN_{max} within a range [0.45−0.57] e and $\Delta N_{max} < 0.45$ e, respectively (see Table 1, last column).

Another aspect related to the global electrophilicity pattern of singlet carbenes is the analysis of substituent effects inducing electrophilic activation/deactivation. The activation/deactivation pattern will be discussed with respect to the global electrophilicity of the triplet ground state of methylene ($:CH_2(T)$) as reference and described by the quantity $\Delta\omega = \omega(\text{carbene}) - \omega(:CH_2(T))$. Methylene in its ground (triplet) state exhibits a global electrophilicity pattern of 1.40 eV. The results are summarized in Table 2, last column. Within the series of electrophilic carbenes (group **I** in Table 2), with the only exception of MeCF, chemical substitution at the carbon site results in electrophilic activation ($\Delta\omega > 0$) for the whole series. For the ambiphilic and nucleophilic series on the other hand (groups **II** and **III** in Table 2), chemical substitution results in electrophilic deactivation ($\Delta\omega < 0$), without exceptions.

Within the electrophilic carbene series, substitution of one hydrogen atom by a fluorine atom brings the electrophilicity pattern from 1.40 eV in methylene to 1.53 eV in fluorocarbene. This marginal enhancement in electrophilicity may be traced to a complex substituent effect that encompasses both the inductive effect of the σ-electron withdrawing capability of Fluorine atom (activating effect) and the π-electron releasing capability of fluorine (deactivating effect). Note that a second replacement of a hydrogen atom in methylene by a fluorine atom in CF_2 leads to an activation pattern similar to that predicted for the monosubstitution (see Table 2). Furthermore, double substitution of hydrogen atom in methylene results in an enhanced electrophilic activation in dichlorocarbene (from 1.40 to 1.94 eV), in agreement with the experimental results ($m_{CXY} = 1.0$ for CCl_2 and $m_{CXY} = 1.47$ for CF_2, see Table 1). For MeCCN and PhCCN, the enhanced electrophilicity pattern may be traced to an activating effect mainly due to the electron-withdrawing effect of the CN group and a marginal electron-releasing effect of the Me and Ph groups. Note also that the marginal activating affect is also shown within the subseries PhCX (X = F, Cl, and Br), which displays comparable electrophilicity patterns.

TABLE 2: Global and Local Electrophilicity, Electrophilic Fukui Function, and Relative Global ElectrophilicityValues of Singlet Carbenes

	ω(eV)	ω_C(eV)	f_C^+	$\Delta\omega$ (eV)
Group I. Electrophilic Carbenes				
CH_2-T	1.40	1.40	1.0000	0.00
MeCF	1.21	1.03	0.8499	−0.19
MeCCl	1.43	1.13	0.7927	0.03
CF_2	1.53	1.34	0.8753	0.13
CHF	1.53	1.41	0.9222	0.13
MeCBr	1.52	1.18	0.7800	0.12
PhCF	1.57	0.72	0.4554	0.17
PhCCl	1.76	0.81	0.4615	0.36
PhCBr	1.85	0.85	0.4583	0.45
CCl_2	1.94	1.48	0.7636	0.54
MeCCN	2.28	1.38	0.6055	0.88
PhCCN	2.40	0.98	0.4085	1.00
Group II. Ambiphilic Carbenes				
MeCOMe	0.82	0.68	0.8359	−0.58
MeOCF	1.10	0.92	0.8347	−0.30
PhCOMe	1.11	0.43	0.3911	−0.29
MeOCCl	1.13	0.91	0.8023	−0.27
MeOCBr	1.13	0.91	0.7978	−0.27
PhOCF	1.14	0.78	0.6826	−0.26
PhOCCl	1.31	0.90	0.6892	−0.09
PhOCBr	1.36	0.94	0.6866	−0.04
Group III. Nucleophilic Carbenes				
$PhCNMe_2$	0.74	0.35	0.4774	−0.66
$MeCNMe_2$	0.77	0.32	0.4219	−0.63
MeOCOPh	0.91	0.48	0.5262	−0.49
$C(OMe)_2$	0.94	0.73	0.7768	−0.46
$C(OH)_2$	1.02	0.86	0.8455	−0.38

Within groups **II** and **III** including ambiphilic and nucleophilic carbenes, the substituent effect is clearly deactivating. For instance, within group **II**, this result may be traced to the strong electron-releasing effect of the XO (X = Me and Ph) groups. Within group **III**, the cooperative electron-releasing effect of the MeO and OPh groups accounts for the decreasing of the electrophilicity pattern of these carbenes. Note that the deactivating effect promoted by the more powerful electron-releasing NMe_2 group results in an even more pronounced deactivating effect in the series of nucleophilic carbenes.

Another pertinent aspect regarding the *philicity* concept in connection with the reactivity and selectivity of molecules is related to the reactivity-selectivity rule. According to the reactivity−selectivity principle (RSP), reactive electrophiles are characterized by low selectivity, and less reactive electrophiles are characterized by high selectivity (normal RSP rule).[19,20] Within a theoretical framework, the comparison between the global electrophilicity, describing reactivity, and the local electrophilicity, describing selectivity, is useful to evaluate whether a normal or inverse reactivity−selectivity principle is fulfilled for a given reagent.[6] The local analysis is made with reference to the local *philicity* ω_C at the carbon center embedded in different chemical environments. The results are shown in Table 2 for the three groups of electrophilic, ambiphilic, and nucleophilic carbenes considered in the present study. For instance, for the subseries XCPh with X = F, Cl, and Br, within group **I** of electrophilic carbenes, the observed reactivity order measured in terms of the rate constants for the addition of XCPh to alkenes is BrCPh > ClCPh > FCPh,[6] in complete agreement with the reactivity order predicted from the global electrophilicity index ω quoted in Table 1: BrCPh ($\omega = 1.85$ eV) > ClCPh ($\omega = 1.76$ eV) > FCPh ($\omega = 1.52$ eV). However, the selectivity pattern described by the ω_C index quoted in Table 2 is predicted to follow an inverse reactivity−selectivity relationship:[6] BrCPh ($\omega_C = 0.85$ eV) > ClCPh ($\omega_C = 0.81$ eV) > FCPh ($\omega_C = 0.72$ eV). Note that this result may be traced to a global electrophilic activation, as the electrophilic Fukui function f_k^+ at the carbon center for all of the three carbenes is almost the same (ca. 0.46). A similar result is predicted for the ambiphilic subseries (group **II**) PhOCX (X = F, Cl, and Br), for which the reactivity−selectivity relationship seems to also follow an inverse RSP relationship (reactivity proportional to selectivity). For the nucleophilic carbenes subseries, with the only exception of $MeCNMe_2$, an inverse RSP rule is also predicted.

4. Concluding Remarks

The global electrophilicity pattern of singlet carbenes has been analyzed and compared with the experimental scale of *philicity* using an absolute scale based on electronic reactivity indexes. The theoretical scale accommodate within a unique scale those carbenes classified as electrophilic, ambiphilic, and nucleophilic. Inductive and resonance effects promoted by chemical substitution correctly accounts for the observed activating/deactivating patterns of *philicity* within the whole series of carbenes considered in the present study. The comparison between the local and global electrophilicity indexes were used to discuss inverse reactivity−selectivity relationships that are expected for this series of reactive intermediates.

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