Density Polarization and Chemical Reactivity

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A qualitative analysis of the main polarization effects in molecular systems is presented. Both the single and multiple site reactivity cases are discussed and illustrative applications are given for selected molecular systems: acrylonitrile, propene, formamide, and the trans-nitrous acid. The polarization effects are expected to determine the directional specificity of an early approach (before the substantial charge transfer and the intramolecular rearrangements) of both reactants in a chemical reaction. The preferred direction of such an approach is therefore postulated as that generating the minimum energy change of reactants in the field of their respective reaction partners, including the stabilization due to the relaxation of their densities in a changed environment. The example of the electrophilic substitution in the five membered heterocycles is examined. It demonstrates the importance of the density polarization effects for explaining the observed α-preference in these reactions for furan, pyrrole and N-methyl pyrrole. Next we discuss the relation between the density relaxation and the internal stability of molecular systems. Finally, we briefly comment on the Atoms-in-a-Molecule description.

1. Introduction

In recent years much effort has been devoted to the development of a charge density based theory of chemical reactivity [1 – 4]. Bader and co-workers [1, 2] have shown that the relative orientation of reactants can be predicted from properties of the Laplacian of a charge distribution, which identifies the regions of space where the electronic charge is locally concentrated or depleted and provides a bridge between the density and orbital approaches to chemical reactivity. The Fukui function approach [3, 4] of Parr and co-workers relates formally the density functional theory to the principal ideas of the frontier orbital theory [5].

An understanding of chemical reactivities requires a knowledge of the main density relaxation effects, i. e. the accomodation of the electronic charge distribution of a reactant to the perturbing electrostatic potential produced by the other reactant. This polarization is an essential feature of many trends in both single and multiple site reactivity [6, 7]. The present work presents a simple, qualitative analysis of the density polarization. Our approach is based on the standard second-order orbital perturbation theory and is related to the earlier ideas advanced by Platt [8] Coulson and Longuet-Higgins [9], Bartell [10], Pearson [11], and Bader [12]. All these treatments regard the perturbing external potential as the *causa prima* of the preferred relative alignment of reactants, shapes of molecules, or trends in force constants.

The electrostatic and polarization interactions should determine the relative approach of reactants at an early stage of a reaction, when there is no charge transfer between yet distant reactants and a molecular rearrangement is negligible. This polarizing stage initiates the chemical interaction at a closer approach, dominated by the frontier orbital interaction on both reactants. As shown by Bader et al. [1, 2] the reaction complex at this later stage is determined by aligning regions of charge concentration with regions of charge depletion in their Laplacian distributions.

The relaxation of density is closely related to the problem of molecular stability. The softest (the most facile) relaxation of a charge density in the perturbing potential of the other reactant should lead to the smallest energy increase during the early approach of reactants. This relaxation corresponds to the lowest eigenvalue of the hardness kernel [13], the inverse [14] of the density response kernel [14] determining the density relaxation by an external electric field.

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2. Qualitative Analysis of Density Relaxation

Consider a molecular system S in the field of an approaching (but distant) reaction partner R. Then, neglecting very small nonlocal contributions, the change of the external potential on S, due to the presence of R, should be the classical electrostatic potential $\Delta v(r)$ generated by the whole charge distribution (electrons and nuclei) of *R*. At even larger S - - - R separations this field approximately becomes the potential due to the net atomic charges on R. As mentioned above, we assume that at this stage there is no charge transfer between *S* and *R*, and we examine the equilibrium (relaxed) state, *S**, of *S* polarized by *R*; we call it the *valence state* of *S* corresponding a given stage of the approach.

The corresponding energy change of S in S* - - - R, relative to S and up to the second-order in the perturbation $\Delta v(r)$, is

$$E = E_{\mathrm{n}} + E_{\mathrm{e}} = \left\{- \sum_{\alpha} Z_{\alpha} \Delta v(\boldsymbol{R}_{\alpha})\right\} + \left\{\int \mathrm{d}\boldsymbol{r}[n(\boldsymbol{r}) + \tfrac{1}{2}\,\delta n^{*}(\boldsymbol{r})]\,\Delta v(\boldsymbol{r})\right\}, \tag{1}$$

where Z_{α} is the atomic number and R_{α} is the position of nucleus α of S, n is the electron density of the isolated S, and the change of the density in the valence state,

$$\delta n^{*}(\boldsymbol{r}) = n^{*}(\boldsymbol{r}) - n(\boldsymbol{r}) = \int \mathrm{d}\boldsymbol{r}\, \beta(\boldsymbol{r}, \boldsymbol{r}')\, \Delta v(\boldsymbol{r}'), \tag{2}$$

preserving the number of electrons, $\int \mathrm{d}\boldsymbol{r}\, \delta n^{*}(\boldsymbol{r}) = 0$, is determined by the symmetric *density response kernel*

$$\begin{aligned}\beta(\boldsymbol{r}, \boldsymbol{r}') &= \delta^{2} E[n, v]/\delta v(\boldsymbol{r})\, \delta v(\boldsymbol{r}') \\ &= \delta n(\boldsymbol{r})/\delta v(\boldsymbol{r}') = \beta(\boldsymbol{r}', \boldsymbol{r}).\end{aligned} \tag{3}$$

The density relaxation δn^{*} represents a *spontaneous* response of the system to the *forced* displacement Δv of S from its initial equilibrium state. By the LeChâtelier principle, the second-order contribution to *E* must be negative:

$$\tfrac{1}{2} \int \mathrm{d}\boldsymbol{r}\, \delta n^{*}(\boldsymbol{r})\, \Delta v(\boldsymbol{r}) < 0. \tag{4}$$

Since direct *perturbation-of-density* methods are not available one may instead use the standard *perturbation-of-orbitals* technique to get workable approximations to $\beta(\boldsymbol{r}, \boldsymbol{r}')$. For real molecular orbitals (MO's), $\{\psi_i\}$, the total density of a closed shell system is

$$n(\boldsymbol{r}) = 2 \sum_{i}^{\mathrm{occd}} \psi_i^{2}(\boldsymbol{r}), \tag{5}$$

where we sum over all occupied MO's. Using the standard perturbational expression for $\delta\psi_i$,

$$\delta\psi_i = - \sum_{j \neq i} \frac{\int \mathrm{d}\boldsymbol{r}\, \psi_i(\boldsymbol{r})\, \Delta v(\boldsymbol{r})\, \psi_j(\boldsymbol{r})}{e_j - e_i}\, \psi_j, \tag{6}$$

where e_k is the MO energy level, and neglecting the quadratic terms in $\delta\psi_i$ gives

$$\begin{aligned}\delta n^{*}(\boldsymbol{r}) = - 4 \sum_{i}^{\mathrm{occd}} \sum_{j}^{\mathrm{virt}} &\frac{\int \mathrm{d}\boldsymbol{r}'\, \psi_i(\boldsymbol{r}')\, \Delta v(\boldsymbol{r}')\, \psi_j(\boldsymbol{r}')}{e_j - e_i} \\ &\cdot \psi_i(\boldsymbol{r})\, \psi_j(\boldsymbol{r})\end{aligned} \tag{7}$$

with the second summation being over all virtual orbitals. Hence [see the definition (3)]

$$\beta(\boldsymbol{r}, \boldsymbol{r}') = - 4 \sum_{i}^{\mathrm{occd}} \sum_{j}^{\mathrm{virt}} \frac{\psi_i(\boldsymbol{r}')\, \psi_j(\boldsymbol{r}')\, \psi_i(\boldsymbol{r})\, \psi_j(\boldsymbol{r})}{e_j - e_i}. \tag{8}$$

By the orthogonality between MO's the kernel (8) automatically satisfies the closed-system constraint:

$$\int \mathrm{d}\boldsymbol{r}\, \beta(\boldsymbol{r}, \boldsymbol{r}') = 0. \tag{9}$$

For the purpose of a qualitative analysis we introduce further approximations, relevant to the reactions in question. For example, in the case of a strong local perturbation at $\boldsymbol{r}' = \boldsymbol{D}$, like that from an atomic ion, the perturbing potential might plausibly be approximated by a δ-function potential,

$$\Delta v(\boldsymbol{r}) \approx \Delta v_{\boldsymbol{D}}(\boldsymbol{r}) = v\, \delta(\boldsymbol{r} - \boldsymbol{D}) = - q\, \delta(\boldsymbol{r} - \boldsymbol{D}); \tag{10}$$

here q is a measure of the perturbing charge at $\boldsymbol{D}$: positive for an electrophilic attack and negative for a nucleophilic attack. For the model potential (10) the coupling matrix elements in (6–7) become the corresponding overlap products

$$\int \mathrm{d}\boldsymbol{r}\, \psi_i\, \Delta v_{\boldsymbol{D}}\, \psi_j = v\, \psi_i(\boldsymbol{D})\, \psi_j(\boldsymbol{D}) \equiv v\, \Omega_{ij}(\boldsymbol{D}) \tag{11}$$

with the *transition density* $\Omega_{ij}(\boldsymbol{r})$ representing the polarization channel resulting from the $\psi_i \rightarrow \psi_j$ "excitation". Hence the resulting model expression for $\delta n_{\boldsymbol{D}}^{*}(\boldsymbol{r})$:

$$\begin{aligned}\delta n_{\boldsymbol{D}}^{*}(\boldsymbol{r}) &= - 4 v \sum_{i}^{\mathrm{occd}} \sum_{j}^{\mathrm{virt}} \Omega_{ij}(\boldsymbol{D})\, \Omega_{ij}(\boldsymbol{r})/\Delta e_{ij} \\ &\equiv - 4 \sum_{k}^{\mathrm{channels}} [v\, \Omega_k(\boldsymbol{D})/\Delta e_k]\, \Omega_k(\boldsymbol{r}) \\ &\equiv - 4 \sum_{k}^{\mathrm{channels}} \lambda_k(\boldsymbol{D})\, \Omega_k(\boldsymbol{r}),\end{aligned} \tag{12}$$

where $\Delta e_{ij} = e_j - e_i \equiv \Delta e_k > 0$.

One of the artefacts of the δ-function approximation (10) is that there is no coupling ($\lambda_{ij} = 0$) between ψ_i and ψ_j for the perturbing charge placed on any of the nodal surfaces of both MO's. In general this is a qualitatively erroneous prediction; e.g., two p_z states *are* coupled by the point charge v at $\boldsymbol{D}$ in the xy plane. Therefore, in order to alleviate this difficulty in qualitative considerations, we introduce the *effective* (mean) transition density, $\Omega_{e,k}(\boldsymbol{D})$, which reproduces through the δ-function expression the coupling matrix element for the point-charge potential:

$$\Omega_{e,k}(\boldsymbol{D}) \equiv \int d\boldsymbol{r}\, \Omega_k(\boldsymbol{r})/|\boldsymbol{r} - \boldsymbol{D}| \equiv \Omega_e[\Omega_k(\boldsymbol{D})]\,. \qquad (13)$$

In qualitative considerations, only the sign and an estimate of the relative magnitude of a given $\Omega_{e,k}$ on constituent atoms are needed to make predictions of the main polarization effects via this channel for the alternative locations of an approaching charge. This limited information is easily available from the known shapes of MO's.

Normally the maximum mixing will occur for the *frontier* MO's, the highest occupied (HO) and the lowest unoccupied (LU) MO's; this interaction gives for the polarized frontier MO's:

$$\begin{aligned} \psi^*_{\mathrm{HO}}(\boldsymbol{D}) &\approx N[\psi_{\mathrm{HO}} - \lambda(\boldsymbol{D})\, \psi_{\mathrm{LU}}]\,, \\ \psi^*_{\mathrm{LU}}(\boldsymbol{D}) &\approx N[\psi_{\mathrm{LU}} + \lambda(\boldsymbol{D})\, \psi_{\mathrm{HO}}]\,, \end{aligned} \qquad (14)$$

where

$$\lambda(\boldsymbol{D}) = v\, \Omega_e(\boldsymbol{D})/(e_{\mathrm{LU}} - e_{\mathrm{HO}}) \qquad (15)$$

and $\Omega_e = \Omega_e[\psi_{\mathrm{HO}}\, \psi_{\mathrm{LU}}]$. This frontier MO mixing provides the dominant channel for the density relaxation [12].

However, in cases where many low-lying virtual orbitals are closely spaced it is questionable to assume that just the lowest of this dense set of orbitals dominates the system polarization and reactivity. Clearly, when there are such bands of almost degenerate low virtual orbitals, one has to take into account all states to adequately represent the relevant modes of polarization. Similarly, when the HO-LU MO mixing does not take place, e.g., for reasons of symmetry, one has to consider the transition densities involving the second HO (SHO) and/or the second LU (SLU) MO's, etc. As demonstrated by the illustrative examples considered in the present work, usually one must include a number of polarization channels to properly account for the observed trends in the polarization of a molecular electronic density by approaching charges.

Clearly, the *fine-grained* description of density relaxation, examining a change in density at each infinitesimal local site around $\boldsymbol{r}$, appears too detailed for qualitative chemical considerations. Namely, in situations of interest for chemistry, one makes observations and statements based upon a limited *chemical resolution* which in general does not distinguish between local sites within an *atom-in-a-molecule* (AIM). Hence, if we consider an atomic region G_X of an atom X, we shall mainly be interested in the AIM, *coarse-grained* parameters, obtained by integrating their local analogs over the atomic regions. The unique division of a molecule into the non-overlapping atomic regions, G_X, required for the rigorous AIM description, follows from the virial partitioning of Bader et al. [15–18].

When examining the polarization trends we therefore ask about changes in the average numbers of electrons, N_X:

$$\begin{aligned} \delta N^*_X(\boldsymbol{D}) &\equiv \int_{G_X} d\boldsymbol{r}\, \delta n^*_D(\boldsymbol{r}) \\ &= -4v \sum_k^{\text{channels}} \frac{1}{\Delta e_k}\, \Omega_{e,k}(\boldsymbol{D}) \int_{G_X} d\boldsymbol{r}\, \Omega_k(\boldsymbol{r}) \\ &\approx -\frac{4v}{\Delta e}\, \Omega_e(\boldsymbol{D}) \int_{G_X} d\boldsymbol{r}\, \Omega(\boldsymbol{r}) \\ &\equiv -\frac{4v}{\Delta e}\, \Omega_e(\boldsymbol{D})\, \Omega_e(X)\,. \end{aligned} \qquad (16)$$

Thus, within the frontier MO approximation the magnitude of a change in the AIM electron population is proportional to the product of the effective frontier MO transition density at the location of the approaching charge, $\Omega_e(\boldsymbol{D})$, and the *atomic transition density*, $\Omega_e(X)$, as defined by (16). The dominant contribution to $\Omega_e(X)$ comes from the atomic orbitals $\{\chi_i\}$ centered on X:

$$\Omega_e(X) \approx \sum_{i \in X} \sum_{j \in X} C_{i,\mathrm{HO}}\, C_{j,\mathrm{LU}} \int_{G_X} d\boldsymbol{r}\, \chi_i(\boldsymbol{r})\, \chi_j(\boldsymbol{r})\,, \qquad (17)$$

where $C_{i,j}$ denotes the LCAO MO coefficient. For the π frontier MO's to which each atom of the π-electron system contributes only one orbital, p_π, this expression can be simplified even further for the purpose of only qualitative predictions:

$$\Omega_e(X) \approx C_{\pi,\mathrm{HO}}\, C_{\pi,\mathrm{LU}} \int_{G_X} d\boldsymbol{r}\, p^2_\pi(\boldsymbol{r}) \propto C_{\pi,\mathrm{HO}}\, C_{\pi,\mathrm{LU}}\,, \qquad (18)$$

where we have assumed an approximate normalization of the atomic orbital within his atomic region.

Finally, the change in molecular energy (1) resulting from the model perturbing external potential (10) is

$$\begin{aligned} E(\boldsymbol{D}) &= \int \mathrm{d}\boldsymbol{r}\, n(\boldsymbol{r})\, \Delta v_{\boldsymbol{D}}(\boldsymbol{r}) \\ &\quad - 2 \sum_{k}^{\text{channels}} \left[\int \mathrm{d}\boldsymbol{r}\, \Omega_k(\boldsymbol{r})\, \Delta v_{\boldsymbol{D}}(\boldsymbol{r})\right]^2/\Delta e_k \\ &= v\, n(\boldsymbol{D}) - 2\, v^2 \sum_{k}^{\text{channels}} \Omega_k^2(\boldsymbol{D})/\Delta e_k \\ &\approx v\, n(\boldsymbol{D}) - 2\, v^2\, \Omega_e^2(\boldsymbol{D})/\Delta e\,, \end{aligned} \tag{19}$$

since the nuclear contribution

$$E_n = -\, \Sigma_\alpha Z_\alpha v\, \delta(\boldsymbol{R}_\alpha - \boldsymbol{D})$$

vanishes for the distant perturbing charge.

3. Multiple Site Reactivity

In large molecular systems, especially those of biological interest, there are competing active sites for a given type of a reaction. An attack on one site is not without an effect on the reactivity of the remaining sites. This problem has been approached by Bartlett and Weinstein [7] by means of the multiple perturbation scheme in which the coupling between alternative reaction sites appears through the second-order correction to the energy. The specific terms representing this interaction are the matrix elements including the perturbation due to the approach of the external charge to one site and the perturbed MO's due to the perturbation on the other active site of a molecule.

We now examine how this interesting density relaxation effect is described within the present qualitative model. Consider the simplest case of a double perturbation by charges located at

$$D = (\boldsymbol{D}_1, \boldsymbol{D}_2)\,,$$

$$\Delta v(\boldsymbol{r}) \approx \Delta v_{\mathrm{D}}(\boldsymbol{r}) = v_1\, \delta(\boldsymbol{r} - \boldsymbol{D}_1) + v_2\, \delta(\boldsymbol{r} - \boldsymbol{D}_2)\,. \tag{20}$$

From (7) and (11) we then have the change in the electronic density,

$$\begin{aligned} \delta n_{\mathrm{D}}^*(\boldsymbol{r}) &= -\,4 \sum_{k}^{\text{channels}} \Omega_k(\boldsymbol{r}) \\ &\qquad \cdot [v_1 \Omega_k(\boldsymbol{D}_1) + v_2 \Omega_k(\boldsymbol{D}_2)]/\Delta e_k \\ &\approx -\frac{4}{\Delta e}\, [v_1\, \Omega_{\mathrm{e}}(\boldsymbol{D}_1) + v_2\, \Omega_{\mathrm{e}}(\boldsymbol{D}_2)]\, \Omega(\boldsymbol{r})\,, \end{aligned} \tag{21}$$

where we have again adopted the frontier MO approximation, $\Omega_{\mathrm{e}} = \Omega_{\mathrm{e}}[\psi_{\mathrm{HO}}\, \Psi_{\mathrm{LU}}]$. The resulting energy change (1) is:

$$\begin{aligned} E(\boldsymbol{D}) &\approx v_1\, n(\boldsymbol{D}_1) + v_2\, n(\boldsymbol{D}_2) \\ &\quad - \frac{2}{\Delta e}\, [v_1^2\, \Omega_{\mathrm{e}}^2(\boldsymbol{D}_1) + v_2^2\, \Omega_{\mathrm{e}}^2(\boldsymbol{D}_2) \\ &\quad + 2\, v_1 v_2\, \Omega_{\mathrm{e}}(\boldsymbol{D}_1)\, \Omega_{\mathrm{e}}(\boldsymbol{D}_2)]\,. \end{aligned} \tag{22}$$

The second-order contribution, responsible for the interaction between active sites, includes both the always negative response of each site to the approach of a charge to that site (the first two terms), and the interaction term between the two active sites (the third term). The latter can be stabilizing or destabilizing, depending on the nature of the external charges and the phases of the frontier MO's at the active sites in question. Notice, however, that the total second-order change in the system energy will always be negative [see (4)].

If we assume the same type of perturbation at both locations, $v_1 v_2 = v^2 > 0$, e.g. the protonation of both sites, the expression (22) becomes

$$\begin{aligned} E(\boldsymbol{D}) &\approx v\, [n(\boldsymbol{D}_1) + n(\boldsymbol{D}_2)] \\ &\quad - 2\, v^2\, [\Omega_{\mathrm{e}}(\boldsymbol{D}_1) + \Omega_{\mathrm{e}}(\boldsymbol{D}_2)]^2/\Delta e\,. \end{aligned} \tag{23}$$

It follows from this expression that the relaxational correction to the system energy strongly depends within the frontier MO approximation on the signs of the frontier MO transition density at the locations of the attacking charges. The different signs diminish the overall effect since there is a competition between the density adjustments resulting from both attacks (destructive interference effect). For identical signs these polarizations enhance each other (constructive interference effect). Another immediate observation is that, in order to maximize the second-order stabilization energy, the approaching charge (charges) should avoid the regions around the nodal surfaces of the frontier MO transition density, where Ω_{e} changes sign. Namely, for such locations of the perturbing charges there is a cancellation of the positive and negative contributions to the matrix element (13).

One similarly arrives at the analogous AIM expressions. For example, for the two-site attack [(20) and (21)] one has

$$\delta N_{\mathrm{X}}^*(\mathrm{D}) \approx -\frac{4}{\Delta e} \cdot [v_1\, \Omega_{\mathrm{e}}(\boldsymbol{D}_1) + v_2\, \Omega_{\mathrm{e}}(\boldsymbol{D}_2)]\, \Omega_{\mathrm{e}}(\mathrm{X})\,. \tag{24}$$

Hence, for the protonation at both sites, at equal stages of the approaches by the two protons at $\boldsymbol{D}_1$ and $\boldsymbol{D}_2$ ($v_1 = v_2 = v < 0$):

$$\delta N_X^*(\mathrm{D}) \propto [\Omega_e(\boldsymbol{D}_1) + \Omega_e(\boldsymbol{D}_2)]\,\Omega_e(\mathrm{X})\,. \qquad (25)$$

We now turn to illustrative examples of the qualitative analysis of the density relaxation effects in selected molecular systems.

4. Illustrative Applications

4.1. *Acrylonitrile and Propene Polarized by a Positive and Negative Charge*

We first discuss the polarization of acrylonitrile and propene (Fig. 1), for which the frontier MO polarization due to a positive (proton) and a negative (hydride) charge has been reported by Houk [6]. These results have been used to rationalize some anomalies observed in cycloaddition regioselectivity [6]. They also provide convenient data on which one can test our qualitative model of density relaxation.

The qualitative analysis requires a knowledge of the frontier MO's. They are shown in Fig. 1 together with the LCAO MO $C_{\pi,\mathrm{HO}}$ and $C_{\pi,\mathrm{LU}}$ coefficients from [6]. The perturbing charges, positive for an electrophilic attack and negative for a nucleophilic attack, are placed at one of the points P on the bisector of the double bond. Next we construct a qualitative contour of the frontier MO transition density, providing the signs of the $\Omega_e(\mathrm{P})$ and $\Omega_e(\mathrm{X})$. The numbers shown with Ω are the $C_{\pi,\mathrm{HO}}C_{\pi,\mathrm{LU}}$ products. The predicted changes in the atomic populations and the polarized frontier MO's (from [6]) are also shown for both the nucleophilic and electrophilic perturbations. The qualitative predictions agree with those from the model calculations on both systems.

The polarization of the frontier MO's is determined by the sign of λ, equal to that of the product $v\,\Omega_e(\mathrm{P})$ [(15)]. The qualitative predictions agree with the changes exhibited by the LCAO MO coefficients. It should be noticed, however, that the deformation due to the perturbing charges is small. This is partly because of the central position of P's, near the nodal surface of Ω, where we have predicted a relatively inefficient frontier MO mixing. Placing the charges near the atom 1 or 2 should produce a greater relaxation of density.

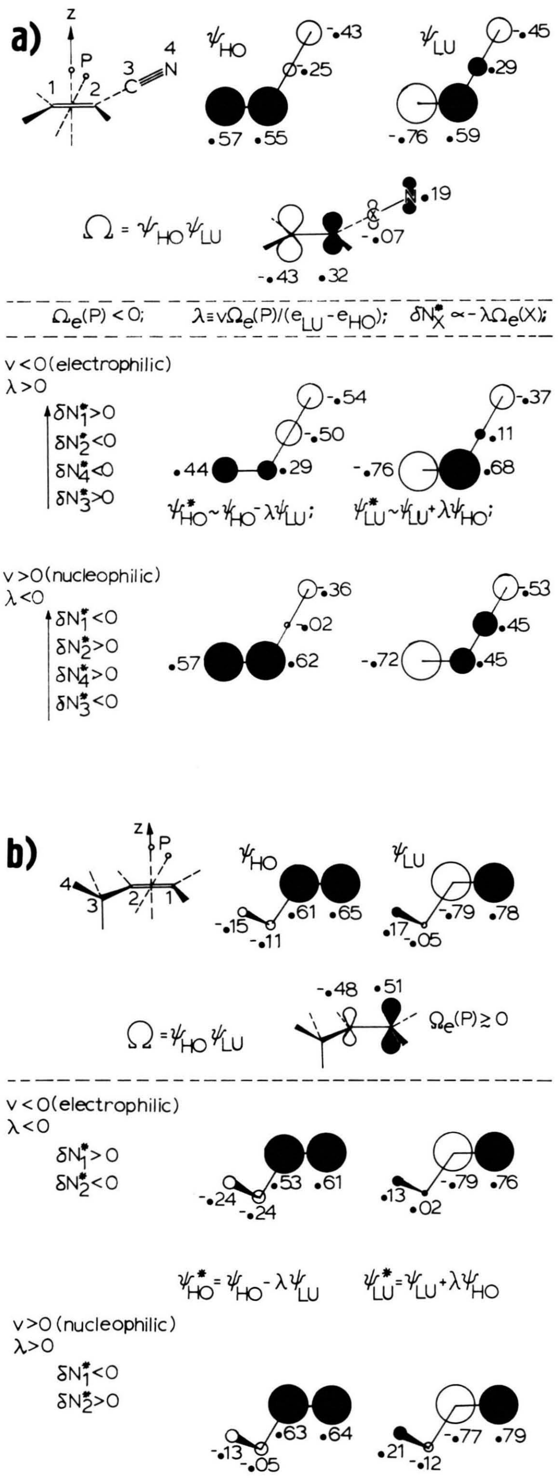

Fig. 1. The frontier MO polarization in acrylonitrile (a) and propene (b), due to the presence of a positive (electrophilic) and a negative (nucleophilic) reagent.

Reference to Fig. 1 a shows that upon approach by an electrophile to the center of the acrylonitrile double bond the HO MO polarization is increased $\delta N_1^* > 0$, $\delta N_2^* < 0$, while the polarization of the LU MO is decreased. Upon approach of a nucelophile the reverse trend is observed: the HOMO polarization is reversed as a result of $\delta N_1^* < 0$, and $\delta N_2^* > 0$, with the LUMO polarization being increased.

In the case of propene (Fig. 1 b) the positive charge increases the HOMO polarization, $\delta N_1^* > 0$, $\delta N_2^* < 0$; also the LUMO polarization (opposite to that of the HO MO) is slightly increased. The negative charge decreases the HOMO polarization, $\delta N_1^* < 0$, $\delta N_2^* > 0$, and reverses the LUMO polarization.

It should also be observed that in propene Ω is almost antisymmetric with respect to the surface of P's and the center of the double bond, while in acrylonitrile it is more polarized. This results in a greater $\Omega_e(P)$ for the latter and $\Omega_e(P) \sim 0$ in the case of propene. This observation rationalizes the greater relaxation changes observed in Figure 1 a.

4.2. *Formamide*

The frontier MO's of formamide [19–21] include the almost degenerate occupied orbitals, $p_n(O)$ (in the molecular plane, perpendicular to the CO-direction) and π_2 (CO bond), as well as the π^* LU MO, as schematically shown in Figure 2. The linear combinations

$$\varphi_1 = N(\psi_{HO} + \psi_{SHO}) \quad \text{and} \quad \varphi_2 = N(\psi_{HO} - \psi_{SHO})$$

generate the corresponding transition densities $\Omega^1 = \varphi_1 \psi_{LU}$ and $\Omega^2 = \varphi_2 \psi_{LU}$, also shown in the Figure. They allow one to make qualitative predictions of $\delta N_X^* \propto \Omega_e(X)\,\Omega_e(P)$ for atoms in the π-electron system, upon approach by an electrophile located at one of the alternative sites at $P = P_1$, P_2, or P_3, expected on the basis of the first-order electrostatic considerations. The predictions from both transition densities are identical. For the P_1 location (above the nitrogen) one predicts a flow of electrons from O to CN. A cation at P_2 or P_3 attracts electrons to O from CN. The simultaneous approach of two electrophiles at P_1 and P_2 or P_3 leads to a partial cancellation of distortions induced by their independent attacks, while the (P_2, P_3) two-site approach should exhibit an enhanced flow of electrons from CN to O. The opposing polarization trends at the nitrogen and oxygen, respectively, indicate that a protonation at N(O) decreases the reactivity of the protonation sites at O(N).

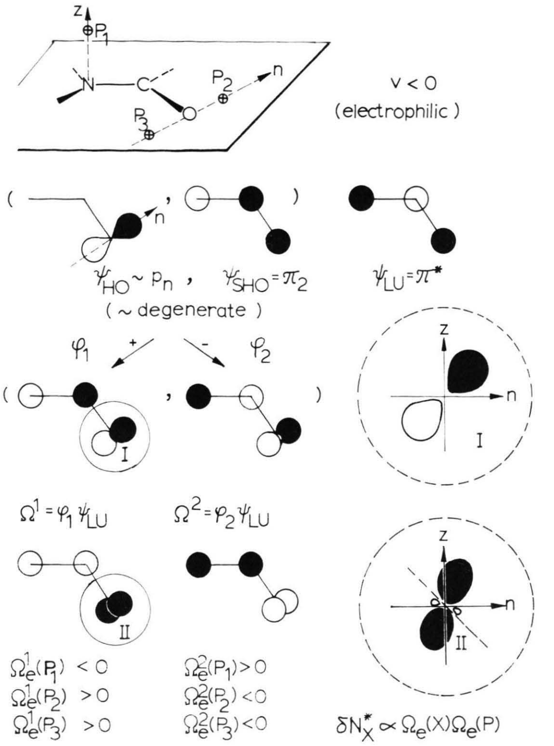

Fig. 2. The transition densities of the main polarization channels during a protonation of formamide.

The predicted polarization of the oxygen-protonated species agrees well with the reported Mulliken populations of the π electrons [22] for the carbon, oxygen, and nitrogen, respecticvely: 0.690, 1.733, 1.576, in the protonated formamide, as opposed to 0.902, 1.234, 1.803, in the isolated molecule.

4.3. *Protonation of the Trans Nitrous Acid*

The four possible protonation sites, $P_1, \ldots, P_4$, in the molecular plane of the trans nitrous acid, corresponding to the lone pairs on the nitrogen and oxygen atoms, are shown in Figure 3. The protonated species of the nitrous acid have been studied at the ab initio STO-3G SCF level by Dargelos et al. [23]. The reported atomic populations correspond to the final charge redistribution, after the

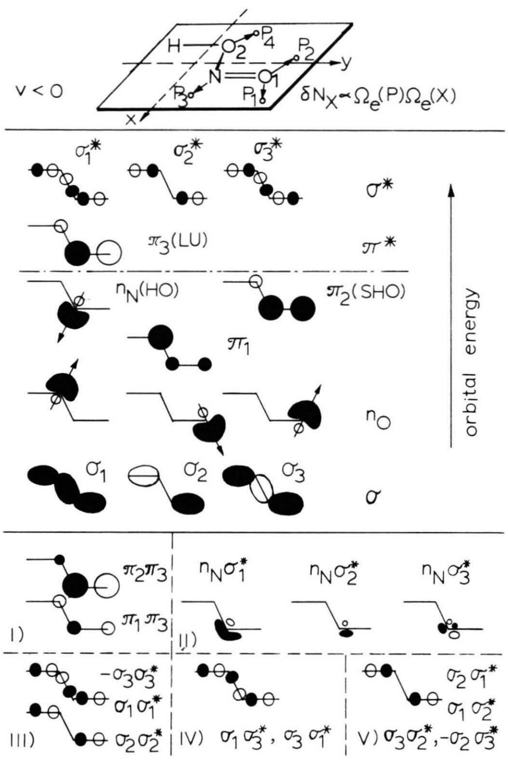

Fig. 3. The protonation sites, molecular orbitals, and transition densities of the trans-nitrous acid.

charge transfer. However, by formally ascribing the H^+ population to the protonated atom one obtains the following changes in atomic populations, relative to the isolated system:

i) Protonation on $O_1(P_1, P_2)$:
  a) the O_1H^+ bond is trans to the NO_2 (P_1): $\delta N_H = -0.133$, $\delta N_{O_2} = -0.154$, $\delta N_N = -0.226$, $\delta N_{O_1} = +0.513$;
  b) the O_1H^+ bond is cis to the NO_2 (P_2): $\delta N_H = -0.134$, $\delta N_{O_2} = -0.115$, $\delta N_N = -0.262$, $\delta N_{O_1} = +0.512$;
ii) Protonation on $O_2(P_4)$: $\delta N_H = -0.208$, $\delta N_{O_2} = +0.547$, $\delta N_N = -0.175$, $\delta N_{O_1} = -0.165$;
iii) Protonation on $N(P_3)$: $\delta N_H = -0.104$, $\delta N_{O_2} = -0.174$, $\delta N_N = +0.567$, $\delta N_{O_1} = -0.289$.

Although these changes do not correspond to the valence state, $\delta N_X \neq \delta N_X^*$, they nevertheless exhibit the main, external field induced charge migration trends of the system, and as such provide a sufficient basis for testing the qualitative predictions for the valence state.

The qualitative valence shell MO's and the corresponding transition densities Ω_k for the polarization modes active during an xy-plane approach by a proton are shown in Figure 3. The most energetically favourable are the $\pi\pi^*$ channels (I). Next are the $n\pi^*$ channels (II) shown for the lone pair on the nitrogen atom. However, due to the localized nature of the n-type orbitals, the resulting transition densities correspond to a local (within an atom) charge redistribution, thus having no effect on the gross atomic populations. The least energetically accessible are the $\sigma\sigma^*$ transition densities (III–V), inclusion of which is necessary to account for the changes of the hydrogen atom electron population. Again, the $\sigma_1\sigma_3^*$ and $\sigma_3\sigma_1^*$ densities represent an internal charge redistribution within the O_2 and N atoms, and the net effect is the electron transfer between the terminal H and O_1 atoms.

The dominant $\pi\pi^*$ channels are responsible for most of the observed polarization trends within the O_2-N-O_1 π-system. For example, in the case of N-protonation, these channels allow one to explain why the outflow of electrons from O_1 is substantially larger than that from O_2. Consideration of these channels also allows one to explain the observed differences in δN for the O_2 and O_1 protonations, respectively. Similarly, the difference in δN_{O_1} during O_2 and N protonation immediately follows from the $\pi\pi^*$ polarization modes.

The next observation to be explained is that the maximum outflow of electrons from H occurs for the O_2 protonation. As mentioned before, only the $\sigma\sigma^*$ densities can be responsible for δN_H. A closer examination of the $\sigma\sigma^*$ transition densities shows that this trend can be explained in terms of the $\sigma_1\sigma_1^*$ and $\sigma_3\sigma_3^*$ densities, for which

$$|\Omega_e(P_4)| > |\Omega_e(P_1 \text{ or } P_2)| .$$

For all channels in the groups III and V the N protonation generates a shift of the σ electrons *from* O_1; the O_2 protonation predicts such a flow only for the group V, while within the group III an approach of a proton to O_2 should polarize the σ electrons from N *to* O_1. These observations have immediate consequences for the 2-site protonation. On the basis of our previous discussion one should expect the proton at P_4 to inhibit the protonation sites at P_1 and P_2 on O_1 much less than the proton at P_3.

The mutual relaxation of the reactant densities, due to the external field of the reaction partner, may have implications for the reaction path at an early stage of the reaction. In the next section we briefly comment upon this aspect of the directional specificity of chemical reactions.

5. Relaxational Criterion of Directional Specificity

The perturbing external potential Δv depends on the mutual arrangement, Q, of both reactants, A and B, $\Delta v_{\mathrm{A}} = \Delta v_{\mathrm{A}}(\mathrm{Q})$ and $\Delta v_{\mathrm{B}} = \Delta v_{\mathrm{B}}(\mathrm{Q})$; so do the respective responses to these perturbations, $\delta n_{\mathrm{A}}^{*}$ and $\delta n_{\mathrm{B}}^{*}$, as well as the resulting total change in the reactants energy [see (1), (19) and (23)],

$$E_{\mathrm{AB}} \equiv E_{\mathrm{A}}[\mathrm{B};\mathrm{Q}] + E_{\mathrm{B}}[\mathrm{A};\mathrm{Q}] = E_{\mathrm{AB}}(\mathrm{Q})\,. \qquad (26)$$

Here $E_{\mathrm{A}}[\mathrm{B};\mathrm{Q}]$ denotes the energy change (1) of A in the field of B for the spatial arrangement Q.

At an early stage of the reaction, before the charge transfer associated with a strong chemical interaction and before an appreciable intramolecular rearrangements of both reactants, the energetically most favourable mutual arrangement, Q_{p}, follows from the minimum energy principle:

$$\min_{\mathrm{Q}} E_{\mathrm{AB}}(\mathrm{Q}) \rightarrow \mathrm{Q}_{\mathrm{p}}\,. \qquad (27)$$

Q_{p} corresponds either to the path of the slowest ascent, when there is an early barrier for the reaction originating from the first-order terms, $E_{\mathrm{n}} + \int \mathrm{d}\boldsymbol{r}\, n\, \Delta v$, or the path of the steepest descent, when the first-order terms do not lead to an increase of the reactants energy.

We call the principle (27) the *relaxational criterion* since one of its vital elements is the second-order energy (4) which will determine the course of a reaction when the first-order contributions remain approximately constant for various alternative arrangements of the reactants, leading to the formation of the same type of bond.

Consider, e. g., the simple case of an attack on A by an atomic ion B (19). The first-order term of the criterion (27) predicts, as should be expected, the approach of B towards the *maximum electron density* of A for an electrophilic (positive charge) B, and towards the *minimum electron density* of A for a nucleophilic (negative charge) B. When the first-order contributions are similar for alternative directions of an approach of B to a nonpolar A, e. g. the alternant hydrocarbon, the second-order relaxational term predicts for both electrophilic and nucleophilic B's the direction towards the *maximum frontier MO transition density* of A.

These qualitative predictions closely parallel those from the π-electron perturbation theory of Coulson and Longuet-Higgins [9] of the classical Hückel MO theory, where the perturbation by the external potential is indirectly taken into account via changes in the α_{X} (coulomb, one-center) and β_{XY} (resonance, two-center) integrals, induced by the approaching agent. Within this method our density response kernel (generalized polarizability) is replaced by the so-called *autopolarizability:* $\pi_{\mathrm{XX}} = \partial^2 E/\partial \alpha_{\mathrm{X}}^2$, etc.

The density relaxational effects have also been examined by Platt [8], who attempted a qualitative explanation of the shapes of small polyhydrides by considering the distortion of the central atom rare gas density caused by the external potential from the successive protons. He has succeeded in demonstrating that such perturbations lead to the creation of directional *valence-cones* in density, in semi-quantitative agreement with the observed geometries. The directional effects in Platt's description appear as a result of the well defined perturbation due to the external potential. This is contrary to the usual orbital hybridization approaches where the directional atomic orbitals (densities) are generated in a way to conform to the assumed arrangement of nuclei, or to satisfy some arbitrary equivalence or localization criteria.

In general, as already illustrated by the examples of the qualitative analysis of the density relaxation, one has to include many transition densities within the valence shell MO's. This is because the perturbation of the system, e. g. by the field of an approaching charge, is strong enough to "open" many polarization channels through which the system can adjust its density to the equilibrium one in the new environment.

Example: Electrophilic Substitution in Five-Membered Heterocycles

The preference for the α-substitution during an electrophilic attack in furan, pyrrole and N-methyl pyrrole is well established, with the degree of selectivity diminishing from furan (almost entirely the α-product) to N-methyl pyrrole [24]. As was pointed out by Politzer and Weinstein [24], the mechanism of the electrophilic substitution in these molecules should involve the shifting of the hydrogen atom on the attacked carbon out of molecular plane (the so-called "Wheland" or "sigma" intermediate), with the consequent development of a negative (attractive) electrostatic potential on the other side of the carbon in question. In the case of furan this negative potential in the α-position becomes part of the extended and highly attractive region near the oxygen, and this explains the almost total preference for the α-substitution. For pyrrole and N-methyl pyrrole it was necessary to additionally invoke the out-of plane "bending" of the N−H, N−CH_3 and $C_\alpha-H_\alpha$ bonds to explain both the preference for α-substitution and the relative selectivities.

Since the first-order terms seem to slightly favour the β-substitution [24] it might seem reasonable to anticipate that the polarization of the electronic cloud upon approach by an electrophile would be instrumental in bringing about, or at least facilitating, the structural changes (out-of-plane "bending") essential for the observed preference for the α-substitution. This aspect of the reaction mechanism has been omitted in the quoted theoretical study [24]. Our primary purpose in this illustrative analysis is to qualitatively examine the effect of such polarization on the relative preference for the α- and β-substitutions in these molecules.

From an energetical point of view the most favourable polarization channels within the valence shell MO's are those represented by the $\pi\pi^*$ transition densities. They are shown in Fig. 4 together with the corresponding generating π MO's. Both the MO's and transition densities are labeled as S (symmetric) or A (antisymmetric) in accordance with their symmetry properties with respect to the $\hat{\sigma}_v$ plane perpendicular to the π-system ring. It should be noticed that in the case of a symmetric (in the $\hat{\sigma}_v$ plane) approach by a proton only the S → S and A → A polarization channels remain active. Such a symmetric approach should be expected at the initial stage of the attack [24].

The Politzer and Weinstein [24] interpretation of the preference for α-substitution in pyrrole and N-methyl pyrrole is similar to that in furan. It assumes a *primary bending* of the N−H and N−CH_3 bonds out of the ring planes, resulting in a fairly extensive and quite deep negative potential on the other side of the nitrogen atom, reminiscent of that in planar furan. Then the *secondary bending* of the α-hydrogen develops a negative potential by the α-carbons, *joined* to the large attractive region of the nitrogen. A similar bending of the β-carbons produces a negative potential by the β-carbons, *separated* by a repulsive barrier from the attractive basin on nitrogen.

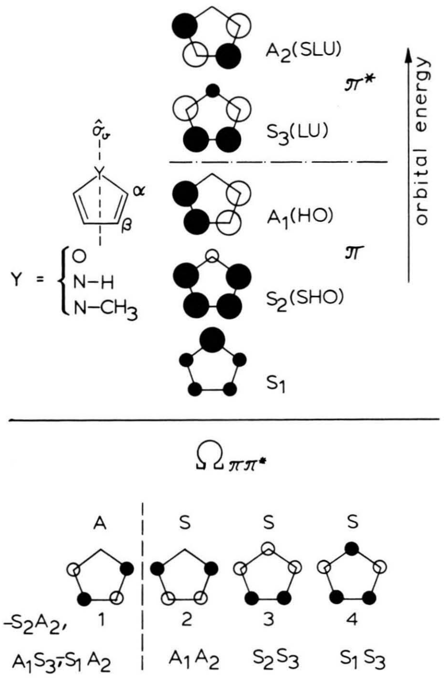

Fig. 4. The pi molecular orbitals and transition densities for a qualitative discussion of the polarization of the five-membered heterocycles by an approaching electrophile.

Obviously, such bendings require the $sp^2 \rightarrow sp^3$ rehybridization on the respective atoms in the π-system ring, and this requires the p_π orbital on a given atom to become essentially non-bonding. In this respect the bending on the nitrogen should be easier than that on the α-carbon since the sums of the pi bond orders are [24]: $2(C_\alpha-N) = 0.9$, $C_\alpha-C_\beta + C_\alpha-N = 1.3$. Clearly, the density relaxation in the field of an approaching proton will have a strong effect on the pi bond orders.

We therefore consider the effect of a polarization on the pi bond orders. Each $\pi\pi^*$ polarization channel represents an electron transfer ("excitation") from the occupied π to the virtual π^* orbital. Reference to Fig. 4 shows that *all* active $\pi \rightarrow \pi^*$

channels, $S_2 \rightarrow S_3$, $S_1 \rightarrow S_3$, and $A_1 \rightarrow A_2$, effect a transfer of electrons from the $C_\alpha - C_\beta$ bonding to the $C_\alpha - C_\beta$ antibonding MO's, thus making the α-carbon virtually π-nonbonding. By way of contrast, the $C_\beta - C_\beta$ pi bond order remains practically unaffected by the $A_1 \rightarrow A_2$ and $S_2 \rightarrow S_3$ polarization, while the $S_1 \rightarrow S_3$ channel should increase the $C_\beta - C_\beta$ pi bond order. Clearly, this enhances the selectivity of the α-substitution. A similar examination of the $N - C_\alpha$ pi bond orders shows that the $S_1 \rightarrow S_3$ relaxation weakens the bond while the remaining channels, $S_2 \rightarrow S_3$ and $A_1 \rightarrow A_2$, have practically no effect on the involvement of the p_π orbital on N in the π-system.

Thus, the polarization of the π-ring is such that the C_α and N atoms can relatively easily undergo a required change in the hybridization, facilitating the primary and secondary bendings responsible for the α-preference.

A further movement of an electrophile, towards a given α-carbon and away from the $\hat{\sigma}_v$ plane, will produce more polarization with no channels being forbidden by symmetry. All six channels shown in Fig. 4 will produce an increase in electron population at C_α and a simultaneous decrease in the average number of electrons at the neighbor C_β (different signs of the transition densities at these positions). This change further increases the degree of selectivity of the α-substitution.

6. Density Polarization and the Internal Stability

As mentioned in the Introduction, the problem of the density relaxation is closely related to that of the internal stability of molecular systems [14, 25–28]. The former examines the second-order energy $\delta^2 E[\Delta v]$ (4) and the density response $\delta n[\Delta v]$ (2) due to a displacement in the external potential Δv, both determined by the density response kernel (2, 8). The latter considers the second-order energy change $\delta^2 E[\Delta n]$ due to a displacement in the electron density Δn. A given equilibrium electron density is stable if any Δn preserving the number of electrons gives rise to

$$\delta^2 E[\Delta n] = \tfrac{1}{2} \iint d\mathbf{r}\, d\mathbf{r}'\, \Delta n(\mathbf{r})\, \eta(\mathbf{r}, \mathbf{r}')\, \Delta n(\mathbf{r}') > 0\,; \quad (28)$$

here $\eta(\mathbf{r}, \mathbf{r}') = \delta^2 E/\delta n(\mathbf{r})\, \delta n(\mathbf{r}') = \delta\mu(\mathbf{r})/\delta n(\mathbf{r}')$ representing a symmetric *hardness kernel* [13] and $\mu(\mathbf{r})$ is the chemical potential. This kernel is the negative inverse of the density response kernel [13, 14]:

$$\eta(\mathbf{r}, \mathbf{r}') = -\,\beta^{-1}(\mathbf{r}, \mathbf{r}')\,. \quad (29)$$

Obviously, a similar relation connects the corresponding eigenvalues of both kernels:

$$\lambda_i^\eta = -\,1/\lambda_i^\beta\,, \quad (30)$$

of the respective eigenvalue equations, e.g.

$$\int d\mathbf{r}'\, \beta(\mathbf{r}, \mathbf{r}')\, u_i(\mathbf{r}') = \lambda_i^\beta\, u_i(\mathbf{r})\,;$$

the u_i's are the orthonormal eigenfunctions. It can be easily demonstrated using (8) that all the eigenvalues of β are negative:

$$\lambda_i^\beta = -4 \sum_k^{\text{channels}} \left[\int d\mathbf{r}\, \Omega_k(\mathbf{r})\, u_i(\mathbf{r})\right]^2 / \Delta e_k < 0\,, \quad (31)$$

so that the stability is indeed assured:

$$\delta^2 E[\Delta n] = \tfrac{1}{2} \sum_i a_i^2 \lambda_i^\eta = -\tfrac{1}{2} \sum_i a_i^2/\lambda_i^\beta > 0\,, \quad (32)$$

where $a_i = \int d\mathbf{r}\, \Delta n(\mathbf{r})\, u_i(\mathbf{r})$. This should be expected for a nondegenerate electronic state.

Clearly, this connection between the internal stability and the system polarization arises from regarding a given virtual *displacement* in density, Δn, as a *response* to a corresponding change in the external potential: $\Delta n = \delta n[\Delta v]$ [see (2)]. It is of some interest to observe that the familiar equilibrium condition

$$\int d\mathbf{r}\, \mu(\mathbf{r})\, \Delta n(\mathbf{r}) = 0\,, \quad (33)$$

which implies the constancy of $\mu(\mathbf{r}) = \mu$ throughout the entire electron distribution [$\int d\mathbf{r}\, \Delta n(\mathbf{r}) = 0$, the closed system constraint] implies for the Δv generating Δn:

$$\begin{aligned} \int d\mathbf{r}\, \mu(\mathbf{r})\, \Delta n(\mathbf{r}) &= \int d\mathbf{r}\, \frac{\delta E}{\delta n(\mathbf{r})} \int d\mathbf{r}'\, \frac{\delta n(\mathbf{r})}{\delta v(\mathbf{r}')}\, \Delta v(\mathbf{r}') \\ &= \int d\mathbf{r}' \left[\int d\mathbf{r}\, \frac{\delta E}{\delta n(\mathbf{r})}\, \frac{\delta n(\mathbf{r})}{\delta v(\mathbf{r}')}\right] \Delta v(\mathbf{r}') \\ &= \int d\mathbf{r}'\, \frac{\delta E}{\delta v(\mathbf{r}')}\, \Delta v(\mathbf{r}') \\ &= \int d\mathbf{r}'\, n(\mathbf{r}')\, \Delta v(\mathbf{r}') = 0\,. \end{aligned} \quad (34)$$

The lowest eigenvalue λ^η, corresponding to the highest (the least magnitude) λ^β, represents the softest (the most facile) relaxation of a charge density. Its character determines the respective eigenfunction. Such a relaxation should lead to the smallest energy increase during the early, polarization stage of the approach by reactants. It would be of great interest for the density based theory of chemical reactivity to explore the information contained in these least energy density relaxations of molecular systems.

7. Concluding Remarks

We conclude with a few additional comments on the AIM, coarse-grained description introduced in Section 2. It assumes a definite partitioning of the molecular charge cloud into the atomic regions G_X; as mentioned before, the virial partitioning [15–18] should provide a sound basis for a practical implementation of such an atomic description.

The consistent set of the AIM parameters, given by the appropriate integrals over the corresponding G's, includes: $N_X = \int_{GX} \mathrm{d}\boldsymbol{r}\, n(\boldsymbol{r})$, the average number of electrons on X, and $V_X = \int_{GX} \mathrm{d}\boldsymbol{r}\, n(\boldsymbol{r})\, v(\boldsymbol{r})/N_X$, the average external field energy per electron. For non-overlapping G's the integration $\int \mathrm{d}\boldsymbol{r}$ becomes $\Sigma_X \int_{GX} \mathrm{d}\boldsymbol{r}$, and the differentiation with respect to V_X, $\partial/\partial V_X$, of the AIM description represents the integro-differential operator $\int_{GX} \mathrm{d}\boldsymbol{r}\, \partial/\partial v(\boldsymbol{r})$ of the fine-grained formalism. Thus the AIM number response matrix elements are:

$$\beta_{XY} = \partial N_X/\partial V_Y = \int_{GX} \mathrm{d}\boldsymbol{r}' \int_{GY} \mathrm{d}\boldsymbol{r}\, \beta(\boldsymbol{r}, \boldsymbol{r}') = \beta_{YX}.$$

The AIM description leads to an algebraization of the basic equations. For example, (1) and (2) read in the AIM representation:

$$E = E_n + (\boldsymbol{N} + \tfrac{1}{2}\,\boldsymbol{\delta N})\,(\boldsymbol{\Delta V})^{\mathrm{T}}, \quad \boldsymbol{\delta N} = \boldsymbol{\beta}\,(\boldsymbol{\Delta V})^{\mathrm{T}},$$

where

$$\boldsymbol{N} = (N_1, \ldots, N_m)\,, \quad \boldsymbol{\Delta V} = (\Delta V_1, \ldots, \Delta V_m)\,,$$

$$\boldsymbol{\beta} = \{\beta_{XY}\}\,, \quad \text{etc.}$$

For the $\Delta n = \delta n[\Delta v]$ of the previous section the corresponding stability conditions,

$$\delta^2 E[\Delta n] = -\,\delta^2 E[\Delta v] > 0\,,$$

also assume a simpler matrix form within the AIM representation:

$$\boldsymbol{\Delta N}\,\boldsymbol{\eta}\,(\boldsymbol{\Delta N})^{\mathrm{T}} = -\,\boldsymbol{\Delta V}\,\boldsymbol{\beta}\,(\boldsymbol{\Delta V})^{\mathrm{T}} > 0\,,$$

and so do the associated eigenvalue equations; here $\boldsymbol{\eta} = \{\eta_{XY}\}$ groups the atomic hardnesses,

$$\eta_{XY} = \partial^2 E/\partial N_X\, \partial N_Y\,.$$

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