JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 273–281
Published online 6 February 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.719

Relationship between nucleophilicity/electrophilicity indices and reaction mechanisms for the nucleophilic substitution reactions of carbonyl compounds

Paola Campodonico,[1] José G. Santos,[1]* Juan Andres[2] and Renato Contreras[2,3]

[1]Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 22, Chile
[2]Departament de Ciències Experimentals, Universitat Jaume I, Campus Riu Sec, E-12071 Castelló, Spain
[3]Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653-Santiago, Chile

Received 15 August 2003; revised 17 September 2003; accepted 24 September 2003

ABSTRACT: Theoretical electrophilicity and nucleophilicity scales, defined in terms of electronic reactivity indices, were tested for the reaction of a series of carbonates with neutral and charged reagents of varying nucleophilicity. The electrophilicity and nucleophilicity scales were used to rationalize some mechanistic aspects developed by these reacting systems: the greater the electrophilicity/nucleophilicity difference, the more concerted the reaction mechanism will be. Conversely, a small electrophilicity/nucleophilicty gap will in general be associated with a stepwise reaction mechanism. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: electrophilicity and nucleophilicity scales; electrophilicity/nucleophilicity difference; reaction mechanisms; substituent effects

INTRODUCTION

The reactions of carbonyl derivatives[1,2] with nucleophiles are processes that have received increasing attention. The available experimental information was mainly derived from kinetic and mechanistic studies of the reaction of these substrates in solution with reagents of varying nucleophilicity. The nucleophile series include neutral and charged species such as secondary alicyclic amines, anilines, quinuclidines, pyridines, alkoxides and phenoxides. Most of these reactions can be described as a nucleophilic attack at the C═O group of the substrates, which are, in most cases, the highest electrophilic sites. Depending on the nature of the electrophile–nucleophile pair, two general mechanisms are possible. In the first the interaction of the nucleophile with the electrophilic carbon may lead to the formation of a tetrahedral intermediate, from which the leaving group detaches. This mechanism is usually referred to as stepwise.[1,2] Another possibility is the concerted pathway,[1,2] in which the nucleophilic attack at the electrophilic carbon occurs concertedly with the leaving group departure within a single step pathway.

**Correspondence to:* J. G. Santos, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 22, Chile.
E-mail: jgsantos@puc.cl
Contract/grant sponsor: Fondecyt; *Contract/grant numbers:* 2010081; 1030548; 1990551.

A useful classification of these processes may also be achieved on the basis of electronic structural information condensed in the form of reactivity indices. For instance, it has been shown that chemical substitution on the diene–dienophile pair may cause a Diels–Alder (DA) reaction to proceed via a concerted or stepwise mechanism. Thus, the concerted mechanism is associated with a small difference in the electrophilicity/nucleophilicity power of the reacting systems, whereas a large gap in electrophilicity/nucleophilicity pattern normally leads to a more polar (stepwise) mechanism[3] in DA processes. A similar result has been reported by Cramer and Barrows for the cycloaddition reaction between the hydroxyallyl cation and dienes of varying nucleophilicity[4]. However, this result may not be a universal rule and we shall examine here the relationship between the electrophilicity/nucleophilicity difference and the reaction mechanism (concerted vs stepwise) for a series of nucleophilic substitution reactions. Such a classification requires the choice of an appropriate scale of nucleophilicity/electrophilicity, which, in the present work, is expressed in terms of electronic quantities defined on the basis of the theoretical framework outlined below. An excellent review that illustrates the usefulness of reactivity indices for the discussion of reactivity and selectivity appeared recently.[5]

The forming and breaking processes of covalent bonds during the interaction of electron-rich and electron-poor

centers, described as nucleophile–electrophile interaction,[6,7] is one of the fundamental processes in chemistry. Several attempts to classify the expected reactivity patterns from absolute scales of electrophilicity/nucleophilicity have been presented to date.[8–11] Electrophilicity (ω^+) has been defined recently by Parr *et al*. as the energy stabilization of a chemical species when it acquires an additional fraction of electronic charge from the environment.[12] A useful representation of this property in terms of electronic descriptors of reactivity, namely the electronic chemical potential μ and the chemical hardness η, allowed these authors to define an absolute scale of electrophilicity for atoms and molecules in their ground states. A quantitative representation of nucleophilicity (ω^-) could not, however, be deduced from the same electronic model since nucleophilic species behave differently, i.e. electrophilicity and nucleophilicity may not be the opposite ends of a unique scale. Whereas ω^+ measures the energy stabilization of a chemical species upon accepting electronic charge from the environment, the quantity ω^- may be associated with the energy change when the flow of charge from the environment is in the opposite direction. An interesting result for our present purpose is that, for negatively charged atoms, the minimum value of the electrostatic potential may be regarded as a measure of the interaction of the anion with a positive charge.[13,14] This implies that one might be able to estimate the nucleophilic power of molecules from the minimum value of the molecular electrostatic potential (MEP).The use of MEPs for predicting the reactivity of carbonyl groups has already been reported by Murray *et al*.[15] in a slightly different context. Even though there is not a rigorous procedure for generalizing this result of Sen and co-workers,[13,14] obtained for spherically symmetric electron densities to other symmetries, this approach yields surprisingly good results for a series of neutral and charged nucleophiles exhibiting a wide diversity of structural and bonding properties, as will be shown below.

In this paper, we present a static reactivity analysis of the reactions between carbonyl derivatives (the electrophiles) and neutral and charged reagents of varying nucleophilicity. The nucleophiles include secondary neutral alicyclic amines, anilines, quinuclidines and pyridines, and also alkoxide and phenoxide ions. The electrophilicity/nucleophilicity patterns of the substrate and reagents are then used to rationalize several of the fundamental kinetic and mechanistic aspects of these reactions.

MODEL EQUATIONS

Electrophilicity index

The quantitative definition of electrophilicity is based on a second-order model for the change in electronic energy as a function of the change in the number of electrons, ΔN, at constant external potential $\nu(\mathbf{r})$, namely[12,16,17]

$$\Delta E = \mu \Delta N + \eta \frac{\Delta N^2}{2} \tag{1}$$

where $\mu = -(I + A)/2 <$ and $\eta = \mathrm{I} - \mathrm{A}$ are the electronic chemical potential and chemical hardness defined in terms of the vertical ionization potential I and electron affinity A, respectively.

Based on this expression, Parr and co-workers[12,16,17] performed a simple variational calculation to obtain both the maximum electronic charge $\Delta N_{\max}$ that the electrophile may accept to stabilize its electronic energy and the global electrophilicity index $\omega^+ = -\Delta E$. The resulting expressions for these quantities are

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

and

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

Note that electrophiles, as chemical species capable of accepting electrons from the environment, decreases their energy ($\Delta E < 0$) in the direction of increasing N ($\Delta N > 0$), so that its electronic chemical potential ($\mu = \Delta E/\Delta N$) is always negative. The electronic chemical potential and chemical hardness were reported by Pearson to be almost unaffected by solvation.[18] Consequently, the electrophilicity pattern of molecules is almost unaffected by solvent[18,19] and the intrinsic (gas-phase) values suffice to characterize the propensity of the molecule to acquire additional electronic charge from the environment.

Nucleophilicity index

Compared with the electrophilicity index, the quantitative representation of nucleophilicity introduces some additional difficulties. While the ω^+ index is defined as a genuine global descriptor of reactivity, the definition of the ω^- index as the minimum value of the MEP,[13,20] i.e. as $\omega^- = \min\{\Phi(r_C)\}$, at the characteristic point in space, r_C, means that the latter is a local or semi-local (regional) quantity. This choice was dictated by a previous work in atoms showing that anions displayed a minimum value of MEP, and that the amount of electronic charge encompassed in the sphere $S(0, r_C)$ was equal to the atomic number Z.[13,14] This result led the authors to propose that the minimum value of MEP should be a measure of the strength of the interaction between an anion and a positive

charge, and therefore it should be related to the concept of nucleophilicity. Our approach assumes that the minimum value of MEP has a similar meaning for molecules. Nevertheless, this definition of nucleophilicity should assess the Lewis basicity of molecules on a relative scale. Within the present model, the nucleophilicity of molecules can be expected to be sensitive to solvent effects, since it is represented in terms of characteristic values of the molecular electrostatic potential instead of the electronic chemical potential and chemical hardness.

While the theoretical definition of electrophilicity is as an energy difference describing the stabilization of the electron acceptor upon receiving electronic charge from the environment, the theoretical definition of nucleophilicity is clearly more complex, as atoms and molecules increase their electronic energy upon releasing charge to the environment. This entails that there is no longer the possibility of representing the nucleophilic power of a molecule within a variational framework similar to that leading to the definition of electrophilicity.[12] From the experimental point of view, there has been some controversy in identifying the physical contributions to the nucleophilicity numbers proposed in different experimental scales. For instance, attempts to build up quantitative scales of nucleophilicity have been made in the past based on experimental data that incorporate thermodynamic, kinetic and electrochemical parameters. The double basicity scale proposed by Edwards[21,22] to describe the chemical reactivity of electron donors is an excellent example of how the nucleophilicity concept has been handled in the past. He suggested that the nucleophilic strength of a donor particle was probably related to its polarizability.[21] Polarizability as a measure of nucleophilicity was modelled through the electrode potentials of the electron donors,[21] and also by means of the molar refraction indices.[22] However, a quantitative relationship between nucleophilicity and polarizability was never characterized. Pearson proposed an empirical relationship between nucleophilicity and the oxidation potential for neutral and anionic bases.[23] He found a slight correlation with the nucleophilic reactivity towards methyl iodide. In summary, it may be that the quantitative evaluation of the nucleophilicity requires the consideration of both basicity and polarizability. The present approach is based on the hypothesis that the former contribution may contain a significant amount of information about nucleophilicity, in the form of a first-order energy variation, equivalent but not similar to the first-order energy changes associated with the variational definition of electrophilicity. The second contribution related to polarizability, that we neglect here as a first approximation, may be further incorporated through modern concepts such as chemical softness, which represents, within perturbation theory, second-order variations in energy. However, solvent effects may not be neglected within the present approach, and they can be incorporated using the experimental models of nucleophilicity. For instance, Ritchie's nucleophilicity scale[24] may be approximated as the negative of the free energy of the anion–cation recombination reaction $-\Delta G_{R,i}$ in the respective phase i. Therefore, if we define the intrinsic nucleophilicity as $\omega^{-,\mathrm{o}} = -\Delta G_{R,i}$, we may write

$$\omega^{-,\mathrm{s}} = \omega^{-,\mathrm{o}} - \delta\Delta G_{\mathrm{solv}} \tag{3}$$

where $\omega^{-,\mathrm{s}}$ is the solution-phase nucleophilicity. The net work associated with solvation is

$$\delta\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{solv}}(\mathrm{Nu}^- : \mathrm{E}^+) - \Delta G_{\mathrm{solv}}(\mathrm{Nu}^-) - \Delta G_{\mathrm{solv}}(\mathrm{E}^+) \tag{4}$$

We may safely neglect the contribution from solvation of the cation–anion complex [Nu^-:E^+) in Eqn (4)], given that the polar contribution to the solvation energy difference will be much smaller than the sum of the ionic terms for solvation of the separated nucleophile and electrophile. If we further assume that the reference electrophile contributes a constant quantity to the solvation energy difference in Eqn (4), then the solution- and gas-phase nucleophilicities can be approximately related by

$$\omega^{-,\mathrm{s}} = \omega^{-\mathrm{o}} + \Delta G_{\mathrm{solv}}(\mathrm{Nu}^-) \tag{5}$$

Equation (5) indicates that the nucleophilicity of a molecule in solution will decrease from its intrinsic (gas-phase) nucleophilicity by an amount dictated by the free energy of solvation of the nucleophile.

COMPUTATIONAL DETAILS

Ab initio HF/3–21G calculations were performed using the Gaussian 98 suite of programs[25] in order to evaluate the electron density required to calculate the MEP for the series of nucleophiles considered in the present study. These calculations also provide the one-electron energies ε_{H} and ε_{L} of the HOMO (H) and LUMO (L) frontier molecular orbitals, respectively, needed to evaluate the electronic chemical potential μ and chemical hardness η according to the approximate expressions[12]

$$\mu \cong \frac{\varepsilon_{\mathrm{H}} + \varepsilon_{\mathrm{L}}}{2} \tag{6a}$$

and

$$\eta \cong \varepsilon_{\mathrm{L}} - \varepsilon_{\mathrm{H}} \tag{6b}$$

respectively. With the μ and η values at hand, the electrophilicity index was evaluated using Eqn (2b). Additional calculations incorporating continuum solvent

effects via the IPCM model[26] were performed in order to evaluate the nucleophilicity index in the presence of a polar solvent using Eqn (5). The value 78.5 was used for the dielectric constant to mimic water as solvent. This scheme permits a more reliable comparison of the theoretical quantities with the experimental data. As mentioned above, electrophilicity has been shown to be relatively unaffected by continuum solvation effects,[19] so that intrinsic (gas-phase) values of ω^+ suffice to determine the reactivity pattern of electrophiles. The calculations of the electrophilicity and nucleophilicity indices were performed at the ground states of molecules at the HF/3–21G level of theory. A detailed exploration of the potential energy surface allowed us to select the most stable conformations.

RESULTS AND DISCUSSION

Relative scales of electrophilicity and nucleophilicity and reactivity

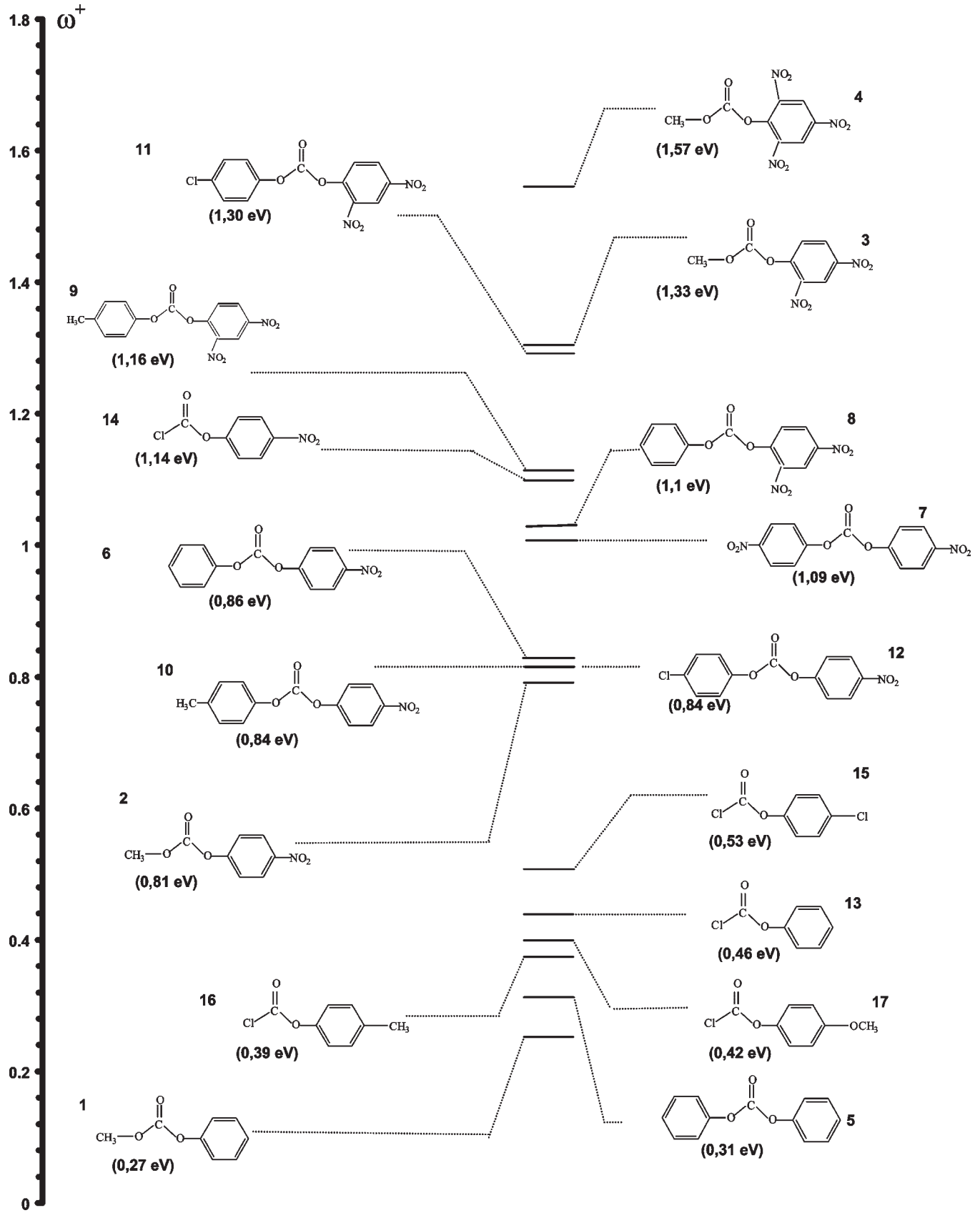
Scheme 1 summarizes the global electrophilicity predicted for a series of methyl aryl carbonates, diaryl carbonates and chloroformates. This series of electrophiles may be roughly classified into three subgroups. The molecules of the first subgroup, with global electrophilicity values >1.0 eV, are classified as strong electrophiles. Those of the second group, with electrophilicity values in the range 0.5–1.0 eV, are classified as moderate electrophiles. Finally, the third group consists of marginal electrophiles exhibiting electrophilicity values <0.5 eV.

It is interesting that the global electrophilicity pattern assesses farily well the substituent effect induced by different functional groups on a given carbonate frames. For instance, starting with methyl phenyl carbonate (**1**) in Scheme 1, which is a marginal electrophile presenting the lowest electrophilicity within the series (0.27 eV), increasing substitution by NO_2 groups on the phenyl ring enhances the electrophilicity to 0.81, 1.33 and 1.57 eV in **2**, **3** and **4**, respectively. Based on previous experimental results,[1,2] the predicted enhancement in electrophilicity at the carbonyl center may be traced to the strong electron-withdrawing effect of the NO_2 group. The same trend is observed in Scheme 1 for the series of diaryl carbonates (the ω^+ values are given in parentheses in eV units) **5** (0.31), **9** (1.16), **10**, (0.84), **11** (1.30), **12** (0.84) and chloroformates **13** (0.46) and **14** (1.14). Chlorine and methyl substitution in aryl compounds results in only marginal changes of the electrophilicity with reference to **6** ($\omega^+ = 0.86$ eV) as compared with $\omega^+ = 0.84$ eV for the Cl derivative **12** and for the methyl derivative **10**. A more pronounced activating effect is observed in the diaryl carbonate series (compare, for instance, compounds **8**, **9** and **11**).

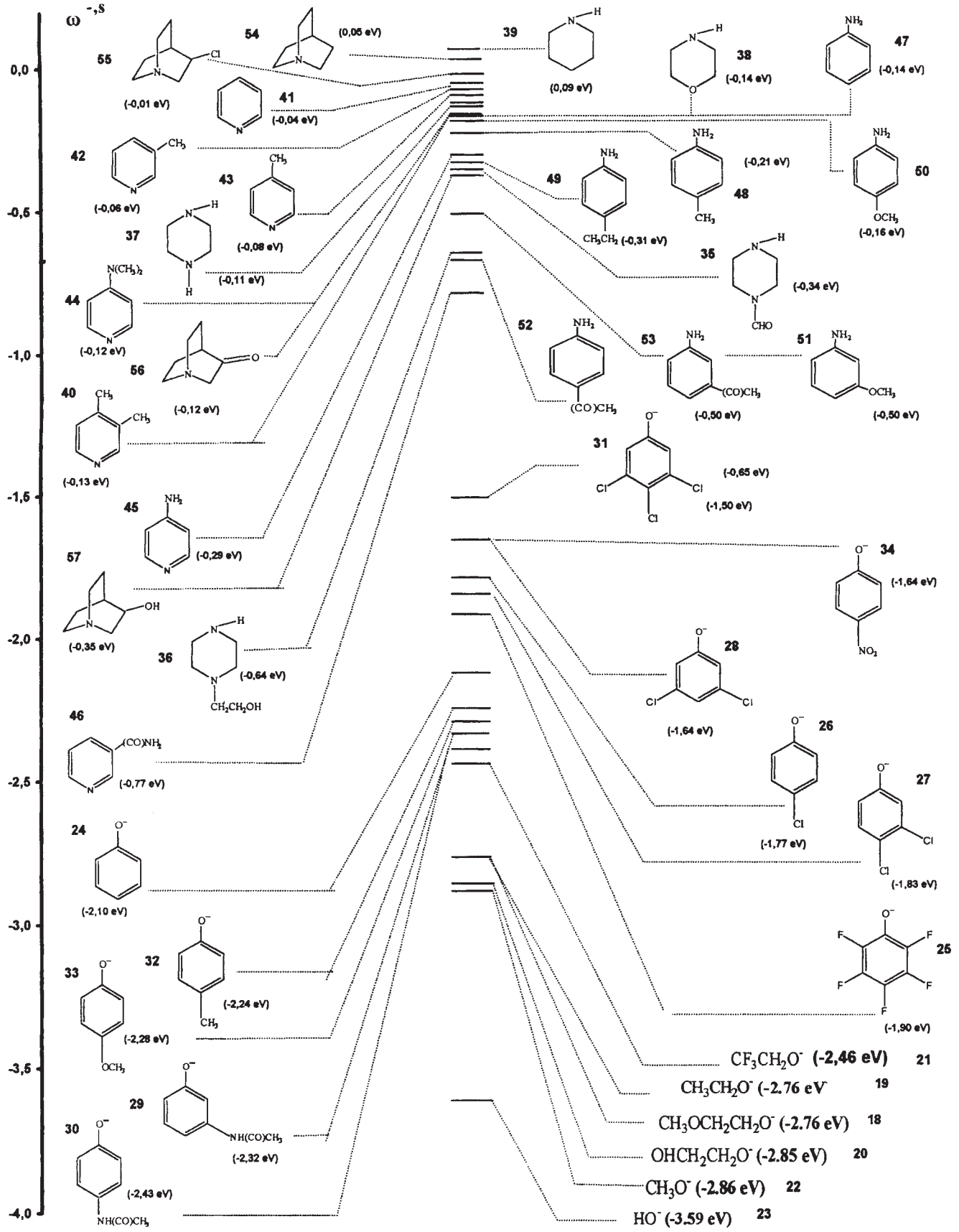
A theoretical scale of electrophilicity/nucleophilicity must be validated against the corresponding experimental scales. Even though nucleophilicity and electrophilicity concepts are not physical observables, they have been ranked using a three-parameter equation based on reaction coefficients.[27] This ranking is referred here to as experimental values of electrophilcity/nucleophilicity. For the case of electrophilicity, this comparison has been already done for a significant number of cases where the experimental information is available. In order to validate our scale of nucleophilicity (see Scheme 2), we compared the theoretical and experimental scales for a series of nucleophiles included in the database reported by Ritchie.[28] We evaluated the nucleophilicity power of a series of first-row neutral electron donors (i.e. neutral nucleophiles containing N and O atoms) using Eqn (5). In Fig. 1, a comparison between the experimental Ritchie nucleophilicity scale and the theoretical nucleophilicity index ω_s^- is displayed. It can be seen that for the series of nine first-row electron donors the experimental trends is roughly assessed: piperidine and morpholine are correctly predicted as the first-row electron donors with the highest nucleophilicity; hydroxylamine and hydroxide ion are predicted as the poorest nucleophiles within the series; hydrazine is predicted as a moderate nucleophile in addition to $CF_3CH_2O^-$ and $CH_3CH_2NH_2$ species. The location of CH_3O^- within the experimental range of strong nucleophiles (i.e. with an experimental nucleophilicity ranking comparable to that of morpholine and piperidine) is somehow striking, because according to our model Eqn (5), the high solvation energy expected for this anion would strongly attenuate its nucleophilicity in aqueous solution. Unfortunately, the experimental nucleophilicity of CH_3O^- in water is not available. The reported value for this anion was measured in methanol,[28] a solvent having a markedly lower polarity than water. This species is expected to behave nucleophilically in a manner closer to that of OH^-, i.e. as a marginal nucleophile in aqueous solution. Note that the theoretical scale does predict this expected nucleophilicity pattern in a solvent of higher polarity such as water. The nucleophilicity of NH_3 is, however, wrongly predicted by the ω_s^- index.

Scheme 2 summarizes the results of the calculation of the global nucleophilicity according to the model based on the minimum value of MEP presented above in the section Nucleophilicity index, with the intrinsic nucleophilicity values corrected for solvent effects. The solvation energies employed to correct the intrinsic nucleophilicity values via in Eqn (5) were obtained from the IPCM model of Miertus *et al.*[26] at the same HF/3–21G level of theory.

In order to test whether or not the predicted order of nucleophilicity was dependent on the basis set used to evaluate the MEP, we performed additional calculations. We first evaluated the nucleophilicity index using the semiempirical AM1 method, and the results for the whole



Scheme 1. Global electrophilicity (eV) of carbonyl compounds, evaluated using Eqn (2b)



Scheme 2. Global nucleophilicity (eV) of a series of neutral and charged nucleophiles, evaluated using Eqn (5)

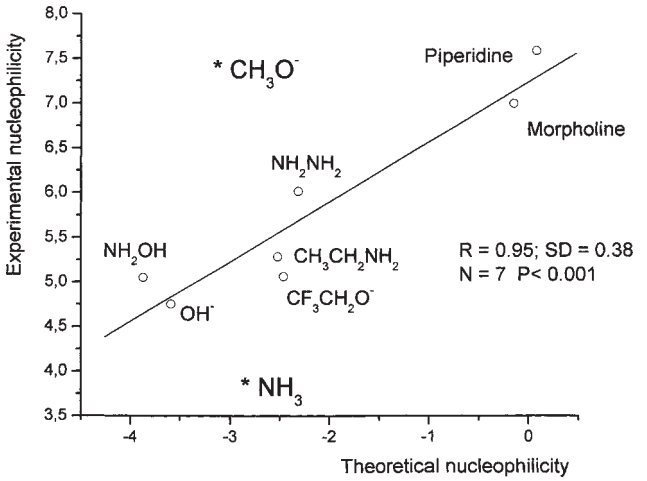


Figure 1. Comparison between the experimental nucleophilicity scale of Ref. 28 and the nucleophilicity index $\omega^{-,s}$ for the first-row electron donors. The correlation shown involves the seven nucleophiles marked with circles

data base were in good qualitative agreement with the HF/3–21G outcomes. We next performed additional calculations at the higher IPCM–HF/6–31G level on the series of secondary neutral alicyclic amines (**35–39** in Scheme 2). This series will be used to examine the reaction mechanisms (concerted vs stepwise) in nucleophilic substitution reactions, with a series of carbonyl compounds of varying nucleophilicity (see below). The results of these calculations showed that the incorporation of a more extended basis set does not alter the predicted order of nucleophilicity. At the IPCM–HF/6–31G level the nucleophilicity order is **39** (-0.12 eV) > **37** (-0.22 eV) > **38** (-0.36 eV) > **35** (-0.42 eV) > **36** (-0.58 eV), in complete agreement with the trends given in Scheme 2.

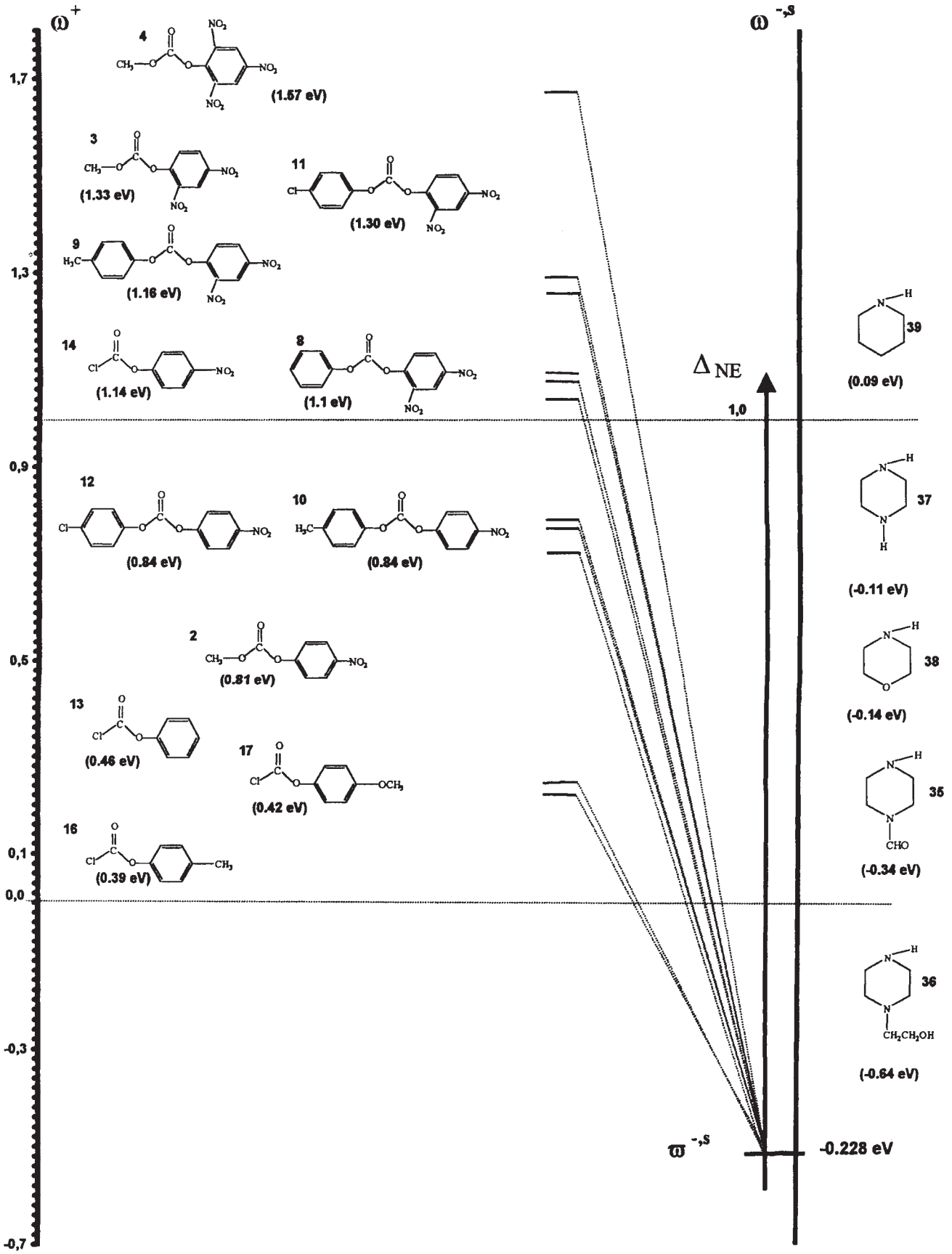
Electrophilicity/nucleophilicity patterns and the nature of reaction mechanisms

The usefulness of these global scales of electrophilicity and nucleophilicity is nicely illustrated by the prediction of the reaction mechanism for some nucleophilic substitution reactions. The reaction mechanism for the displacement reactions involving many of the electrophiles and nucleophiles shown in Schemes 1 and 2 have been experimentally characterized.[1–2] Two general mechanisms have been proposed for these processes: a stepwise reaction involving a tetrahedral intermediate and a concerted route. We introduce the following model, based on the electrophilicity/nucleophilicity scales, to predict the reaction mechanism expected for a given electrophile–nucleophile pair. This model uses the nucleophilicity −electrophilicity difference index $\Delta_{NE} = |\bar{\omega}^{-,s} - \omega^{+}|$ as a criterion to predict the degree of ionic character of the electrophile/nucleophile interaction, where $\bar{\omega}^{-,s}$ is the mean of the $\omega^{-,s}$ values of the set of nucleophiles under consideration. This choice is dictated by the experimental protocol, in which the reaction mechanism is deduced from the kinetic data for a given electrophilic substrate in reaction with a set of structurally related nucleophiles.

The Δ_{NE} index may be defined as a 'distance' along an unique scale defined in electronvolts (see Scheme 3). As an example, we consider the reaction mechanism for a series of carbonyl compounds (carbonates and chloroformates) reacting with the following series of secondary alicyclic amines: 1-formylpiperazine (**35**), 1-(2-hydroxyethyl)piperazine (**36**), piperazine (**37**), morpholine (**38**) and piperidine (**39**), all of which are shown in Scheme 3. For this set of nucleophiles, the resulting $\bar{\omega}^{-,s}$ value is -0.228 eV. Scheme 3 shows the corresponding Δ_{NE} index for the electrophiles that have been kinetically evaluated to react with these nucleophiles (**35–39**) via either a concerted or stepwise mechanism.[29–35] The results are compared in Table 1. It can be seen that those electrophiles which react via a stepwise route display Δ_{NE} values smaller than or approximately equal to 1.1 eV. Compounds that have been evaluated as reacting via a concerted route, on the other hand, consistently show Δ_{NE} values much greater than 1.1 eV. However, the dividing line around $\Delta_{NE} = 1.1$ eV is certainly arbitrary. A more reliable criterion may be obtained by taking an interval between the maximum and minimum values around the mean nucleophilicity value, leading to a dividing interval ranging from 1.10 to 1.40 eV rather than a single line. As a result, the compounds comprised within this dividing region are consistently quoted as borderline cases in Table 1. Based on these results, the following empirical rule may be proposed for the nucleophilic substitution reactions examined here: the larger the electrophilicity/nucleophilicity difference, the more concerted the reaction mechanism will be. Conversely, a small electrophilicity/nucleophilicty gap will, in general, be associated with a stepwise reaction mechanism.

CONCLUSION

The reactivity of carbonyl compounds towards reagents of varying nucleophilicity has been examined for a wide range of molecules. The basicity of the nucleophiles is correctly predicted by a nucleophilicity index defined as the minimum value of the molecular electrostatic potential, corrected for solvation, while the electrophilicity of the carbonyl substrate may be conveniently described in terms of the electronic reactivity index proposed by Parr *et al.*[12] The electrophilicity/nucleophilicty difference index introduced in the present work appears to be a useful tool for predicting the degree of polar character involved in the nucleophilic substitution reactions of these compounds.



Scheme 3. Electrophilicity–nucleophilicity difference (eV)

Table 1. Nucleophilicity–electrophilicity difference (Δ_{NE})[a], predicted and experimental reaction mechanism for a series of neutral secondary alicyclic amines reacting with some electrophiles[b]

	HF/3–21G		Mechanism		
Compound	ω^+	Δ_{NE}	Predicted	Experimental	Ref.
17	0.42	0.65	Stepwise	Stepwise	29
16	0.39	0.62	Stepwise	Stepwise	29
13	0.46	0.69	Stepwise	Stepwise	30
2	0.81	1.04	Stepwise	Stepwise	32
10	0.84	1.07	Stepwise	Stepwise	31
12	0.84	1.07	Stepwise	Stepwise	33
14	1.14	1.37	Borderline	Stepwise	30
8	1.10	1.33	Borderline	Concerted	32
9	1.16	1.39	Borderline	Concerted	31
11	1.30	1.53	Concerted	Concerted	34
3	1.33	1.56	Concerted	Concerted	32
4	1.57	1.80	Concerted	Concerted	35

[a] $\Delta_{NE} = |\bar{\omega}^{-,s} - \omega^+|$, ($\bar{\omega}^{-,s} = -0.228$ eV, see text).
[b] See Schemes 1 and 3 for compound numbering.

Acknowledgements

This work received financial support from Fondecyt, under contracts 2010081, 1030548 and 1990551. R. C. and P. C. are grateful to the Departament de Ciènces Experimentals, Universitat Jaume I, Castelló, Spain, for the warm hospitality extended to them. The authors are indebted to Dr Sergio Marti for preparing a smart routine that quickly locates the minima in the MEP surfaces.

REFERENCES

1. Williams A. *Concerted Organic and Bio-Organic Mechanism*. CRC Press: Boca Raton, FL: 2000; Chapt. 4, and references cited therein.
2. Johnson SL. *Adv. Phys. Org. Chem.* 1967; **5**: 237–330; Satterthwait AC, Jencks WP. *J. Am. Chem. Soc.* 1974; **96**: 7018–7031; Stefanidis D, Cho S, Dhe-Paganon S, Jencks WP. *J. Am. Chem. Soc.* 1993; **115**: 1650–1656; Gresser MJ, Jencks WP. *J. Am. Chem. Soc.* 1977; **99**: 6963–6970.
3. Domingo LR, Aurell MJ, Perez P, Contreras R. *Tetrahedron.* 2002; **58**: 4417–4423.
4. Cramer CJ, Barrows SE. *J. Org. Chem.* 1998; **63**: 5523–5532.
5. Geerlings P, De Proft F, Langenaeker W. *Chem. Rev.* 2003; **103**: 1793–1874.
6. Domingo LR, Arno M, Contreras R, Perez P. *J. Phys. Chem. A* 2002; **106**: 952–961.
7. Domingo LR, Aurell MJ. *J. Org. Chem.* 2002; **67**: 959–965.
8. Ingold CK. *J. Am. Chem. Soc.* 1933; **42**: 1122–1126.
9. Legon AC, Millen DJ. *J. Am. Chem. Soc.* 1987; **109**: 356–358.
10. Legon AC. *Chem. Commun.* 1998; 2585–2586.
11. Mayr H, Patz M. *Angew. Chem., Int. Ed. Engl.* 1994; **33**: 938–957.
12. Parr RG, Szentpály LV, Liu S. *J. Am. Chem. Soc.* 1999; **121**: 1922–1924.
13. Sen KD, Politzer P. *J. Chem. Phys.* 1989; **90**: 4370–4372.
14. Sen KD, Seminario JM, Politzer P. *J. Chem. Phys.* 1989; **90**: 4373–4378.
15. Murray JS, Lane P, Brinck T, Politzer P, Sjoberg P. *J. Phys. Chem.* 1991; **95**: 844–848.
16. Parr RG, Yang W. *Density-funtional Theory of Atoms and Molecules*. Oxford University Press: New York, 1989.
17. Parr RG, Pearson RG. *J. Am. Chem. Soc.* 1983; **105**: 7512–7516.
18. Pearson RG. *J. Am. Chem. Soc.* 1986; **108**: 6109–6114.
19. Pérez P, Toro-Labbe A, Contreras R. *J. Am. Chem. Soc.* 2001; **123**: 5527–5531.
20. Foresman JB, Keith TA, Wiberg KB, Snoonian J, Frisch MJ. *J. Phys. Chem.* 1996; **100**: 16098–16104.
21. Edwards JO. *J. Am. Chem. Soc.* 1954; **76**: 1540–1547.
22. Edwards JO. *J. Am. Chem. Soc.* 1956; **78**: 1819–1820.
23. Pearson RG. *J. Org. Chem.* 1987; **52**: 2131–2136.
24. Ritchie CD. *Can. J. Chem.* 1972; **5**: 348–354.
25. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe MW, Gill PM, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA. *Gaussian 98*. Gaussian; pittsburgh, PA, 1998.
26. Miertus S, Scrocco E, Tomasi J. *J. Chem. Phys.* 1981; **55**: 117–125.
27. Mayr H, Kempf B, Ofial AR. *Acc. Chem. Res.* 2003; **36**: 66–77.
28. Ritchie CD. *Can. J. Chem.* 1986; **64**: 2239–2250.
29. Castro EA, Ruiz MG, Santos JG. *Int. J. Chem. Kinet.* 2001; **33**: 281–287.
30. Castro EA, Ruiz MG, Salinas S, Santos JG. *J. Org. Chem.* 1999; **64**: 4817–4820.
31. Castro EA, Andujar M, Campodónico P, Santos JG. *Int. J. Chem. Kinet*. 2002; **34**: 309–315.
32. Castro EA, Aliaga M, Campodónico P, Santos JG. *J. Org. Chem.* 2002; **67**: 8911–8916.
33. Castro EA, Andujar M, Toro A, Santos JG. *J. Org. Chem*. 2003; **68**: 3608–3613.
34. Castro EA, Campodónico P, Toro A, Santos JG. *J. Org. Chem*. 2003; **68**: 5930–5935.
35. Castro EA, Cubillos M, Santos JG. *J. Org. Chem.* 2001; **66**: 6000–6003.