Theor Chem Acc (1998) 99:183–191

Theoretical
Chemistry Accounts

Regular article

Theory of non-local (pair site) reactivity from model static-density response functions

Renato Contreras[1,3]*, Juan Andrés[1], Patricia Pérez[1,3]*, Arie Aizman[2], Orlando Tapia[3]

[1] Departament de Ciénces Experimentals, Universitat Jaume I, Box 242, E-12080, Castelló, Spain
[2] Facultad de Ciencia, Universidad F. Santa Marìa, Casilla 110-V, Valparaìso, Chile
[3] Department of Physical Chemistry, Uppsala University, Box 532-75121, Uppsala, Sweden

Received: 30 September 1997 / Accepted: 30 December 1997

Abstract. Activation is a fundamental and well-known concept in chemistry. It may be *qualitatively* defined as an increase in the chemical reactivity pattern of a molecule at a given site k when the system is locally perturbed at a different site l, say. This external perturbation arise from a localized molecular rearrangement, a substitution, a selective solvation or simply by the approach of a reagent of variable hardness. This work presents a theoretical approach intending to *quantify* this activation concept in the density functional framework. This is done here by first calculating the fluctuation of the electron density at a given site k for the ground state of the isolated substrate (static reactivity model) and then incorporating the substrate and model electrophile reagents in a spatial disposition related to a virtual transition structure for the parent system. This perturbation is assumed representable by local changes in the external potential. It is shown that a local approximation to the softness kernel $s(\mathbf{r}, \mathbf{r}')$ yields a simple expression for the fluctuation of the electron density $\delta\rho(\mathbf{r}_k)$, which shows that this change becomes proportional to the variation of an effective potential $\delta u(\mathbf{r}_k)$, containing the information on the variation in the chemical potential and the external perturbing potential at site k; the proportionality constant being the local softness $\mathbf{s}^0(\mathbf{r}_k)$ at that site. The strong local approximation made to the kernel $s(\mathbf{r}, \mathbf{r}')$ causes the second reactivity site (l) to implicitly appear in the formulation through the changes in the electronic chemical potential term. It is shown that the introduction of a less restrictive approach to the linear response function, obtained from a model Kohn-Sham one-electron density matrix, leads to the same result. Non-locality is therefore self-contained in the electronic chemical potential contribution to the modified potential, and may be associated with an intramolecular charge transfer between the active sites of the ambident nucleophilic/electrophilic substrate, promoted by the presence of the reagents. The resulting formulation of pair-site reactivity is illustrated for the electrophilic attack on the CN^- ion by different model electrophile agents of variable hardness. It is shown that correct reactivity indexes are obtained only when the topology of the transition structure is used as a vantage point to perturb the CN^- ion. The calculations were performed at both density functional theory and ab-initio Hartree-Fock levels. The results show that the proposed model is independent of the method used to obtain $\rho(\mathbf{r})$.

Key words: Chemical reactivity – Density functional – Non-local reactivity – Response function – CN – Cyanide ion reactivity

1 Introduction

Reactivity indexes have been introduced in chemistry since the early days of empirical molecular orbital approaches. Derivatives of the energy with respect to the α-parameter in the Hückel approach were extremely useful to study the reactivity of particular centers of polynuclear π-electron molecules. In a chemical reaction, be it in gas phase, liquid or solid state, there are two major factors determining the way atoms and molecules are interconverted into different species. The first concerns the relative energies of reagents and products which determine the thermodynamic properties of the process. The second involves mechanistic and kinetic aspects. Modern quantum chemistry provides useful tools to rationalize and predict the thermodynamics involved in chemical reactions. For instance, in density functional theory (DFT), there are a number of global properties that have been used in connection with the energetic aspects that determine the relative stability of different reacting species, and energy barriers to interconversion between reagents and products [1–4]. One of the most useful global descriptors of chemical reactivity is the electronic chemical potential μ [1–3], defined as the derivative of the electronic energy E with respect to the

---

* On leave from Departamento de Quìmica, Facultad de Ciencias, Universidad de Chile, Casilla 653-Santiago, Chile

Correspondence to: O. Tapia

total number of electrons N, at constant external potential $\upsilon(\mathbf{r})$. This quantity may be approached by a finite difference procedure, in terms of the first ionization potential I and electron affinity A, $\mu \cong -(I+A)/2$. Another pertinent global quantity is the chemical hardness η, which has been given the following definition in the context of DFT [1–3]: second derivative of the energy with respect to the particle number; or the first partial derivative of the chemical potential with respect to the particle number at constant external potential $\upsilon(\mathbf{r})$. η may be also approached in terms of the quantities I and A, namely, $\eta \cong (I-A)/2$. Chemical hardness has been associated with the ability of the system to establish long-range electrostatic interactions [5]. While the global softness S is defined as the inverse of η: $S = 1/\eta \cong 2/(I-A)$ [1–6]. This index measures the electronic polarizability of the system, or its ability to exchange electrons with another system. These concepts are often used in connection with some empirical principles, to qualitatively predict the thermodynamically preferred products in a given reaction. For instance, the maximum hardness principle (MHP) [5–7] relates the minimum total energy criterion with a maximum hardness value, as indicative of the thermodynamic stability of the system. On the other hand, the well-known Pearson's principle of hard and soft acids and bases (HSAB) suggests that hard-hard or soft-soft interactions are more energetically favorable in an acid-base reaction [7, 8]. These approaches have limitations such as the failure of the HSAB principle to describe one of the simplest systems: hydrogen cyanide. For this and many other reasons it is desirable to search for more detailed indexes for describing reactivity.

The second aspect of chemical reactivity is related to the dynamics of reactions, including kinetic factors, i.e. the rate at which different products are formed. Such processes involve passage through bottleneck regions where the system interconverts. One way to look at the kinetics involves reaction paths, defined as the most probable trajectories in a potential energy surface (PES), connecting reagents and products. For thermally activated processess, the calculation of activated complexes as saddle points on a PES is usually required to estimate the activation energies. One way to calculate cross sections (rates) is to use molecular dynamics techniques and computer simulation [9]. If reactivity is sought, one resorts to approximated representations which are formally time-independent, but they contain, within a perturbative approach, the most probable evolution of the reacting system, by studying the slope of the potential energy in the vicinity of the ground states (GS) representing reagents or products, to predict the height of the potential barrier separating both GS. The transition state theory is usually used in this context [10–12]. Knowledge of privileged sites of reactions in a molecule provides important clues as to how to postulate and then calculate transition state structures. These potential active sites may also be represented by local reactivity indexes, like electron density $\rho(\mathbf{r})$, and other local properties that depend on it. They have also been defined in the context of DFT [1–6]. For instance, the Fukui function $f(\mathrm{r})$ is defined as:

$$f(\mathbf{r}) = \left[\frac{\partial \rho(\mathbf{r})}{\partial N}\right]_{\upsilon(\mathbf{r})} , \tag{1}$$

for an N electron system at constant external potential $\upsilon(\mathbf{r})$. A high value of $f(\mathbf{r})$ at a site in a molecule is indicative of a high reactivity at that site, in nucleophilic, electrophilic or radical attacks. It is also possible to define a local softness as $s(\mathbf{r}) = f(\mathbf{r})\, S$ [1–6]. This local index quantifies the electronic polarizability at point $\mathbf{r}$, and it may be interpreted as the propensity of the system at that site to exchange electrons with another system. Unfortunately, the inverse relationship between local softness and hardness is not as simple as that displayed by their global counterparts. Different definitions for local hardness have been suggested [13–15], the simplest one being that proposed by Fuentealba [15], namely: $\eta(\mathbf{r}) \approx \rho(\mathbf{r})/2Ns(\mathbf{r})$, which shows that $s(\mathbf{r})$ and $\eta(\mathbf{r})$ are at least inverse to each other.

For chemical processes where non-local effects are important a generalized approach is required. In fact, there are many examples where the reactivity pattern is determined by at least a pair of sites in a molecule. For instance, it is well known in the chemistry of aromatic compounds that substitution at a given site in a molecule may activate the reactivity at another site towards an electrophilic substitution [16]. Another non-local effect on chemical reactivity concerns enolate ion chemistry [17]: an alkylating agent approaching the enolate ion has, in general, two possible reactive sites: the alpha-carbon and the oxygen atoms. When this reaction occurs in solution, the oxygen atom is preferentially solvated by polar solvents, leaving the alpha-carbon as the available site for alkylation [18]. This activating effect produced by selective solvation may be also viewed as a non-local (pair site) reactivity.

Non-local reactivity must be associated with non-local reactivity indexes. In the examples considered above, it seems that the activation at a given site in a molecule is produced by a local perturbation in a different region of the molecular system. If we assume that this local perturbation is representable by local changes in the external potential, then a natural description of non-local reactivity will be that based on the static-density response function of DFT $\chi(\mathbf{r}, \mathbf{r}')$ [6], which gives the change in the electron density at point $\mathbf{r}$ (and therefore the variation at the same point of all the local properties that depend on it), when the external potential υ is modified at the different point $\mathbf{r}'$. This is a well-defined quantity in DFT and may be expressed in terms of reactivity indexes [1, 6]. In this work, we will present a simple model to account for pair site reactivity, based on two approaches to the response function $\chi(\mathbf{r}, \mathbf{r}')$. We first consider a local approximation that yields an interesting relationship between the changes in the electron density at any point (or region) in a molecule, and the local reactivity indexes at the site of the perturbation. Next, this relationship is generalized by using a less restrictive representation of the static response function.

As the direct linear attack on the N or C center produces inadequate HSAB results, the next natural geometric setup to look at is the transition structure

(TS). There, the electronic structure of CN⁻ would highlight properties related both to the reactant and the product channels. Since the TS is a stationary point on the Born-Oppenheimer hypersurface having a unique negative eigenvalue for the Hessian, the techniques of the DFT can be successfully applied. The model is probed from a virtual TS geometry by moving the electrophile between the actual configuration of the TS in a direction perpendicular to the C—N bond and away by about 3Å. The theoretical model is illustrated with the analysis of the chemical reactivity of the CN^- ion towards electrophilic agents of variable hardness. The study probes the electronic properties of the CN system in the neighborhood of a TS. The results show that it is here that the HSAB principle holds.

2 Theory

2.1 General approach

Within the $\{N, \upsilon(\mathbf{r})\}$ representation of DFT, the total differential of the electron density, for the change between two GS of the system $\rho = \rho[N, \upsilon(\mathbf{r})]$, is given by:

$$d\rho(\mathbf{r}) = f(\mathbf{r})\, dN + \int d\mathbf{r}'\, \chi(\mathbf{r},\mathbf{r}')\, \delta\upsilon(\mathbf{r}') \ , \tag{2}$$

where Eq. (1) for $f(\mathbf{r})$ has been used. According to Senet [19], Eq. (2) is a first-order density variation, within a perturbation theory scheme, in the sense that the n-th order variation of the electron density is proportional to the n-th power of the perturbation potential, under the constraint that the number of electrons of the system is conserved. The second contribution to the changes in $\rho(\mathbf{r})$ is then written in terms of the *static* density linear response function for a constant N, defined as [1, 6]:

$$\chi(\mathbf{r},\mathbf{r}') = \left[\frac{\delta\rho(\mathbf{r})}{\delta\upsilon(\mathbf{r}')}\right]_N \ , \tag{3}$$

which describes the change in the electronic density at point $\mathbf{r}$, when the system is locally perturbed at the different point $\mathbf{r}'$, by an additional external perturbation that adds to the external unperturbed potential $\upsilon^0(\mathbf{r}')$. This quantity is expressed in terms of the non-local softness kernel $s(\mathbf{r}, \mathbf{r}')$, and local and global softness $s(\mathbf{r})$ and S, respectively, as [6]:

$$\chi(\mathbf{r},\mathbf{r}') = -s(\mathbf{r},\mathbf{r}') + \frac{s(\mathbf{r})\, s(\mathbf{r}')}{S} \ . \tag{4}$$

The main problem with Eq. (4) is the presence of the kernel $s(\mathbf{r}, \mathbf{r}')$ which is very difficult to represent analytically. The most simple representation of this quantity is the local approximation proposed by Vela and Gázquez [20]:

$$s(\mathbf{r},\mathbf{r}') \approx f(\mathbf{r})\, S\, \delta(\mathbf{r}-\mathbf{r}') \ . \tag{5}$$

Introducing the definition of local softness ($s(\mathbf{r}) = f(\mathbf{r})\, S$) and Eqs. (4) and (5) into Eq. (2) we obtain:

$$d\rho(\mathbf{r}) = f(\mathbf{r})\, dN - s(\mathbf{r})\, \delta\upsilon(\mathbf{r}) + s(\mathbf{r}) \int d\mathbf{r}'\, f(\mathbf{r}')\, \delta\upsilon(\mathbf{r}') \ . \tag{6}$$

Equation (6) contains a local contribution to the changes in electron density given by the first two terms. The non-local contribution to $d\rho(\mathbf{r})$ is represented here by the third term, which may be easily simplified by using the identity [21]:

$$\Delta N = S\, \Delta\mu - \int d\mathbf{r}'\, s(\mathbf{r}')\, \delta\upsilon(\mathbf{r}') \ . \tag{7}$$

Dividing both sides of Eq. (7) by the global softness S, and using again $s(\mathbf{r}) = f(\mathbf{r})S$, we get:

$$\int d\mathbf{r}'\, f(\mathbf{r}')\, \delta\upsilon(\mathbf{r}') = \Delta\mu - \frac{\Delta N}{S} \tag{8}$$

Finally, introducing Eq. (8) into Eq. (6), and again using Eq. (5), we obtain for a finite change in the total number of electrons ΔN, the following expression for the change in the electron density:

$$d\rho(\mathbf{r}) = -s(\mathbf{r})\, \delta\upsilon(\mathbf{r}) + s(\mathbf{r})\, \Delta\mu \tag{9}$$

We may seek to localize the fluctuation of the electron density $d\rho(\mathbf{r})$ at a particular point $\mathbf{r}_k$ say, by integrating Eq. (9) over the $\mathbf{r}$ space with the Dirac distribution, $\delta(\mathbf{r}-\mathbf{r}_k)$. The result is:

$$d\rho(\mathbf{r}_k) = -s(\mathbf{r}_k)\, \delta\upsilon(\mathbf{r}_k) + s(\mathbf{r}_k)\, \Delta\mu \tag{10}$$

At this stage, two comments about the approximate expression in Eq. (10) are pertinent. First of all, and despite the crudeness of the local approximation introduced in the softness kernel in Eq. (5), Eq. (10) shows some interesting aspects: the first term (of local character) reveals that the electrostatic contribution to the fluctuation in the electron density at point $\mathbf{r}_k$ appears to be proportional to the variation of the external potential at that site, the proportionality constant being the local softness $s(\mathbf{r}_k)$, a reactivity parameter associated with the electronic polarization at this point. Secondly, the non-local contribution to the fluctuation of the electron density, represented here by the second term, only considers the second site implicitly through the changes in the electronic chemical potential. This variation is due to an intramolecular charge transfer between sites k and l, as we will show below. Equation (10) may be further simplified by introducing the effective potential $u(\mathbf{r}_k) = \upsilon(\mathbf{r}_k) - \mu$ [1]. The result is:

$$d\rho(\mathbf{r}_k) = -s(\mathbf{r}_k)\, \delta u(\mathbf{r}_k) \ . \tag{11}$$

The form of the external perturbation $\delta\upsilon(\mathbf{r}_k)$ that determines the changes in the modified potential $\delta u(\mathbf{r}_k)$, will depend on the nature of the electrophile/nucleophile considered. The electronic chemical potential contribution to $\delta u(\mathbf{r}_k)$, $\Delta\mu = \mu - \mu^0$, is obtained by comparing the quantity μ, in the presence and absence of the perturbing potential, for each point $\mathbf{r}_k$ of the progress reaction coordinate. In order to compute the fluctuation in the electron density using Eq. (11), we used the intrinsic local softness $\mathbf{s}^0(r_k)$. The local softness of the isolated substrate $\mathbf{s}^0(r_k)$ and the perturbed one $\mathbf{s}(r_k)$ are proportional. This approximation is consistent with the first-order nature of master Eq. (2), stating that changes in electron density are proportional to first-order changes in the external potential.

We shall now show that the approximations made to obtain Eqs. (10) and (11), although crude, mainly due to the strong approximation of the softness kernel introduced in Eq. (5), do not produce spurious results but they remain as reliable relationships between the variation in the electron density, local softness, and the variation in the modified potential.

Let us consider a different model static density response function, derived from a model Kohn-Sham (KS) density proposed by Fuentealba and Savin [22]:

$$\chi_S(\mathbf{r},\mathbf{r}') = -\frac{2}{\Delta\varepsilon}\,\gamma_S(\mathbf{r},\mathbf{r}')\,\delta(\mathbf{r}-\mathbf{r}') + \frac{2}{N\Delta\varepsilon}\,\rho(\mathbf{r})\,\rho(\mathbf{r}')\ , \tag{12}$$

which is expressed in terms of the KS one-electron density matrix $\gamma_S(\mathbf{r}, \mathbf{r}')$, and a mean orbital difference $\Delta\varepsilon$. Substitution of Eq. (12) into Eq. (2) yields:

$$d\rho(\mathbf{r}) = f(\mathbf{r})\,dN - \frac{2}{\Delta\varepsilon}\int d\mathbf{r}'\,\gamma_S(\mathbf{r},\mathbf{r}')\,\delta\upsilon(\mathbf{r}')\,\delta(\mathbf{r}-\mathbf{r}') + \frac{2\rho(\mathbf{r})}{\Delta\varepsilon}\int d\mathbf{r}'\,\frac{\rho(\mathbf{r}')}{N}\,\delta\upsilon(\mathbf{r}')$$

which may be further simplified by noting that

$$s(\mathbf{r}) = \frac{2}{\Delta\varepsilon}\,\rho(\mathbf{r})\ , \tag{13}$$

which results upon comparing the first terms of Eqs. (4) and (12), and integrating over the $\mathbf{r}'$ space coordinate to obtain the local softness $s(\mathbf{r})$ according to:

$$s(\mathbf{r}) = \int d\mathbf{r}'\,s(\mathbf{r},\mathbf{r}') \tag{14}$$

Introducing the approximation $f(\mathbf{r}) \approx \rho(\mathbf{r})/N$ together with Eq. (8), Eqs. (10) and (11) are recovered.

2.2 Particular models

Let us now consider some special types of potentials. The form of the perturbing potential $\delta\upsilon(\mathbf{r}_k)$ that determines the changes in the modified potential at the site (or group) k will be given by:

$$\delta\upsilon(\mathbf{r}_k) = \sum_{l\neq k}\frac{q_l}{|\mathbf{r}_k - \mathbf{r}_l|}\ , \tag{15a}$$

and

$$\delta\upsilon(\mathbf{r}_k) = \sum_{l\neq k}\frac{q_l}{|\mathbf{r}_k - \mathbf{r}_l|} - \int d\mathbf{r}'\,\frac{\rho(\mathbf{r}')}{|\mathbf{r}_k - \mathbf{r}'|}\ , \tag{15b}$$

for the case of a point charge or a polarizable electrophile model, respectively. Apart from the charge-induced potential (including that of the point charge representing the electrophile/nucleophile agent, which here has the form of a fractional nuclear charge of the same magnitude), Eq. (15b) contains the electronic effect due to the presence of orbitals, which contributes with a Hartree-like potential to $\delta\upsilon(\mathbf{r})$, given by the second term.

In summary, the working Eq. (10), obtained from a different model for the static density response function, shows that independent of the approximations made on the softness kernel, the variation of the electron density at $\mathbf{r}_k$ is proportional to the changes in the electrostatic potential variations at the site plus the variation in electronic chemical potential, the proportionality constant being the local softness at the site. Whereas the first term $-s(\mathbf{r}_k)\,\delta\upsilon(\mathbf{r}_k)$ is completely local in nature, because it is expressed as a product of two local descriptors evaluated at the same point in space, the second one has indeed a non-local character, because

$$s(\mathbf{r})\int d\mathbf{r}'\,f(\mathbf{r}')\,\delta\upsilon(\mathbf{r}') = s(\mathbf{r})\,\Delta\mu\ , \tag{16}$$

plus a term that cancels out the first contribution $f(\mathbf{r})\,\Delta N$ in Eq. (6). Therefore, non-locality is taken into account here implicitly through the quantity $\Delta\mu$, probably in the form of an intramolecular charge transfer between the active sites of an ambident nucleophile/electrophile substrate, promoted by the presence of reagents of variable hardness. In the case of a simple ambident nucleophilic agent, for instance the CN^- ion, these sites will trivially correspond to the carbon and nitrogen atoms. In Sect. 4, we will apply the present formulation of pair site reactivity to this system, in order to discuss the nature of the forces that make possible a fluctuation in the electron density along a progress reaction coordinate, which may eventually change the pattern of reactivity expected from a static picture containing only global and local descriptors of chemical reactivity.

3 Local properties and computing details

The electronic properties of the CN^- ion are calculated to define a reference and establish a static reactivity model for the electrophilic attack reaction. These calculations were performed at different levels of theory, using the Amsterdam density functional (ADF) code, which solves the KS equations with a BP86 Hamiltonian [23], using a double-zeta basis set, containing polarization functions (ADF, basis set III); B3LYP/6-311G(*d*) hybrid DFT calculations; Hartree-Fock (HF)/6-311G(*d*) and CISD/6-311G(*d*) calculations, implemented in the Gaussian 94 package [24]. The resulting equilibrium C–N distances were: 1.16 Å, 1.17 Å, 1.15 Å and 1.17 Å, respectively. Unfortunately, experimental values for bond distance and dipole moments are not available for this ion. The Mulliken population at each center, together with some local properties condensed to atoms C and N, are summarized in Table 1. These properties are evaluated as follows: we first approximate the Fukui function at center k, as the difference in the electron population on atom k in the system with N and $(N-1)$ electrons [25, 26]:

Table 1. Electronic Mulliken population, Fukui function and local softness and hardness condensed to atoms for the carbon and nitrogen and global softness (S) for the cyanide ion in atomic units at different levels of the theory

Method	ρ_C	ρ_N	f_C	f_N	s_C^0	s_N^0	η_C^0	η_N^0	S
ADF/III[a]	4.4946	5.5054	0.94	0.06	0.0048	0.0003	0.0540	0.6354	0.0051
B3LYP/6-311G(*d*)	6.5562	7.4438	0.70	0.30	4.1600	1.7800	1.5300	4.0600	5.9400
HF/6-311G(*d*)	6.4690	7.5310	0.61	0.39	1.8400	1.1700	3.4200	6.2600	3.0100
CISD/6-311G(*d*)	6.4596	7.5404	0.61	0.39	1.8500	1.1900	3.3900	6.1600	3.0400

[a] The Amsterdam density functional (ADF) code is based on the valence electrons theory. See the text for details of the calculation of the condensed to atom properties

$$f_k^- = \rho_k(N) - \rho_k(N-1) \ . \tag{17}$$

With the Fukui function condensed to atom, we may evaluate the condensed to atom softness using the Eq. (1):

$$s(\mathbf{r}) = f(\mathbf{r})S \ . \tag{18}$$

The condensed to atom hardness is obtained by using Fuentealba's equation [15]

$$\eta(\mathbf{r}) \cong \rho(\mathbf{r})/2NS(\mathbf{r}) \ . \tag{19}$$

From the information summarized in Table 1, on the basis of a local HSAB principle [7, 27], one would expect a hard electrophile like a proton to attack the N center, in view of its markedly higher hardness value, as compared to that of the C center. On the other hand, from the net charge at the C and the N centers, one would expect the attack by a positively charged electrophile like H^+ to be at either the C or N atomic center in view of the very small differences in this index. Note that while ADF, HF and CISD calculations predict the N atom to be slightly more negative than the C center, the B3LYP calculation predicts the opposite situation.

On the other hand, it is known from experimental findings that the isomer HCN is more stable than the isomer HNC by 14.8 kcal/mol [28]. The full calculation of the PES of HCN reveals that protonation at C is thermodynamically more favorable than protonation at the N site in all four calculations performed here: ADF: 14.4; B3LYP: 15.7; HF: 11.8 and CISD: 15.3 kcal/mol. The calculated intramolecular proton transfer energy barrier measured from the HCN ground state was as follows: ADF: 45.2; B3LYP: 49.3; HF: 50.7 and CISD: 51.0 kcal/mol (in the absence of the experimental value, the reference estimation of this magnitude is 44.6 kcal/mol [29]). In summary, on the basis of the net charge alone, it is very difficult to unambiguously predict the site of protonation in the cyanide ion. Also, the local HSAB principle is violated in this case: the hard-hard interaction involving the interaction of the proton with the N center in CN^- does not yield the more stable product (HNC). A possible explanation for this result may be found in our working hypothesis establishing that the approach of the electrophilic agent changes the initial reactivity pattern by promoting a fluctuation in the electron density at the C and N sites, in a way described by Eq. (10).

4 The reactivity towards model electrophiles of variable hardness

We will illustrate the usefulness of Eq. (10) by studying the reactivity of CN^- ion towards the attack by two model electrophilic E^+ agents of variable hardness, represented by a point charge and a ghost atom, respectively. The former represents an infinitely hard electrophile, whereas the presence of orbitals in the latter may help to simulate some degree of electronic polarization in E^+.

In order, to test this hypothesis, calculations of the electron density variations upon approach of the two model electrophiles were performed. For this purpose, the E^+ reagents were allowed to approach the CN^- frame, within a trajectory perpendicular to the C≡N bond, to form a T-shaped arrangement compatible with the calculated TS stationary geometry of the parent system, HCN. This is shown in Fig. 1. In order to prove that these changes are independent of the method used to approach the electron density, we selected the B3LYP and CISD calculations. Both methods predict opposite Mulliken net populations at the C- and N-centers (see Table 1) for the isolated cyanide ion. In general, there is no significant change in the TS geometries calculated by the four methods used in this work. At the TS, the

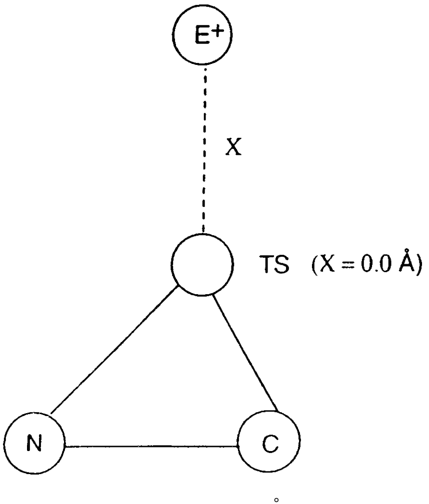


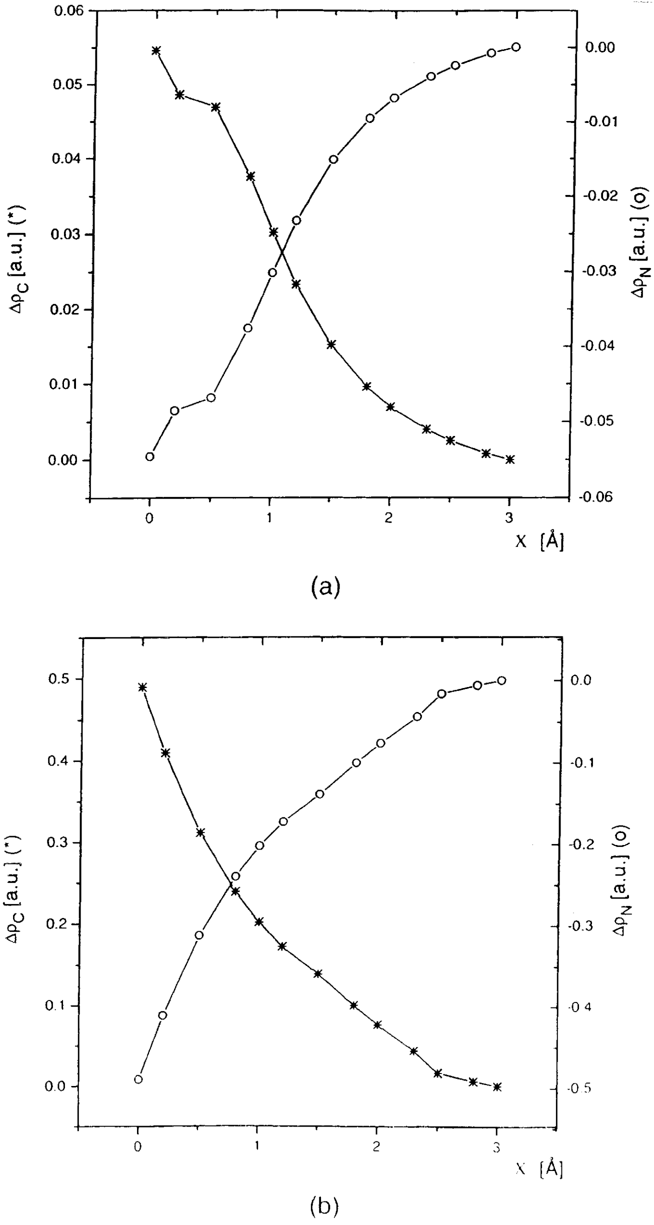
Fig. 1. Coordinate X (in Å) measuring the approach of model electrophiles towards the cyanide ion with a transition structure topology. The C—N distance is set at the equilibrium value in order to measure the response of the reactant and the susceptibility to the topology

proton displays a net charge of about 0.3 electron units. In Fig. 1, the distance X to the virtual transition structure was varied from $R = 3.0$ Å to $R = 0.0$ Å, corresponding to the TS structure. Observe that distance C—N is the equilibrium one for the ion while the distance and orientation of the electrophile vary around the virtual transition structure.

4.1 Unpolarizable electrophiles

We first evaluated the variations in electron density for the approach of a point charge, simulating the attack on the cyanide frame by an infinitely hard electrophile. We used a point charge having a net value of 0.3 electron units, compatible with the net charge shown by the proton at the TS. The results of the calculations are depicted in Figs. 2a and 3a. It may be observed that upon approach of an extremely hard electrophile, there is an inversion in the electronic population at both sites, so that, in a neighborhood of the TS, the reactivity pattern predicted from local predictors (cf. Table 1) is completely reversed, both at the B3LYP and CISD levels of the theory. ADF and HF calculations yielded the same response. Figures 2b and 3b show the predicted changes in electron density. It may be seen that our working Eq. (10) correctly follows the trend displayed by the calculated values (see Figs. 2a, 3a). To evaluate the electronic changes in electron density at both sites, we used the s_k^0 values given in Table 1, which correspond to the values of the local softness (the proportionality constant between the electron density and modified potential variations within the present approach), at the C and N centers of the isolated cyanide ion. This approach, even though it may be criticized, because one would expect the local softness also to vary with the electron density, is consistent with the first-order perturbation theory nature of the master Eq. (2). The inversion in the electronic population, for the case of a point-charge model electrophile, may be traced back to an intramolecular charge transfer (CT) from the N to the C centers.

In summary, the observed reactivity of the cyanide ion with a hard electrophile, as in the $[H^+ + CN^-]$ system, may be described in classical reaction coordinate terms as follows: at the beginning of the reaction, the N atom displays a slightly higher propensity to establish a favorable electrostatic interaction with the proton (it is more negative, except for the B3LYP case). However, upon approach of a hard electrophile, the electron density at the N and C sites fluctuates in a manner shown in Figs. 2 and 3, so that at the TS ($X = 0.0$), this situation is completely reversed by a charge transfer from the N to C of the cyanide ion. This result, which is independent of the quantum chemical method used to approximate the electron density, stresses the non-local character of the electrophile-nucleophile interaction, in the sense that the electronic properties of more than one site are required to correctly explain the observed reactivity in this system, and that becomes compatible with a local HSAB principle.



(a)

(b)

Fig. 2a, b. Variations in the electron density at the nitrogen and carbon sites, upon the approach of a point charge model electrophile. **a** Calculated values and **b** predicted values from Eq. (10). B3LYP/6-311G(*d*) calculations

4.2 Polarizable electrophiles

We allowed the approach along the X coordinate of a model polarizable electrophile simulated by a ghost atom having an extra basis set compatible with that of HCN, and with a fractional nuclear charge $Z = 0.3$. By this procedure, we intended to imitate the approach of a softer electrophile to the CN^- frame. The results of these calculations are shown in Fig. 4a and correspond to B3LYP/6-311G(*d*) calculations. It may be seen that the electronic population of both N and C atoms decreases due to a charge transfer process towards the electrophile (not shown in Fig. 4). CISD, ADF and HF calculations yielded the same response. This result indicates that the

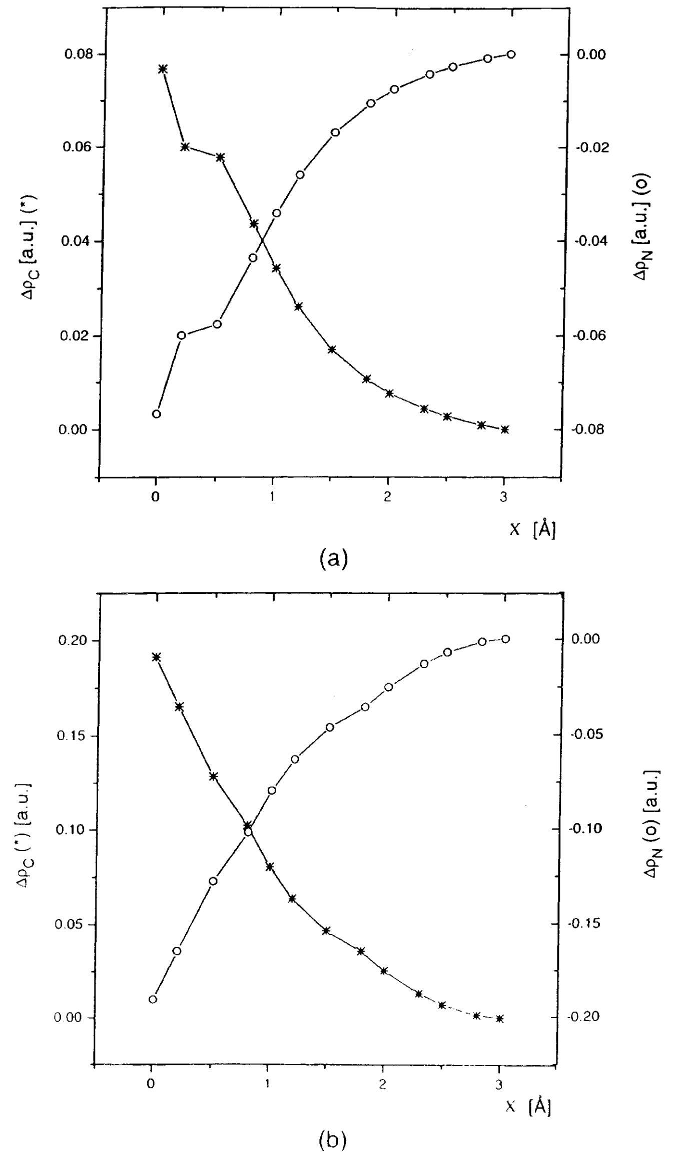


Fig. 3a, b. Variations in the electron density at the nitrogen and carbon sites, upon the approach of a point charge model electrophile. **a** Calculated values, and **b** predicted values from Eq. (10). CISD/6-311G(*d*) calculations

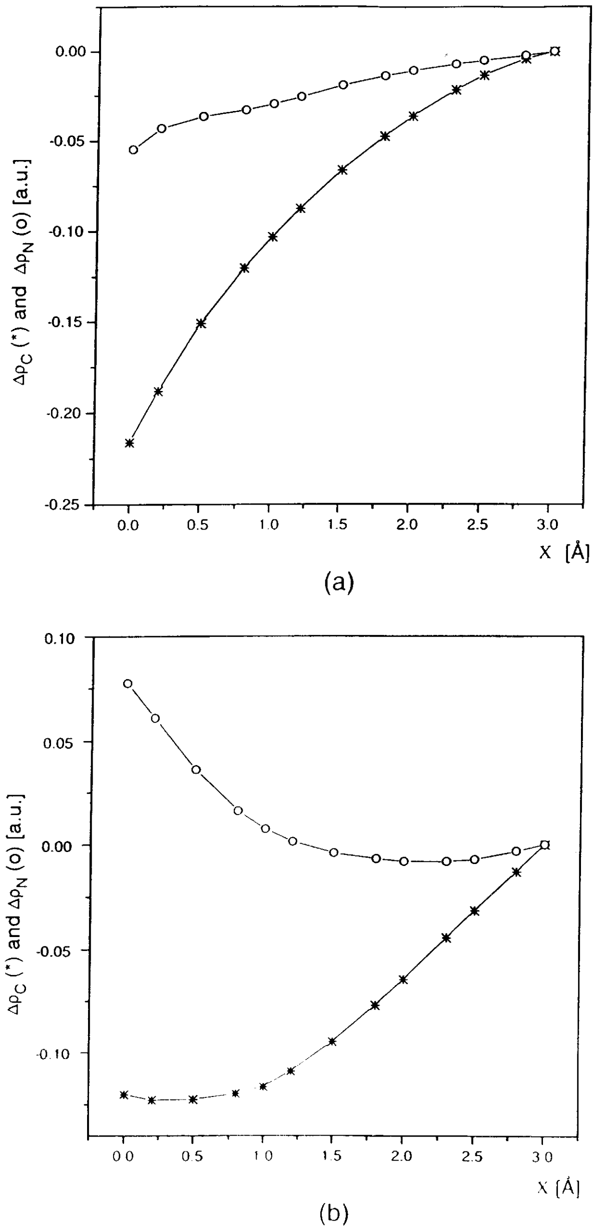


Fig. 4a, b. Variations in the electron density at the nitrogen and carbon sites, upon the approach of a polarizable model electrophile. **a** Calculated values and **b** predicted values from Eq. (10). B3LYP/6-311G(*d*) calculations

approach of a softer electrophile to the CN^- ion will not predict the correct reactivity pattern observed in the HCN/HNC system, compatible with a local HSAB principle. This becomes apparent after inspection of Fig. 4a, because it shows that upon approach of the model soft electrophile, the decrease in electronic charge at the C center is markedly greater than the corresponding decrease in electronic charge of the N center. As a result, at the TS, the C atom will display a still more positive charge than it has for reactants, and the N center will be the more favorable site for protonation. This result is consistent with previous reports on the reactivity of the cyanide ion towards the Li^+ and Na^+ electrophiles [29, 30]. In the former case, it was found by Clementi [31] that Li^+ could orbit around the CN^- frame, that is, when the electrophile becomes a little softer, the N center may display a site reactivity comparable to that of the C center. This conclusion is reinforced by the fact that for Na^+, which is expected to behave as a softer electrophile as compared to H^+ and Li^+, the lowest ground state displays a T-shaped structure very similar to the TS structure found for HCN [27, 32]. It is also interesting to stress that the values predicted by our model Eq. (10) follow fairly well the calculated trend along the whole progress coordinate, as shown in Fig. 4b, despite the fact that the predicted values this time present an opposite curvature compared to that of the calculated values. However, this effect does not change the main results discussed above, in the sense that soft-hard electrophile-nucleophile interactions in this system make the N atom as reactive as the C center.

4.3 Charge transfer effects

Equation (10) may be also useful to discuss the nature of the forces that drive the intramolecular CT observed in the present case. Table 2 summarizes the partitioned contribution to the changes in electron density at the N and C sites, in terms of the contributions that depend on the external perturbation $\delta v(\mathbf{r})$, and that due to the changes in the electronic chemical potential, upon the approach of a point-charge model electrophile to the TS, for some selected values of the progress coordinate. First of all, we observe that in the long-range interaction regime, the electrostatic contribution $-s_k^0\delta v_k$ dominates the changes in electron density at both the C and N centers. This result stresses the major role of the *charge control* interactions for the case of an infinitely hard model electrophile. The contribution due to the changes in the electronic chemical potential, which should be related to a CT from the N to the C center, becomes significant at a distance of 1.0 Å from the TS. It may also be observed that while this second contribution to the changes in electron density has a cooperative character for N, it shows an opposite contribution to the C center.

The corresponding results of the calculations for the approach of a polarizable model electrophile are shown in Table 3. Here, as expected, the electrostatic contributions given by the first term of Eq. (10) are markedly lower than those produced by the approach of a point charge (see Table 2). The CT from the N to the C center is less clear in this case, due to the presence of orbitals in the model electrophile. In fact, we observed a CT towards the electrophile of about 0.25 electron units at the TS that may be responsible for the different pattern in the electron density variations shown in Figs. 2 and 3 for the case of an infinitely hard eletrophile, and Fig. 4 for the case of a polarizable electrophile. From Fig. 4, we note that in the long-range interaction regime (i.e. up to 1.5 Å from the TS), both the calculated and predicted values show a systematic decrease in the C electron population, whereas the N center tends to maintain the same electron population independent of the X coordinate.

Table 2. Contributions to the changes in electron density at carbon and nitrogen sites as predicted by Eq. (10), for the approach of a point charge to the CN$^-$ ion, for selected values of the reaction coordinate X[a]

X	Site k	$\Delta\rho_k =$	$-s_k^0\delta v_k$	$+s_k^0\Delta\mu$
3.0	C	0.0	0.0	0.0
	N	0.0	0.0	0.0
2.5	C	0.0158	0.0158	0.0
	N	−0.0158	−0.0158	0.0
2.0	C	0.0761	0.1177	−0.0416
	N	−0.0761	−0.0345	−0.0178
1.5	C	0.1381	0.2213	−0.0832
	N	−0.1381	−0.0549	−0.0356
1.0	C	0.2022	0.3270	−0.1248
	N	−0.2022	−0.1488	−0.0534
0.0	C	0.4884	0.7422	−0.2538
	N	−0.4884	−0.3798	−0.1086

[a] All values in atomic units, using B3LYP/6-311G(d) approximated electron density. The value at X = 3.0 Å is taken as the reference. The $\Delta\mu = \mu - \mu^{\circ}$ values were obtained by comparing the differences of the electronic chemical potentials in the presence and absence of the external perturbation, at each point of the progress coordinate. S_k^0 values from Table 1

Table 3. Contributions to the changes in electron density at carbon and nitrogen sites as predicted by Eq. (10), for the approach of a ghost atom to the CN$^-$ ion, for selected values of the progress coordinate X[a]

X	Site k	$\Delta\rho_k =$	$-s_k\delta v$	$+s_k\Delta\mu$
3.0	C	0.0	0.0	0.0
	N	0.0	0.0	0.0
2.5	C	−0.0316	−0.0341	0.0025
	N	−0.0073	−0.0084	0.0011
2.0	C	−0.0645	−0.0811	0.0166
	N	−0.0082	−0.0153	0.0071
1.5	C	−0.0948	−0.1356	0.0408
	N	−0.0041	−0.0215	0.0174
1.0	C	−0.1165	−0.1935	0.0770
	N	0.0073	−0.0256	0.0329
0.0	C	−0.1202	−0.2800	0.1606
	N	0.0774	0.0087	0.0687

[a] See footnote in Table 2

5 Concluding remarks

A simple formulation of a non-local reactivity theory, based on the first-order static density response function of DFT, has been presented. Two approaches to obtain this quantity were used. The first one considers the static density response function proposed by Berkowitz and Parr [6] and used in the context of a local approximation to the softness kernel [20]. This approach, yet crude, produced a simple and physically meaningful expression for the variations in electron density. They become proportional to a modified potential, containing the information about the electrostatic perturbing potential due to the electrophile, and the changes in the electronic chemical potential accounting for the intramolecular charge transfer between the reactive sites of an ambident nucleophile, the proportionality constant being the intrinsic softness of the nucleophile at the site. The second approach, which used a less restrictive static density response function, derived from a model KS one-electron density matrix [22], showed that the main theoretical result, namely the reliability of Eq. (10) to account for non-local effects, is conserved. The model was successfully applied to the study of the gas phase chemical reactivity of the cyanide ion towards the electrophilic attack by model electrophiles of variable hardness. Our Eq. (10) correctly reproduced the calculated variation of the electron density, at different levels of electronic theory. This model shows that the local electronic properties of more than one site in a molecule may be required to correctly describe the chemical reactivity pattern, especially in the case of ambident reagents. In the present case, we showed that a non-local criterion is necessary to explain the observed gas-phase reactivity of the cyanide ion, which becomes compatible with the experimental results and a local HSAB principle, when the geometry explored is found in the vicinity of the corresponding TS.

Finally, a comment about the form of Eq. (10) is pertinent. While this simple expression is able to describe the reactivity pattern of the cyanide ion towards electrophilic agents of variable hardness one step beyond the current static picture of chemical reactivity, it has its weakness in the proportionality constant. This relates the changes in electron density and the modified potential at different sites in a molecule, as the local softness $s^{\circ}_{k,}$ defined for the substrate in the absence of the reagent. This result even though consistent with the first-order perturbation character of Eq. (2) used to derive our working Eq. (10), is worthy of further study. If we think in a more complete picture of non-local reactivity having a variable softness factor, one should go at least one order further and incorporate higher derivatives (for instance second-order) of the electron density. Such a formalism should contain a static response function for the Fukui function, as it may be deduced from Eqs. (1) and (18). This response function has been already proposed in the literature by Fuentealba and Parr [33], and it is at present being considered for further studies on non-local reactivity in our group.

Acknowledgements. This work has received financial support from FONDECYT, under contracts 1970212, 1950677 and 2960011. R.C. is indebted to Fundación Andes, Project C-13222/3 for financial support. R.C. and P.P. acknowledge support from the Departament de Ciènces Experimentals, Universitat Jaume I and Institute of Physical Chemistry, Uppsala University, where this work was completed. The authors are grateful to the Sevei d'Informàtica de la Universitat Jaume I for providing them with CPU time. O.T. gratefully acknowledges financial support from NFR.

References

1. Parr RG, Yang W (1989) Density functional theory of atoms and molecules. Oxford University Press, New York
2. Pearson RG (1963) J Am Chem Soc 85:3533
3. Parr RG, Pearson RG (1983) J Am Chem Soc 105:7512
4. Chattaraj PK, Lee H, Parr RG (1991) J Am Chem Soc 113:1855
5. Yang W, Parr RG (1985) Proc Natl Acad Sci USA 82:6723
6. Berkowitz M, Parr RG (1988) J Chem Phys 88:2554
7. Pearson RG (1987) J Chem Educ 64:561
8. Parr RG, Chattaraj PK (1991) J Am Chem Soc 113:1854
9. van Gunsteren WF, Weiner PK, Wilkinson AJ (eds) (1993) Computer simulation of biomolecular systems 2: theoretical and experimental applications. ESCOM, Leiden. For a recent example see: Zhu W, Wang D, Zhang JZH (1997) Theor Chem Acc 96:31
10. Polanyi JC, Zewail AH (1995) Acc Chem Res 28:119
11. Tapia O, Andrés J, Stamato FLM (1996) In: Tapia O, Bertrán J (eds) Solvent effects and chemical reactivity. Kluwer, Amsterdam, p 283
12. Hu WP, Truhlar DG (1994) J Am Chem Soc 116:7797
13. Ghosh SK, Berkowitz M (1985) J Chem Phys 83:2976
14. Berkowitz M, Ghosh SK, Parr RG (1985) J Am Chem Soc 107:6811
15. Fuentealba P (1995) J Chem Phys 103:6571
16. Lowry TH, Richardson KS (1987) Mechanism and theory in organic chemistry, 3rd edn. Harper Collins New York, p 723
17. Jones ME, Kass SR, Filley J, Barkley RM, Ellison GB (1985) J Am Chem Soc 107:109
18. Jackman LM, Lange BC (1981) J Am Chem Soc 103:4494
19. Senet P (1996) J Chem Phys 105:6471
20. Vela A, Gázquez JL (1990) J Am Chem Soc 112:1490
21. Gázquez JL (1993) In: Sen KD (ed) Structure and bonding 80: chemical hardness. Springer, Berlin Heidelberg New York, p 27
22. Fuentealba P, Savin A (private communication) We thank these authors for making their results available to us prior to publication
23. te Velde G, Baerends EJ (1992) J Comput Phys 99:84
24. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheesman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JV, Ciolowski J, Stephanov BB, Nanayakkara A, Challombe M, Peng CY, Ayala TY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox VJ, Binkley JS, Defrees JP, Baker J, Stewart JP, Head-Gordon M, González C, Pople JA (1995) Gaussian 94. Gaussian Inc., Pittsburgh, Pa
25. Yang W, Mortier WJ (1986) J Am Chem Soc 108:5708
26. De Proft F, Langenaeker W, Geerlings P (1995) Int J Quantum Chem 55:459
27. Contreras R, Safont VS, Pérez P, Andrés J, Moliner V, Tapia O (1998) J Mol Struct (Theochem) (in press)
28. Lee TJ, Rendell AP (1991) Chem Phys Lett 177:491
29. Makarewicz J, Ha TK (1995) Chem Phys Lett 232:497
30. Klein ML, Goddard JD, Bounds DG (1981) J Chem Phys 75:3909
31. Clementi E, Kistenmacher H, Popkie H (1973) J Chem Phys 58:2460
32. Fan L, Ziegler T (1990) J Chem Phys 92:3645
33. Fuentealba P, Parr RG (1991) J Chem Phys 94:5559