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Chemical Reactivity and the Concept of Charge- and Frontier-Controlled Reactions

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Abstract: A general treatment of chemical reactivity is described. It is based on a polyelectronic perturbation theory involving both reactants and the solvent. The perturbation equation reproduces the known qualitative features of the concept of hard and soft Lewis acids and bases, of nucleophilic order, and of other reactivity indices. It emphasizes the importance of charge- and frontier-controlled effects, connected with charge transfer or partly covalent bonding in the transition state. Several specific examples are examined such as nucleophilic addition and electrophilic substitution on heterocyclic molecules. Satisfactory agreement with unexpected experimental evidence is obtained. The treatment seems to be particularly appropriate for the study of generalized ambident reactivity.

It is the usual practice to relate the chemical reactivity of organic compounds to a particular MO index such as free valence, charge density, *Z* value, and localization energies.[2] This procedure, however, does not account for the nature of the reagent and fails to reproduce the changes in relative reactivity of various positions of attack. Thus, changes in orientation observed in the electrophilic attack on aromatic derivatives by several acceptors cannot be explained satisfactorily[3] (Table I).

Table I. Isomer Distribution in Electrophilic Substitution on Toluene

Reaction	*o*	*m*	*p*
Chlorination[a]	75	2	23
Nitration[a]	59	4	37
Bromination[b]	33	1	66
Mercuration[c]	19	7	74

[a] Reference 2. [b] V. Gold and M. Whittaker, *J. Chem. Soc.*, 1184 (1951). [c] W. J. Klapproth and F. H. Westheimer, *J. Am. Chem. Soc.*, **72**, 4461 (1950).

Steric effects are clearly responsible for the anomalous behavior of some reagents but can certainly not account for all observed differences. The situation is rather similar for all ambident reactions, where no fundamental explanation could be found for why a given reagent attacks a particular position and another reagent a different one,[4] *e.g.*

$$\mathrm{MeNO_2} \xleftarrow{\mathrm{MeI}} \mathrm{O{=}N{-}O^-} \xrightarrow{\mathrm{^*BuCl}} \mathrm{^*BuONO}$$

$$\mathrm{MeSCN} \xleftarrow{\mathrm{MeI}} \mathrm{N{\equiv}C{-}S^-} \xrightarrow{\mathrm{RCOX}} \mathrm{RCONCS}$$

However, experience has shown that some atoms have a specific affinity for some other atoms, and an order of nucleophilicity could be determined to fit this requirement.[5,6] Nevertheless, it appeared that the nucleophilic order itself is different for various reaction centers. Thus, it also varies with the type of reaction and is, for example, quite different for alkylation than for acyla-

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(1) Chemistry Department, Case-Western Reserve University, Cleveland, Ohio 44106.

(2) J. Koutecky, R. Zahradnik, and J. Cizek, *Trans. Faraday Soc.*, **57**, 169 (1961).

(3) See, however, R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

(4) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. J. Iffland, *J. Am. Chem. Soc.*, 77, 6269 (1955).

(5) C. G. Swain and C. B. Scott, *ibid.*, **75**, 146 (1953).

(6) J. O. Edwards, *ibid.*, **76**, 1540 (1954).

tion or phosphonylation.[7] In the latter case, it is found to be related to the pK_a of the nucleophile.

The interpretation of inorganic reactivity and of stabilities of complexes is in an even worse situation since no direct calculations could yet be made to help understanding the chemical behavior of inorganic species. For example, no theoretical explanation can be given for the fact that, in solution, some metals M form their stable complexes with halogens as in the following sequence, F > Cl > Br > I, while others as I > Br > Cl > F. This is illustrated in Table II for the stability constants (log K) of several complexes in water.[8]

Table II. Stability Constants (Log K) of Complex Formation in Water

	F^-	Cl^-	Br^-	I^-
Fe^{+3}	6.04	1.41	0.49	...
Zn^{+2}	0.77	−0.19	−0.6	−1.3
Cd^{+2}	0.57	1.59	1.76	2.09
Hg^{+2}	1.03	6.74	8.94	12.87

This situation is encountered quite commonly in solution but contrasts with that observed in the gas phase where the sequence of stability is usually found to be $MF_n > MCl_n > MBr_n > MI_n$. This undoubtedly demonstrates the fundamental importance of solvent effects. The main problem lies in the difficulty of handling quantitatively the simultaneous effects of the solvent and of the ligand interaction with M. To our knowledge, such an approach has not yet been described, but qualitative attempts have been made to rationalize the behavior observed. Here also, specific affinities have been found between particular atoms in definite oxidation states. Ahrland, Chatt, and Davies thus compiled available data and suggested dividing the acceptors into (a) and (b) categories.[8] The (a) acceptors are those which form their most stable complex with the first ligand of each group: F > Cl > Br > I; N > P > As > Sb > Bi; O > S > Se > Te. The (b) acceptors are those which show approximately the reverse order.

This general idea of classifying reagents with respect to their chemical behavior stimulated further research on the physical properties of complexes and has more recently been extended by Pearson to the general acid–base reaction.[9] He has suggested the name soft bases for those bases (donors or nucleophiles) whose valence electrons are easily polarizable, and hard bases for those whose valence electrons are not. Hard acids (acceptors or electrophiles) are recognized as small sized, highly positively charged, and not easily polarizable; soft acids are defined as those possessing the reverse properties. Pearson then formulates a general principle based on experimental observations according to which hard acids prefer to coordinate with hard bases and soft acids prefer to coordinate with soft bases.

This concept, which found its first applications in rationalizing inorganic stability constants, quickly developed and was shown to be useful even in organic chemistry. Thus, Hudson showed that by considering hard and soft reagents, some ambident reactions can be rationalized.[10] Saville, using this concept, interpreted electrophilic catalysis and described a number of new reactions.[11]

However, predictions remain qualitative, as the general concept suffers from the lack of physical basis, and the hardness or softness of an acid or a base to some extent remains a matter of personal appreciation.[12] This weakness of the concept has been noted by several authors; quantitative physical definition have subsequently been proposed, and analogies found between the idea one has of hardness and softness and several properties such as polarizability, low-lying d orbitals, and oxidizing properties. None of these, however, correlates very well with the experimental facts nor stands on a well-defined physical basis, and none accounts for all properties attributed to hardness and softness.

A more interesting idea relates the hard–hard and soft–soft character respectively to ionic and covalent interaction.[13] An empirical equation was even suggested by Drago[14] to correlate heats of formation of acid–base complexes, such as

$$-\Delta H = E_A E_B + C_A C_B \qquad (1)$$

where the E terms represent the susceptibility of the acid or the base to undergo electrostatic interaction, and the C terms represent their ability to participate in covalent bonding.

This equation seems to give excellent agreement with experiment and compares very favorably with that suggested by Pearson,[9] where the pK_a and a softness index are used for the correlation. However, its empirical nature and the number of independent parameters involved in the calculations make it very impractical to use. Also, no physical reason or explanation for hard and soft behavior is provided by such an approach. Nevertheless, in spite of all the possible criticisms, the HSAB concept has undoubtedly proved to be useful, and therefore we have tried to look more deeply into its physical implications. In this paper, we show how the polyelectronic perturbation treatment of chemical reactivity, published elsewhere,[15] can be used in this context and accounts for most of the phenomena described above. Such a treatment leads to a reasonable definition of hardness and softness; it implies Pearson's principle and provides a general interpretation of ambident reactivity.

Theory

When two reactants approach each other, a mutual perturbation of the molecular orbitals of both reactants occurs. The resulting change in energy can be estimated from SCFMO calculations. When the bonds are completely formed and when the systems are simple enough, then good accuracy can be obtained for the calculations of the heats of formation. We have previ-

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[7] R. F. Hudson, *Chimia*, (Aaraw), **16**, 173 (1962).

[8] S. Ahrland, J. Chatt, and N. R. Davies, *Quart. Rev.* (London), **12**, 265 (1958).

[9] R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); *Chem. Eng. News*, **43**, 90 (May 31, 1965); *Chem. Brit.*, **3**, 103 (1967).

[10] R. F. Hudson, *Chem. Eng. News*, **43**, 102 (May 31, 1965); *Struct. Bonding* (Berlin), **1**, 221 (1966).

[11] B. Saville, *Chem. Eng. News*, **43**, 100 (May 31, 1965); International Conference on Hard and Soft Acids and Bases, London, 1967.

[12] C. K. Jørgensen, *Struct. Bonding* (Berlin), **1**, 234 (1966).

[13] R. J. P. Williams and J. D. Hale, *ibid.*, **1**, 249 (1966).

[14] R. S. Drago and B. B. Wayland, *J. Am. Chem. Soc.*, **87**, 3571 (1965).

[15] G. Klopman and R. F. Hudson, *Theoret. Chim. Acta*, **8**, 165 (1967).

ously used such a method to calculate heats of formation of diatomic[16] and polyatomic molecules.[17]

A polyelectronic perturbation treatment consistent with the previous calculation has also been described.[15] It has two advantages. The first one is that it can be handled very easily even for complicated species and thus allows predictions to be made for systems which are too complicated to be treated in a complete SCF calculation. The second advantage is that it allows one to visualize the various phenomena which occur during the process of bonding and to gain more insight into the factors governing the reaction rate. These factors are masked by the numerical complexity when a full SCF treatment is performed.

Thus, let two systems R and S interact through their atoms r and s. The total perturbation energy is produced by two distinct effects (a) the neighboring effect which accounts for the interaction due to the formation of an ion pair without any charge or electron transfer, and (b) the partial charge transfer usually accompanied by covalent bonding

$$\mathrm{R^-}_{\mathrm{solv}} + \mathrm{S^+}_{\mathrm{solv}} \xrightarrow{\mathrm{a}} \mathrm{R^-}_{\mathrm{solv}}\,\mathrm{S^+}_{\mathrm{solv}} \xrightarrow{\mathrm{b}} (\mathrm{R}^{\delta-}\text{–}\mathrm{S}^{\delta+})_{\mathrm{solv}}$$

Neglecting all intermolecular ion-pair interactions involving atoms other than r and s, these effects can be evaluated with the same approximations and symbolism as used in previous calculations[16] as follows.

A. **Neighboring Effects.** These are essentially produced by the perturbation operator H_1 on the unperturbed molecular orbitals ψ_R and ψ_S of R and S.

$$\Delta E_{(1)} = \int \psi_\mathrm{R}\psi_\mathrm{S}H_1\psi_\mathrm{R}\psi_\mathrm{S}\,\mathrm{d}\tau$$

The resulting energy change accounts for the Coulomb interaction (Madelung energy) between charged species and possibly also for some partial desolvation $\Delta\mathrm{solv}_{(1)}$ which follows the union of R and S

$$\Delta E_{(1)} = -q_\mathrm{r}q_\mathrm{s}\frac{\Gamma}{\epsilon} + \Delta\mathrm{solv}_{(1)} \tag{2}$$

where q_r and q_s are the total initial charges respectively of atoms r and s, Γ is the Coulomb repulsion term[16] between atoms r and s, and ϵ is related to the local dielectric constant of the solvent (see the section on solvation).

B. **Electron-Transfer Effects.** These effects are produced by the direct interaction between overlapping molecular orbitals. They lead to covalent bonding and decrease the ionicity of the reactants. They are thus also responsible for the desolvation of initially charged species. The procedure consists here in calculating separately the perturbation produced on each orbital ψ_m of one species (R) by each orbital ψ_n of the other (S). Such a perturbation involves new partly perturbed molecular orbitals ψ_mn such that for only two orbitals

$$\psi_\mathrm{mn} = a\psi_\mathrm{m} + b\psi_\mathrm{n}$$

where a and b are variational parameters such that $a^2 + b^2 = 1$ (the overlap being neglected in this treatment). Only those pairs of orbitals which contain together at least one but at most three electrons contribute to the change in energy. When ψ_m was originally doubly occupied, with ψ_n empty, the change in energy ΔE_mn produced by this partial perturbation is equal to the difference between the energy of the two electrons in the new molecular orbitals minus their energy in the absence of any mixing between the two orbitals ψ_m and ψ_n ($a = 1$, $b = 0$ or $b = 1$, $a = 0$), that is, their energy in the isolated molecule plus that produced by the neighboring effect

$$\Delta E_\mathrm{mn} = \int \psi_\mathrm{mn}(1)\psi_\mathrm{mn}(2)H\psi_\mathrm{mn}(1)\psi_\mathrm{mn}(2)\,\mathrm{d}\tau_1/\mathrm{d}\tau_2 - \int\psi_\mathrm{m}(1)\psi_\mathrm{m}(2)H_0\psi_\mathrm{m}(1)\psi_\mathrm{m}(2)\,\mathrm{d}\tau_1\mathrm{d}\tau_2 + \Delta\mathrm{solv}_\mathrm{mn}$$

where H is the total Hamiltonian operator of the joined RS system, and $\Delta\mathrm{solv}_\mathrm{mn}$ is the desolvation produced by the partial transfer of electrons from ψ_m to ψ_n.

The first two terms of the right-hand side of this equation can easily be evaluated (see Appendix I for the procedure and symbolism), and the resulting energy change becomes that shown in eq 3. The last step consists now

$$\Delta E_\mathrm{mn} = 2b^2\left\{\mathrm{IP_n} - \mathrm{EA_m} + (c_\mathrm{s}^\mathrm{n})^2[q_\mathrm{r} + 2(c_\mathrm{r}^\mathrm{m})^2]\frac{\Gamma}{\epsilon} - (c_\mathrm{r}^\mathrm{m})^2q_\mathrm{s}\frac{\Gamma}{\epsilon} - (c_\mathrm{r}^\mathrm{m})^2(c_\mathrm{s}^\mathrm{n})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right\} + 4ab[c_\mathrm{r}^\mathrm{m}c_\mathrm{s}^\mathrm{n}\beta] - b^4\left[\mathrm{IP_n} - \mathrm{EA_n} + \mathrm{IP_m} - \mathrm{EA_m} - 2(c_\mathrm{r}^\mathrm{m})^2(c_\mathrm{s}^\mathrm{n})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right] + \Delta\mathrm{solv}_\mathrm{mn} \tag{3}$$

in the minimization of the energy with respect to the variational parameters a and b.

Before proceeding, one needs to find a reasonable estimate of the desolvation, $\Delta\mathrm{solv}_{(1)}$ and $\Delta\mathrm{solv}_\mathrm{mn}$.

Influence of Solvent. There have been only a few attempts in the past to include systematically solvation energy into the quantum mechanical treatments of molecules or ions. However, as demonstrated in our introductory section, this term is essential for a correlation of reactivity and stability constants. The previous attempts usually consisted in simply adding the experimental solvation energy to the calculated heats of formation in the gas phase. It has been recognized that some chemical properties such as the basicity of heteronuclear aromatic derivatives[18] and the properties of charge-transfer complexes can only be correlated when the solvation energy is being included in the treatment.

A more reasonable approach for our treatment can be provided by the recently suggested solvaton theory[19] which allows the minimization of the energy to be made in the presence of the interaction forces of the solvent. This theory makes use of the Born[20] equation.

$$E_\mathrm{solv} = \frac{q^2}{2R_\mathrm{eff}}\left(1 - \frac{1}{\epsilon}\right) \tag{4}$$

where q is the total charge, R_eff the effective radius[21] of the ions, and ϵ the dielectric constant of the medium.[22] Although eq 4 does not seem to give a good account

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(16) G. Klopman, *J. Am. Chem. Soc.*, **86**, 4550 (1964).

(17) G. Klopman, *ibid.*, **87**, 3300 (1965); M. J. S. Dewar and G. Klopman, *ibid.*, **89**, 3089 (1967).

(18) R. Daudel, *Tetrahedron Suppl.*, **2**, 351 (1963).

(19) G. Klopman, *Chem. Phys. Letters*, **1**, 5 (1967).

(20) M. Born, *Z. Physik*, **1**, 45 (1920).

(21) W. M. Latimer, K. S. Pitzer, and C. M. Slansky, *J. Chem. Phys.*, 7, 108 (1939).

(22) The same equation remains valid for enthalpies of solvation but ϵ then is related to the dielectric constant D of the medium by[21] $\epsilon = D/[1 + (\partial \ln D/\partial \ln T)]$.

for changes in solvent, it nevertheless reproduces fairly well the experimental heats of solvation of several ions in a given solvent (Table III).

Table III. Experimental and Calculated (Born Equation) Heats of Hydration of Ions

Ion	Radius[a] + 0.82 (A)	Heat of solvation, kcal/mole Exptl[b]	Calcd
Be^{+2}	1.17	560	573
Al^{+3}	1.33	1109	1082
Ga^{+3}	1.44	1024	1088
Mg^{+2}	1.48	443	438
Li^{+}	1.50	109	112
Fe^{+2}	1.56	420	438
Sr^{+2}	1.94	338	324
Ag^{+}	2.08	79	103
Ba^{+2}	2.16	303	290
Tl^{+}	2.22	74	67

[a] L. Pauling, "Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960. [b] F. D. Rossini, *et al.*, "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular 500, U. S. Government Printing Office, Washington, D. C.

In order to be able to deal with the desolvation which must be estimated, the following hypotheses are made. (a) The desolvation, if any, produced by the union of R and S without any charge transfer can possibly be attributed to a steric inhibition of solvation and might be accounted for either by increasing the effective radius of the ion by a small constant or alternatively by decreasing the dielectric constant (ϵ) around the reacting species. (b) The desolvation produced by the partial electron transfer from ψ_m to ψ_n results from a decrease of the total charge of the reagents.[23] It will tentatively be given the form[19]

$$\Delta \mathrm{solv}_{mn} = \frac{[q_r + 2b^2(c_r^{m})^2x]^2 - q_r^2}{2R_r}\left(1 - \frac{1}{\epsilon}\right) + \frac{[q_s - 2b^2(c_s^{n})^2x]^2 - q_s^2}{2R_s}\left(1 - \frac{1}{\epsilon}\right) \quad (5)$$

where b is the variational parameter defined before, and x is empirically set equal to $q - (q - 1)\sqrt{\kappa}$ for $q > 0$, κ being a universal constant. This formalism is introduced so that when complete charge transfer occurs then the solvation energy of the remaining ions is

$$E_{\mathrm{solv}} = \frac{(q \pm 1)^2\kappa}{2R}\left(1 - \frac{1}{\epsilon}\right) \quad (6)$$

and accounts for the experimental observation that the solvation energy decreases faster with decreasing charge than would have been calculated by the Born equation. This is probably due to the fact that charge variations alter the ionic radius and are accounted for by setting $\kappa < 1$.

We can now go back to the variational treatment and calculate the perturbation energy (see eq A3, Appendix II) which becomes

$$\Delta E_{mn} = E_n^* - E_m^* + b^2\,[(E_m^* - E_n^*)_{b^2} - (E_m^* - E_n^*)_{b^2=0}] + \sqrt{(E_m^* - E_n^*) + 4(c_r^{m})^2(c_s^{n})^2\beta^2} \quad (7)$$

where E_m^* and E_n^* can be associated with the energy of the molecular orbitals ψ_m of molecule R and ψ_n of molecule S under their mutual influence.

Results and Discussion

A. **Chemical Reactivity.** Our treatment of chemical reactivity is based, as already discussed briefly in a previous paper,[15] on the limits of eq 8 for small perturbations, *i.e.*, small β (eq A4, Appendix II)

$$\Delta E_{\mathrm{total}} = \Delta E_{(1)} + \frac{1}{2}\sum_{mn} \Delta E_{mn}$$

$$\Delta E_{\mathrm{total}} = -q_r q_s \frac{\Gamma}{\epsilon} + \Delta \mathrm{solv}(1) + \sum_{\substack{m \\ \mathrm{occ}}} \sum_{\substack{n \\ \mathrm{unocc}}} \left[\frac{2(c_r^{m})^2(c_s^{n})^2\beta^2}{E_m^* - E_n^*}\right] \quad (8)$$

It follows essentially from the consideration of the difference in energy, $E_m^* - E_n^*$, between the highest occupied orbital of the nucleophile (donor), ψ_m, and the lowest empty orbital of the electrophile (acceptor), ψ_n, *i.e.*, the frontier orbitals.[24] In this respect, the treatment is a generalization of Fukui's F.O.D.[24] and of Brown's[25] Z values, but the analogy is only superficial since the frontier orbitals are used here only as a criterion for determining the type of controlling effect and do not necessarily determine the reactivity. Superdelocalizability,[26] on the other hand, would have been conceptionally closer to this treatment if it had accounted also for the nature of the reactant.

B. **Hard and Soft Behavior.**[27] When the difference between E_m^* and E_n^* for the frontier orbitals is large, $|E_m^* - E_n^*| \gg 4\beta^2$, then obviously $E_{m'}^* - E_{n'}^*$ for all pairs of orbitals will be large, all b^2's tend to zero, and very little charge transfer occurs. The small energy differences between the various molecular orbitals of each molecule can be neglected (Figure 1). The total perturbation energy then becomes

$$\Delta E_{\mathrm{total}} = -q_r q_s \frac{\Gamma}{\epsilon} + \Delta \mathrm{solv}(1) + 2\sum_{\substack{m \\ \mathrm{occ}}}(c_r^{m})^2 \sum_{\substack{n \\ \mathrm{unocc}}}(c_s^{n})^2\gamma \quad (9)$$

where $\gamma = \beta^2/(E_m^* - E_n^*)_{\mathrm{average}}$. It is apparent that in such a case the perturbation energy is primarily determined by the total charges on the two reagents. Very little electron transfer occurs, and the reaction will thus be called a *charge-controlled reaction*. Such an effect reflects an ionic type of interaction; it is predominant between highly charged species, when E_m^* is very low, that is, when the donor is difficult to ionize or polarize, and when E_n^* is very high, that is, when the acceptor has a low tendency to accept electrons and when both reactants are strongly solvated, *i.e.*, are of small size. It is also enhanced by small values of β, corresponding to low tendency to form covalent bonds and high Γ, again favored by small radius and low polarizability of the two reactants.

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(23) R. M. Noyes, *J. Am. Chem. Soc.*, **84**, 513 (1962).

(24) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952); **22**, 1433 (1954).

(25) R. D. Brown, *J. Chem. Soc.*, 2232 (1959).

(26) K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **27**, 1247 (1957).

(27) Part of the material presented in this section has been the subject of a communication at the 2nd Symposium on Hard and Soft Acids and Bases, London, 1967.

Table IV. Type and Rate of Reaction between Hard and Soft Reagents

Case	Donor E_m^*	Acceptor E_n^*	Conclusion $E_m^* - E_n^*$	Γ	β	Reactivity	
1	High (soft) large orbital	High (hard) small orbital	Medium	Small	Very small	Undef	Low
2		Low (soft) large orbital	Small	Very small	Large	Frontier controlled	High
3	Low (hard) small orbital	High (hard) small orbital	Large	Large	Small	Charge controlled	High
4		Low (soft) large orbital	Medium	Small	Very small	Undef	Low

All these properties correspond perfectly to those associated with hard–hard interaction, and the charge-controlled effect can thus be directly identified with it.

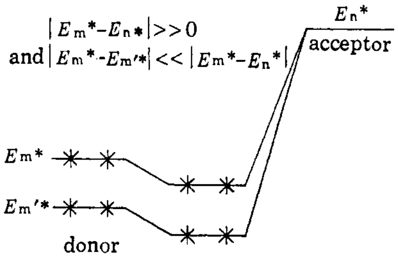

Figure 1. Charge-controlled effect.

On the other hand, when the two frontier orbitals are nearly degenerate, *i.e.*, $|E_m^* - E_n^*| \approx 0$, then, their interaction becomes predominant (Figure 2 and eq 8), and strong electron transfer occurs between them. When such a case happens, we will call the reaction a *frontier-controlled reaction*, and the total perturbation energy can be approximated by

$$\Delta E = 2c_r^m c_s^n \beta \qquad (10)$$

It occurs only in reactions between nucleophiles of low electronegativity and electrophiles of high electronegativity with a good overlap of the interacting orbitals. The reactivity in this case is essentially determined by the frontier electron density ($c_r^{m^2}$ and $c_s^{n^2}$), when the reaction occurs between uncharged or weakly charged species. It is enhanced by high polarizability of the reagents, low solvation energies, and, in fact, by all properties reverse to those producing the previous case. It leads to covalent bonding ($b^2 \rightarrow 0.5$) and can be associated with soft–soft interaction. In fact, it is easy to predict qualitatively from eq 8 which properties of the reagents would favor one or another controlling effect. In Table IV several possible cases have been summarized.

Only two combinations, cases 2 and 3, lead to high reactivity, namely, that occurring between hard reagents and that between soft reagents. Table IV thus shows that hard acceptors will tend to complex hard donors and soft acceptors will prefer soft donors. In other words, Pearson's principle[9] is a direct result of such a treatment.

Another interesting conclusion follows from the previous considerations. Hard–hard interactions are charge controlled and depend mainly on the ionic interaction of the reagents. In water such an interaction leads to the most favorable decrease of free energy, but to an increase of the enthalpy as $\partial \ln D/\partial \ln T$ is equal to[28] -1.357.

$$\Delta H_{hh} = -\frac{q_x q_y \Gamma}{D}\left(1 + \frac{\partial \ln D}{\partial \ln T}\right) = \frac{e^2}{r}\left(\frac{0.357}{80}\right) > 0$$

In addition, the steric inhibition of solvation which may occur during the union of the ions further accentuates the endothermicity of the reaction characteristic of hard–hard interaction.

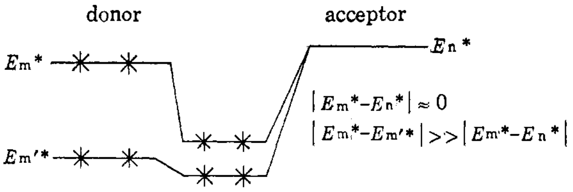

Figure 2. Frontier-controlled effect.

On the other hand, in the case of soft–soft interaction (eq 10), these phenomena are counterbalanced by the stabilization brought about by covalent bonding, and the reaction thus becomes exothermic.

$$\Delta H_{ss} = \Delta H_{hh} + 2c_x c_y \beta < 0$$

This is exactly what has been observed by Ahrland[28] and is illustrated in Table V for several inorganic complexes in water. For each halogen, the enthalpy decreases regularly with the softness of the metal, and for each metal, with the softness of the halogen.

Table V. Enthalpy (kcal/mole) of Formation of Mono Complexes in Water

	Cl^-	Br^-	I^-
Cr^{+3}	6.6	5.1	...
Fe^{+3}	4.2	...	...
Sn^{+2}	2.6	1.4	...
Cd^{+2}	−0.10	−1.0	−2.26
Tl^+	−1.1	−2.5	...
Ag^+	−2.7	...	...
Hg^{+2}	−5.79	−9.57	−18
Tl^{+3}	−6.04	−8.96	...

The question which arises now is whether this treatment allows a theoretical scale to be established for the hard or soft character of a reagent. Until now, we have based all our qualitative conclusions on the relative values of E_m^* and E_n^*. If these are correct, then these values should also provide a quantitative basis for es-

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(28) S. Ahrland, *Helv. Chim. Acta*, **50**, 306 (1967).

Table VI. Calculated Softness Character (Empty Frontier Orbital Energy) of Cations

X^z	IP,[a] ev	EA,[a] ev	Orbital energy, ev	$r^b + 0.82$, A	Desolvation	$E_n^{\ddagger}$, ev	
Al^{+3}	28.44	18.82	26.04	1.33	32.05	6.01	↑
La^{+3}	19.17	11.43	17.24	1.96	21.75	4.51	
Ti^{+4}	43.24	28.14	39.46	1.50	43.81	4.35	Hard
Be^{+2}	18.21	9.32	15.98	1.17	19.73	3.75	
Mg^{+2}	15.03	7.64	13.18	1.48	15.60	2.42	
Ca^{+2}	11.87	6.11	10.43	1.81	12.76	2.33	
Fe^{+3}	30.64	15.95 (16.18)	26.97	1.46	29.19	2.22	
Sr^{+2}	11.03	5.69	9.69	1.94	11.90	2.21	
Cr^{+3}	30.95	16.49	27.33	1.45	29.39	2.06	
Ba^{+2}	10.00	5.21	8.80	2.16	10.69	1.89	
Ga^{+3}	30.70	20.51	28.15	1.44	29.60	1.45	
Cr^{+2}	15.01[d] (16.49)	7.28[d] (6.76)	13.08	1.65	13.99	0.91	
Fe^{+2}	16.18	7.90	14.11	1.56	14.80	0.69	Borderline
Li^{+}	5.39	0.82	4.25	1.50	4.74	0.49	
H^{+}	13.60	0.75	10.38	...	10.8[c]	0.42	
Ni^{+2}	17.11[d] (18.15)	8.67[d] (7.63)	15.00	1.51	15.29	0.29	
Na^{+}	5.14	0.47	3.97	1.79	3.97	0	
Cu^{+2}	17.57[d] (20.29)	9.05[d] (7.72)	15.44	1.54	14.99	−0.55	
Tl^{+}	6.10	(2.0)	5.08	2.22	3.20	−1.88	
Cd^{+2}	16.9	8.99	14.93	1.79	12.89	−2.04	
Cu^{+}	7.72	2.0	6.29	1.78	3.99	−2.30	
Ag^{+}	7.57	2.2	6.23	2.08	3.41	−2.82	
Tl^{+3}	29.30	20.42	27.45	1.77	24.08	−3.37	Soft
Au^{+}	9.22	2.7	7.59	2.19	3.24	−4.35	
Hg^{+2}	18.75	10.43	16.67	1.92	12.03	−4.64	↓

[a] C. E. Moore, "Atomic Energy Levels," National Bureau of Standards Circular 467, U. S. Government Printing Office, Washington, D. C., 1949. [b] See footnote *a*, Table III. [c] Experimental value; see footnote *b*, Table III. [d] The values refer to ionization of s orbital.

tablishing a theoretical scale for the hard and soft character of reactants. The quantities E_m^* and E_n^* have been given an algebraic form (see eq A2, Appendix II) and can thus be evaluated directly. However, their evaluation requires the knowledge of the molecular Coulomb interaction Γ which will vary slightly from molecule to molecule. We can, however, define an intrinsic quantity $E^{\ddagger}$ (softness) independent of the other reagent by setting $\Gamma = 0$ for all acids or bases. The softness character of the reagents will thus be established within a constant factor. This procedure does not affect to a first approximation their relative order.

$$E_m^{\ddagger} = \mathrm{IP}_m - a^2(\mathrm{IP}_m - \mathrm{EA}_m) - \frac{x_r(c_r^{m})^2}{R_r}\left(1 - \frac{1}{\epsilon}\right)[q_r + 2b^2x_r(c_r^{m})^2]$$

$$E_n^{\ddagger} = \mathrm{IP}_n - b^2(\mathrm{IP}_n - \mathrm{EA}_n) - \frac{x_s(c_s^{n})^2}{R_s}\left(1 - \frac{1}{\epsilon}\right)[q_s - 2b^2x_s(c_s^{n})^2] \quad (11)$$

A hard base (nucleophile) is characterized by a low value for the energy of the occupied frontier orbital, E_m^*, a soft base by a higher value of E_m^*. Accordingly, the hardness of a base increases with the decrease of $E_m^{\ddagger}$. A hard acid on the contrary is characterized by a high value for the energy of the empty frontier orbital E_n^*, and its hardness will decrease with the decrease of $E_n^{\ddagger}$.

When a complete charge transfer occurs (frontier-controlled reaction), then $b^2 = {}^1/_2$ and $a^2 = {}^1/_2$. When no charge transfer occurs (charge-controlled reaction), then $b^2 = 0$ and $a^2 = 1$. The softness $E^{\ddagger}$ which measures the tendency for a given reagent to form either covalent or ionic interactions is calculated, by analogy with gas phase, for the intermediate situation such as $b^2 = {}^1/_4$, $a^2 = {}^3/_4$. This is illustrated below for Ba^{+2} and done in Table VI for several acids or acceptors and in Table VII for bases or donors. The calculations refer to water ($\epsilon = 80$), and the value of κ (see eq 6) which led to these results was empirically set equal to 0.75. For example, for Ba^{+2}

$$Ba^{+2} \xrightarrow{\mathrm{IP}_n\ =\ -10.0\ \mathrm{ev}} Ba^{+} \xrightarrow{\mathrm{EA}_n\ =\ -5.21\ \mathrm{ev}} Ba$$

$$\text{ionic radius of } Ba^{+2} = 1.34 \text{ A}$$

$$R_s = 1.34 + 0.82 = 2.16 \text{ A}$$

$$b^2 = {}^1/_4 \qquad q_s = 2 \qquad (c_s^{n})^2 = 1$$

$$x_s = q_s - (q_s - 1)\sqrt{\kappa} = 2 - \sqrt{0.75}$$

$$\text{ⓐ orbital energy} = \mathrm{IP}_n - b^2(\mathrm{IP}_n - \mathrm{EA}_n) = 8.80 \text{ ev}$$

$$\text{ⓑ desolvation} = \frac{x_s(c_s^{n})^2}{R_s}\left(1 - \frac{1}{\epsilon}\right) \times [q_s - 2b^2x_s(c_s^{n})^2 = 10.69 \text{ ev}$$

$$\text{softness } E_n^{\ddagger} = -\text{ⓐ} + \text{ⓑ} = -8.80 + 10.69 = 1.89 \text{ ev}$$

The result agrees extremely well with the qualitative description of softness and hardness given by Pearson[9] and established on the consideration of the chemical properties of these acids and bases, and can be used as a direct criterion of such properties for other species. The treatment does not require any preestablished knowledge of the *chemical* properties of the ions, contrary to most of the previous attempts to correlate hard and soft behavior.[9,13,27,29] Hence the definition of softness becomes the tendency for an acid to accept electrons (or a base to give electrons) in chemical bonds *in solution*. The analogy with electronegativity is obvious not only qualitatively but also quantitatively.[30]

(29) A. Yingst and D. H. McDaniel, *Inorg. Chem.*, **6**, 1067 (1967).

(30) G. Klopman, *J. Am. Chem. Soc.*, **86**, 1463 (1964).

Table VII. Calculated Softness Character (Occupied Frontier Orbital Energy) of Donors

X^z	IP,[a] ev	EA,[a] ev	Orbital energy, ev	r, A[b]	Desolvation, ev	$E^{\mp}_m$, ev	
F^-	17.42	3.48	6.96	1.36	5.22	−12.18	↑
H_2O	25.4	12.6	15.8	(1.40)	(−5.07)[c]	−(10.73)	
OH^-	13.10	2.8	5.38	1.40	5.07	−10.45	Hard
Cl^-	13.01	3.69	6.02	1.81	3.92	−9.94	
Br^-	11.84	3.49	5.58	1.95	3.64	−9.22	
CN^-	14.6	3.2	6.05	2.60	2.73	−8.78	Soft
SH^-	11.1	2.6	4.73	1.84	9.86	−8.59	
I^-	10.45	3.21	5.02	2.16	3.29	−8.31	
H^-	13.6	0.75	3.96	2.08	3.41	−7.37	↓

[a] See footnote *a*, Table VI. [b] See footnote *a*, Table III. [c] This value is negative, as it would be in general for neutral ligands, because the solvation increases rather than decreases during the removal of the first electron. The numerical value has been put equal to the value for OH^- in absence of more reliable data.

Equation 12 was shown to be the mathematical definition of electronegativity for a *neutral* atom in the gas phase. Equation 13 represents the softness which

$$\chi = \left(\frac{\partial E_{\text{at}}}{\partial a^2}\right)_{a^2 = 1/2} \tag{12}$$

$$E^{\mp} = \left(\frac{\partial E_{\text{at}}}{\partial a^2}\right)_{a^2 = 3/4} \tag{13}$$

hence can be defined as the electronegativity of the *ion* in solution. As for electronegativity, however, care should be taken when using the values derived from this treatment in dealing with chemical reactions. For example, the alkali metals are found to be on the borderline between hard and soft on the $E^{\mp}$ criterion. However, in these cases the value of β is so small[16] that, although $E^{\mp}$ is relatively high, they still behave as hard acceptors.

An interesting application is also provided by the study of the variation of $E^{\mp}$ with the local or microscopic dielectric constant ϵ. Although no precise correlation should be made between the value ϵ and the nature of the solvent,[31] it is seen that when ϵ decreases the softness parameter is shifted toward higher values.

This does not necessarily mean that the softness of all acids increases by decreasing the dielectric constant since other factors like those associated with Γ are varying at the same time. But the relative order of $E^{\mp}$ may remain an important qualitative indication of the character of the reagent. The magnitude of the shift is approximately proportional to the oxidation number and therefore, when ϵ decreases, a drastic modification of the softness scale occurs (Figure 3).

Acids with high oxidation numbers thus become relatively softer in nonpolar solvents as is illustrated, for example, by the fact that Ti^{IV} coordinates diarsines (soft bases) in dioxane to a higher extent than Fe^{III} or Cr^{III}.[32]

A last application is provided by the study of the stability of $B(CH_3)_3$ adducts with various amines. The softness parameter for amines cannot be calculated accurately as their second ionization potential is not known. A reasonable guess can, however, be made by assuming that it is equal to the first ionization potential plus the atomic electronic interaction. Since desolvation is to the first approximation constant for all amines, it appears that the hardness increases proportionally to the ionization potentials of the amine. This conclusion can be checked by considering the data of Drago[14] based on his equation (eq 1) which correlates the enthalpy of formation of adducts with two parameters; C is related to the susceptibility of amines to form covalent bonds and E to undergo electrostatic interaction.

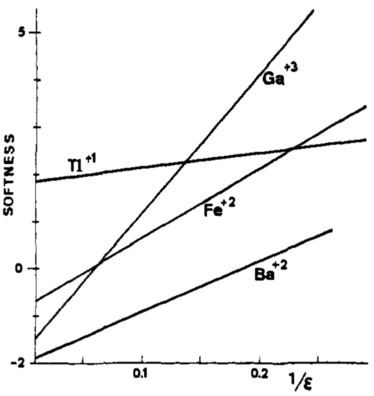

Figure 3. Variation of the softness ($E^{\mp}$) of acids with changes of dielectric constant (ϵ).

Table VIII. Correlation between the Ionization Potential of Amines and the Ratio of Ionic to Covalent Bonding

Amines	EA_m, ev	$(E/C) \times 10^{-2}$
NH_3	10.15	39
CH_3NH_2	8.97	19
$(CH_3)NH_2$	8.24	13
$(CH_3)_3N$	7.82	5

As shown before the softness parameter can be considered as a measure of the ratio of these two tendencies. This is actually found as shown in Table VIII where the first ionization potentials (EA_M) are compared with the E/C ratios.

C. **Nucleophilic Order.** Providing that the necessary interaction terms β and Γ are known, the treatment allows an estimation of the reactivity order toward a particular reagent. This order is determined by both reactants, and it is intrinsically incorrect to relate reactivity to a particular reactivity index. It is well known for example that electrophilic centers possessing a high positive charge, such as $RC(=O)-$, $RS(=O)_2-$, $(RO)_2P(=O)-$, and H^+, react rapidly with F^- or OH^- whereas electronically saturated centers, such as RCH_2-, R_2P-, $RS-$, and $Br-$, react preferentially with I^- or R_3P. The treatment is likely to reproduce these phenomena, and quantitative calculations based on eq 2 and 7 for specific reactions are being investigated. However, it appeared that even a crude model may be used to provide interesting conclusions.

Neglecting the minor contribution of Δsolv(1), the total perturbation as represented by eq 8 can be calculated for the reaction of several nucleophiles with electrophiles defined by their value of E_n^*.

The calculations have been made with the following values: $q_r = -1, q_s = +1, c_r^{m2} = c_s^{n2} = 1, \epsilon = 80, \Gamma$

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(31) E. Grunwald, G. Baughan, and G. Kohnstam, *J. Am. Chem. Soc.*, **82**, 5801 (1960).

(32) R. J. H. Clark, personal communication.

Table IX. Reactivity Scales

	I^-	Br^-	Cl^-	F^-	SH^-	CN^-	OH^-
R_{XH}, A	1.60	1.41	1.27	0.92	1.34	1.06	0.96
$-2\beta_X$, ev	3.16	3.60	4.10	4.48	4.0	3.8	4.50
$-E_m^*$, ev	8.31	9.22	9.94	12.18	8.59	8.78	10.45
$-\Delta E$ ($E_n^* = -7$ ev)	2.52	1.75	1.54	1.06	2.64	2.30	1.49
($E_n^* = -5$ ev)	1.07	0.98	0.97	0.82	1.25	1.17	1.01
($E_n^* = +1$ ev)	0.451	0.479	0.516	0.535	0.551	0.557	0.58

Table X. Nucleophilic Order

E_n^*		Nucleophilic order
-7	Calcd	$HS^- > I^- > NC^- > Br^- > Cl^- > HO^- > F^-$
	$k \times 10^4$, reaction with peroxide oxygen	Too fast 6900 10 0.23 0.0011 ≈ 0
-5	Calcd	$HS^- > NC^- > I^- > HO^- > Br^- > Cl^- > F^-$
	$k \times 10^6$, attack on saturated carbon	(25) 10 12 1.2 0.5 0.11
	E (Edwards)	2.79 2.06 1.65 1.51 1.24 1.0
$+1$	Calcd	$HO^- > NC^- > HS^- > F^- > Cl^- > Br^- > I^-$
	k for attack on carbonyl carbon (acylation)	890 10.8 ... 0.001 ... Unreactive ...
	pK_a	15.7 9.1 7.1 3.2 ... (−4.3) (−7.3)

$= e^2/R_{XH}$, where R_{XH} is the bond distance in the XH molecule, and the β_X's are the values obtained in previous calculations[16] and such that $\beta_{XR} = \sqrt{\beta_X\beta_R}$. β_R was set equal to 1. The results are summarized in Table IX. Although these results involve crude approximations and remain questionable until the full treatment confirms them, it is interesting to find that the various reactivity scales agree closely with experiments. Thus, when $E_n^* = -7$ ev, the order of reactivity which is found refers to a reaction toward an extremely soft electrophile. This is the case, for example, of the reaction with peroxides,[33] and it is seen from Table X that the predicted order agrees very well with the results. Similarly $E_n^* = -5$ ev refers to a moderately soft center such as a saturated carbon atom. Here again the correlation with reactivity is satisfactory as shown in Table X. Also, the data fit very well with Edward's nucleophilic order[6] for the various basis.

Finally, for a hard center characterized by a value of E_n^* of $+1$ ev, a good correlation is found both with pK_a[6] and with the nucleophilic reactivity order toward carbonyl carbon atoms.[34] The treatment thus reproduces the experimental reactivity numbers and provides a theoretical basis for the four-term free-energy equations.[6]

Another important analysis which can be made would be based on the variation of the nucleophilic order with the nature of the solvent. It is clear, for example, that the smaller ϵ is, the bigger the charge-controlled effect will be. In other words, solvents with low dielectric constants are bound to enhance charge-controlled interactions. Very polar solvents, on the other hand, favor frontier-controlled reactions.

D. **Ambident Reactivity.** Reasonable nucleophilic orders are thus provided by the above treatment. Various scales of nucleophilicity are found, for example, for alkylation and for acylation. One may therefore expect that the field of ambident reactivity in its most general sense might be particularly fruitfully studied by such a treatment. It is of interest to consider in detail the case of reactions between uncharged or weakly charged species ($q_rq_s \approx 0$) which are often encountered in organic chemistry.

For large molecules, accurate values of E_m^* and E_n^* are difficult to obtain although semiempirical SCF methods might be promising for approaching this problem. But even such results have not yet been sufficiently established for heterocyclic molecules. However, reasonable Hückel one-electron energies are readily available and might possibly be used to approximate the necessary values of E_m^* and E_n^*. In such a first approximation the reaction will be primarily controlled by any of the two limits of the last term of eq 8

$$\Delta E = \sum_{\substack{m \\ \text{occ}}} \sum_{\substack{n \\ \text{unocc}}} \frac{2(c_r^m)^2(c_s^n)^2\beta^2}{E_m^* - E_n^*} \qquad (14)$$

This equation is identical with the chemical perturbation equation, but the point we are interested in studying here and which has not attracted much attention so far is the variation of this perturbation energy with that of $E_m^* - E_n^*$. As before, when $|E_m^* - E_n^*|$ for the frontier orbitals of the reactants is large, then the reaction is charge controlled (see eq 9) (in this case, it is the total electronic charge density which determines the reactivity)

$$\Delta E = 2\sum_{\substack{m \\ \text{occ}}}(c_r^m)^2\sum_{\substack{n \\ \text{unocc}}}(c_s^n)^2\gamma$$

otherwise it is frontier controlled (see eq 10) and leads to strong covalent bonding between the centers possessing the highest charge in the frontier orbitals, *i.e.*, $\Delta E = 2c_r^mc_s^n\beta$. The fact that the two alternatives still exist for weakly charged organic substances is particularly

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(33) J. O. Edwards, *J. Am. Chem. Soc.*, **84**, 22 (1962).
(34) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

important to realize.[35] However, their origin differs from that producing charge- or frontier-controlled effects for ionic reagents. They result from the fact that in organic compounds the total electronic charge of an atom is often distributed among various delocalized molecular orbitals of different energy. Therefore, in contrast to ions, the frontier electron density is usually not proportional to the total electronic charge density. Equation 14 automatically includes this duality as will be shown for a few examples at the end of this section. However, approximations are conceivable such as linear combinations of the two limiting cases. This may give rise to an equation such as

$$\Delta E = \left(\sum_{\substack{\mathrm{m}\\ \mathrm{occ}}} (c_{\mathrm{r}}^{\mathrm{m}})^2 \sum_{\substack{\mathrm{n}\\ \mathrm{unocc}}} (c_{\mathrm{s}}^{\mathrm{n}})^2\right)\alpha_{\mathrm{RS}} + (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\beta_{\mathrm{RS}} \quad (15)$$

where α_{RS} and β_{RS} are now variable parameters, characterizing the reaction of R and S in such a way that, when α_{RS} is large and β_{RS} small, the reaction is charge controlled, whereas, when α_{RS} is small and β_{RS} large, the reaction is frontier controlled.

Such equations as already mentioned have been empirically suggested and in fact used successfully by Drago,[14] whose equation (eq 1) can be recognized by making the following transformations

$$\sum_{\substack{\mathrm{m}\\ \mathrm{occ}}} (c_{\mathrm{r}}^{\mathrm{m}})^2\alpha_{\mathrm{R}} = E_{\mathrm{R}}$$

$$\sum_{\substack{\mathrm{n}\\ \mathrm{unocc}}} (c_{\mathrm{s}}^{\mathrm{n}})^2\alpha_{\mathrm{s}} = E_{\mathrm{s}}$$

$$(c_{\mathrm{r}}^{\mathrm{m}})^2\beta_{\mathrm{R}} = C_{\mathrm{R}}$$

$$(c_{\mathrm{s}}^{\mathrm{n}})^2\beta_{\mathrm{S}} = C_{\mathrm{S}}$$

and

$$\alpha_{\mathrm{R}}\alpha_{\mathrm{S}} = \alpha_{\mathrm{RS}}$$

$$\beta_{\mathrm{R}}\beta_{\mathrm{S}} = \beta_{\mathrm{RS}}$$

More recently, Rogers[36] has studied several reactions of aromatic species using eq 15 and found that the use of both indexes, total electron density and frontier electron density, largely improves the correlation.

As would have been expected from the previous discussion he found that the best correlation for deuterium exchange (hard) with conjugated vinyl ethers is obtained when $\alpha/\beta \sim 2.8$, but the free-radical phenylation of 2-methylnaphthalene is best correlated for $\alpha/\beta = 0.31$.[36] Free radicals show very soft properties as would have been expected from the fact that they interact mainly through their nonbonding orbital. This behavior has been extensively discussed by Dewar,[37] who showed that radical recombination largely involves this particular orbital.

Finally it may be noted that the fact that Fukui's frontier orbital density is working at all for aromatic hydrocarbons is easily understood by noticing that the absence of total charge differences in such compounds leaves as the only controlling factor the frontier electron density. On the other hand, the lack of correlation for reactions of heterocyclic molecules using Fukui's treatment can certainly be attributed to the fact that in such cases a definite variation in total charge density occurs. This will be illustrated in the following examples where eq 14 is used to show how several similar centers are behaving toward a particular reagent and how the nature of this reagent modifies their relative reactivity through an intimate mixing of charge- and frontier-controlled effects.

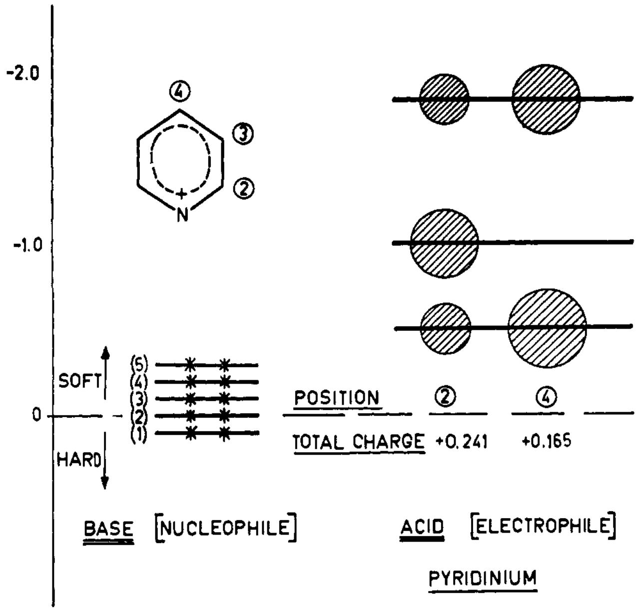

Figure 4. Schematic representation of the interaction between several nucleophiles and the antibonding orbitals of pyridinium salts.

The procedure consists in calculating in the Hückel approximation the various molecular orbital energies of conjugated organic reagents. The perturbation which is produced by the other reactant R at each possible center of the conjugated species is then calculated from eq 14. Various degrees of softness of the attacking reagent are taken into account by varying E_{m}^*. The parameters used for these calculations are those suggested by Streitwieser[38] except for O⁻ (in pyridine oxide) where the high negative charge suggests a lower value for the Coulomb integral (Table XI).

Table XI

$\alpha_x = \alpha_0 + k_x\beta_0$	$\beta_{xy} = h_{xy}\beta_0$	
$k(-\ddot{\mathrm{O}}-) = 2.0$	$k(\mathrm{O}{=}) = 1.0$	$k(\bar{\mathrm{O}}-) = 0.1$
$k(-\overset{+}{\mathrm{N}}{=}) = 2.0$	$k(-\dot{\mathrm{N}}-) = 1.5$	$k(-\dot{\mathrm{N}}{=}) = 0.5$
$h(\mathrm{C{=}N}) = 1.0$	$h(\mathrm{N{-}O}) = 0.75$	$h(\mathrm{C{=}O}) = 1.0$

(1) Nucleophilic Addition to the Pyridinium Ion. Figure 4 shows on the right the antibonding molecular orbitals of pyridinium ions. The circles represent the $(c_{\mathrm{s}}^{\mathrm{n}})^2$, *i.e.*, the square of the coefficients of the atomic orbitals for positions 2 and 4 which are the two possible reacting centers. On the left side, five nucleophiles of increasing hardness ($k_{\mathrm{m}} = -0.3, -0.2, -0.1, 0, 0.1$) are represented through their highest filled orbital. The perturbation produced by each of these nucleophiles both on positions 2 and 4 is calculated by means of eq

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(35) A preliminary discussion of these effects has already been published: R. F. Hudson and G. Klopman, *Tetrahedron Letters*, 1103 (1967).

(36) N. A. J. Rogers, personal communication.

(37) M. J. S. Dewar, *J. Am. Chem. Soc.*, 74, 3345 (1952).

(38) A. Streitwieser, Jr., "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961, p 120.

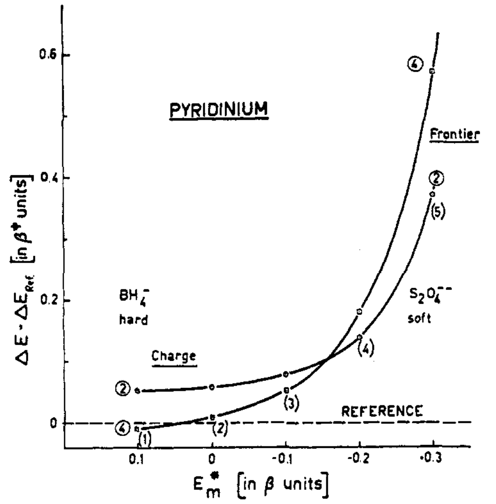
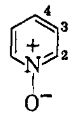


Figure 5. Nucleophilic addition on pyridinium ions.

14, and the result is plotted in Figure 5. In order to bring all the results into a single representative graph, the values of ΔE for the two possible reacting centers are compared to that obtained for the reactivity of a reference compound whose orbital $E_m{}^*$ would be at $\alpha - 0.65\beta$. Since we are interested only in comparing the possible reacting centers of pyridine, this procedure does not modify the conclusions. This plot shows that for hard nucleophiles ($k_m = 0.1$), the most reactive center is position 2 ($\Delta E_{(2)} > \Delta E_{(4)}$), but as the softness of the nucleophile increases (k_m decreases), a progressive change to position 4 occurs; $\Delta E_{(4)} > \Delta E_{(2)}$. This is exactly what has been observed as BH_4^-, aniline, and hydroxide ions, which are hard, attack position 2 whereas the soft CN^- and $S_2O_4^{-2}$ react at position 4.[39] Kosower had suggested that reactions occurring at position 4 may go through an activated state consisting of a charge-transfer complex,[40] but this explanation could not account for the fact that CN^- attacked position 4 as no evidence for the complex formation was found in this case. Our explanation thus provides a reasonable alternative to the charge-transfer mechanism but does not oppose it as it also suggests that the soft nucleophiles are the most likely to produce charge-transfer complexes with the pyridinium ion.

(2) Electrophilic Substitution on Pyridine Oxide. The procedure is similar to that described in the previous example. The perturbation is calculated here for the possible interaction of positions 2, 3, and 4



with electrophiles of increasing hardness ($k_n = -1, -1.5, -2, -2.5, -3$). The results, compared to that for attack on position 1 of naphthalene as reference, are plotted in Figure 6 and lead to the unexpected conclusion that all three positions may become the most reactive depending on the softness of the electrophile. Very soft reagents attack position 2, rather hard reagents, position 4, and very hard ones, position 3. This conclusion is entirely verified experimentally as mercuration was shown to occur at position 2, nitration at position 4, and sulfonation at position 3.[41]

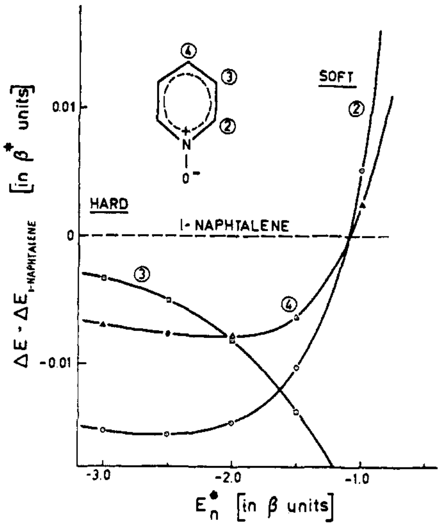
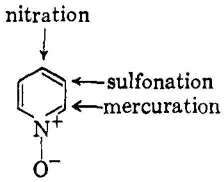
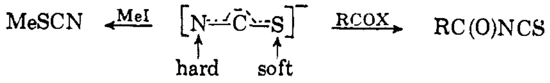


Figure 6. Electrophilic substitution on pyridine oxide.



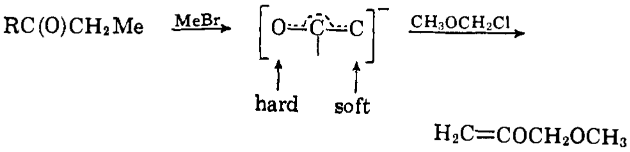
These predictions are valid for the free base; the conjugated acid which is preponderant in acidic conditions (sulfonation?) is found to react at position 3 irrespective of the softness of the reagent.

Other applications of such a treatment are provided by the study of most reactions of conjugated centers but can also be applied to classical ambident ions such as thiocyanate



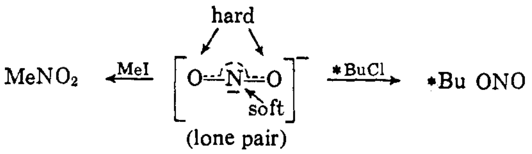
$$\mathrm{MeSCN} \xleftarrow{\mathrm{MeI}} [\mathrm{N}\cdots\mathrm{C}\cdots\mathrm{S}]^- \xrightarrow{\mathrm{RCOX}} \mathrm{RC(O)NCS}$$

enolate ions



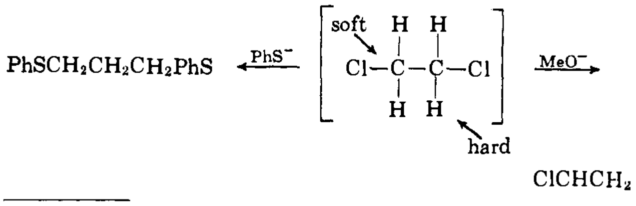
$$\mathrm{RC(O)CH_2Me} \xrightarrow{\mathrm{MeBr}} [\mathrm{O}\cdots\mathrm{C}\cdots\mathrm{C}]^- \xrightarrow{\mathrm{CH_3OCH_2Cl}} \mathrm{H_2C{=}COCH_2OCH_3}$$

nitrites



$$\mathrm{MeNO_2} \xleftarrow{\mathrm{MeI}} [\mathrm{O}\cdots\mathrm{N}\cdots\mathrm{O}]^- \xrightarrow{*\mathrm{BuCl}} *\mathrm{Bu\ ONO}$$

dichlorides, etc.



$$\mathrm{PhSCH_2CH_2CH_2PhS} \xleftarrow{\mathrm{PhS^-}} [\mathrm{Cl{-}CH_2{-}CH_2{-}Cl}] \xrightarrow{\mathrm{MeO^-}} \mathrm{ClCHCH_2}$$

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(39) E. M. Kosower, *J. Am. Chem. Soc.*, 78, 3497 (1956).

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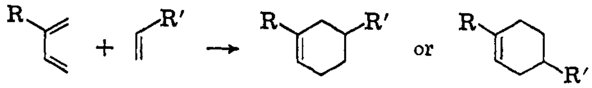
Finally, the Woodward–Hofmann rule and the orientation in Diels–Alder additions between asymmetric dienes and dienophiles might possibly also be explained satisfactorily by such an approach.



In the latter case a four-center attack should be considered and eq 14 should be replaced by

$$\Delta E = \sum_{\substack{\mathrm{m} \\ \mathrm{occ}}} \sum_{\substack{\mathrm{n} \\ \mathrm{unocc}}} \frac{2[(c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2 + (c_{\mathrm{r}'}^{\mathrm{m}})^2(c_{\mathrm{s}'}^{\mathrm{n}})^2\beta^2}{E_{\mathrm{m}}^* - E_{\mathrm{n}}^*}$$

Conclusion

The various applications discussed in this paper are by no means restrictive but are rather intended to provide models for the wide variety of cases where the information from general eq 8 can be used. Even if a part of the above agreement is fortuitous, as might well be the case, since one-electron treatments are after all very crude and depend so much on parameters, it remains that the general trend found in these examples shows the potential applicability of the method. The treatment defines hardness and softness of reactants and explains the particular behavior associated with these properties.

The classification of reagents into hard and soft classes is a useful one, but as demonstrated above it does not necessarily lead to a universal order of reactivity. The more general treatment based on eq 8 has a far greater potential applicability to the study of the factors influencing reactivity such as attacking reagent, leaving group, substituent, and solvent. Further examples need, however, to be investigated, and a more quantitative examination of the data provided by semiempirical SCF procedures might lead to a better understanding of chemical reactivity. This work is now in progress for accounting quantitatively for such properties as equilibrium constants, pK_a, and reaction rates.

Acknowledgments. The author wishes to thank Dr. C. K. Jørgenson and Professor R. F. Hudson for continuous help in the preparation of the manuscript and for numerous helpful suggestions.

Appendix I

The calculation of the change in energy produced during the interaction of two systems, R and S, by the partial transfer of electrons from an initially doubly occupied ψ_{m} of R to an initially empty orbital ψ_{n} of S is given here. The interaction occurs through atoms r (atomic orbital φ_{r}) of R and s (atomic orbital φ_{s}) of S.

$$\psi_{\mathrm{m}} = \sum_{\rho} c_{\rho}^{\mathrm{m}}\varphi_{\rho} \quad \psi_{\mathrm{n}} = \sum_{\sigma} c_{\sigma}^{\mathrm{n}}\varphi_{\sigma} \quad \psi_{\mathrm{mn}} = a_{\mathrm{m}} + b\psi_{\mathrm{n}}$$

$$\Delta E_{\mathrm{mn}}' = \int \psi_{\mathrm{mn}}(\mathrm{i})\psi_{\mathrm{mn}}(\mathrm{j})H\psi_{\mathrm{mn}}(\mathrm{i})_{\mathrm{mn}}(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}} - \psi\int\psi_{\mathrm{m}}(\mathrm{i})\psi_{\mathrm{m}}(\mathrm{j})H\psi_{\mathrm{m}}(\mathrm{i})\psi_{\mathrm{m}}(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}}$$

where φ_{ρ} and φ_{σ} are atomic orbitals, respectively, of systems R and S. ψ_{mn} is the new molecular orbital; i and j are the two electrons initially occupying orbital ψ_{m}. a and b are variational parameters, and H is the total Hamiltonian operator of the joined RS system.

$$\begin{aligned}\Delta E_{\mathrm{mn}}' = {} & \int[a\psi_{\mathrm{m}}(\mathrm{i}) + b\psi_{\mathrm{n}}(\mathrm{i})] \times \left[-{}^1/_2\,\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{si}}}\right] \times [a\psi_{\mathrm{m}}(\mathrm{i}) + b\psi_{\mathrm{n}}(\mathrm{i})]\,\mathrm{d}\tau_{\mathrm{i}} + \int[a\psi_{\mathrm{m}}(\mathrm{j}) + b\psi_{\mathrm{n}}(\mathrm{j})] \times \\ & \left[-{}^1/_2\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{rj}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{sj}}}\right][a\psi_{\mathrm{m}}(\mathrm{j}) + b\psi_{\mathrm{n}}(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{j}} - \\ & \int[a^2\psi_{\mathrm{m}}^2(\mathrm{i}) + b^2\psi_{\mathrm{n}}^2(\mathrm{i})]\,\frac{1}{R_{\mathrm{ij}}}[a^2\psi_{\mathrm{m}}^2(\mathrm{j}) + b^2\psi_{\mathrm{n}}^2(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}} - \\ & \int\psi_{\mathrm{m}}(\mathrm{i})\left[-{}^1/_2\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{si}}}\right]\psi_{\mathrm{m}}(\mathrm{i})\,\mathrm{d}\tau_{\mathrm{i}} - \\ & \int\psi_{\mathrm{m}}(\mathrm{j})\left[-{}^1/_2\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{sl}}}\right]\psi_{\mathrm{m}}(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{j}} + \\ & \int\psi_{\mathrm{m}}^2(\mathrm{i})\frac{1}{R_{\mathrm{ij}}}\,\psi_{\mathrm{m}}^2(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}}\end{aligned}$$

where $c_{\mathrm{r}}^{\mathrm{m}}$ and $c_{\mathrm{s}}^{\mathrm{n}}$ are the coefficients of atomic orbitals φ_{r} and φ_{s}, respectively, in the unperturbed orbitals ψ_{m} and ψ_{n}, and q_{r} and q_{s} are the total initial charges of atoms r and s and include the core and all electrons: $q_{\mathrm{r}} = Z_{\mathrm{r}} - 2\Sigma_{\mathrm{occ}}(c_{\mathrm{r}}^{\mathrm{m}})^2$; $q_{\mathrm{s}} = Z_{\mathrm{s}} - 2\,\Sigma_{\mathrm{occ}}(c_{\mathrm{s}}^{\mathrm{n}})^2$. In establishing this equation, the neglect of differential overlap between ψ_{m} and ψ_{n} was assumed, and the only transmolecular interactions taken into account are those involving atoms r and s. We may now make the following substitutions

$$\int\psi_{\mathrm{m}}(\mathrm{i})\left[-{}^1/_2\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{si}}}\right]\psi_{\mathrm{m}}(\mathrm{i})\,\mathrm{d}\tau_{\mathrm{i}} = \mathrm{IP}_{\mathrm{m}} + (c_{\mathrm{r}}^{\mathrm{m}})^2 q_{\mathrm{s}}\Gamma$$

$$\int\psi_{\mathrm{n}}(\mathrm{i})\left[-{}^1/_2\nabla^2 + \frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{si}}}\right]\psi_{\mathrm{n}}(\mathrm{i})\,\mathrm{d}\tau_{\mathrm{i}} = \mathrm{IP}_{\mathrm{n}} + (c_{\mathrm{s}}^{\mathrm{n}})^2\,[q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2]\Gamma$$

$$\int\psi_{\mathrm{m}}(\mathrm{i})\left[\frac{q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{ri}}} + \frac{q_{\mathrm{s}}}{R_{\mathrm{si}}}\right]\psi_{\mathrm{n}}(\mathrm{i})\,\mathrm{d}\tau_1 = c_{\mathrm{r}}^{\mathrm{m}}c_{\mathrm{s}}^{\mathrm{n}}\beta$$

$$\int\psi_{\mathrm{m}}^2(\mathrm{i})\frac{1}{R_{\mathrm{ij}}}\psi_{\mathrm{m}}^2(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}} = \mathrm{IP}_{\mathrm{m}} - \mathrm{EA}_{\mathrm{m}}$$

$$\int\psi_{\mathrm{n}}^2(\mathrm{i})\frac{1}{R_{\mathrm{ij}}}\psi_{\mathrm{n}}^2(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}} = \mathrm{IP}_{\mathrm{n}} - \mathrm{EA}_{\mathrm{n}}$$

$$\int\psi_{\mathrm{m}}^2(\mathrm{i})\frac{1}{R_{\mathrm{ij}}}\psi_{\mathrm{n}}^2(\mathrm{j})\,\mathrm{d}\tau_{\mathrm{i}}\mathrm{d}\tau_{\mathrm{j}} = (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma$$

where IP_{m}, IP_{n}, EA_{m}, and EA_{n} are the energies of ionizations of electrons for the following processes

$$\mathrm{R} \xrightarrow[-\mathrm{EA_m}]{-\mathrm{e}} \mathrm{R}^+ \xrightarrow[-\mathrm{IP_m}]{-\mathrm{e}} \mathrm{R}^{2+} \text{ (for removal of electrons from } \psi_{\mathrm{m}})$$

$$\mathrm{S} \xrightarrow[\mathrm{IP_n}]{+\mathrm{e}} \mathrm{S}^- \xrightarrow[\mathrm{EA_n}]{+\mathrm{e}} \mathrm{S}^{2-} \text{ (for adding electrons on } \psi_{\mathrm{n}})$$

and Γ is the Coulomb interaction between r and s in a central field approximation.[16] In solution, all these Coulomb interactions Γ become Γ/ϵ except that for the interaction between electrons initially belonging to the same orbital. In this case Γ must be replaced by $\Gamma\cdot[(2/\epsilon) - 1]$ as required by solvaton theory.[19]

Finally, by replacing a^2 by $1-b^2$, one obtains

$$\begin{aligned}\Delta E_{\mathrm{mn}}' = {} & 2b^2\left\{\mathrm{IP_n} - \mathrm{EA_m} + (c_{\mathrm{s}}^{\mathrm{n}})^2[q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2]\frac{\Gamma}{\epsilon} - \right. \\ & \left.(c_{\mathrm{r}}^{\mathrm{m}})^2 q_{\mathrm{s}}\frac{\Gamma}{\epsilon} - (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right\} + 4ab(c_{\mathrm{r}}^{\mathrm{m}}c_{\mathrm{s}}^{\mathrm{n}}\beta) - \\ & b^4\left[\mathrm{IP_n} - \mathrm{EA_n} + \mathrm{IP_m} - \mathrm{EA_m} - 2(c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right]\end{aligned} \quad \text{(A1)}$$

The interaction between all other combinations of orbitals can be found easily by a similar treatment.

Appendix II

Minimization of the electron transfer energy with respect to the variational parameters a and b is included here.

$$\Delta E_{\mathrm{mn}} = \Delta E_{\mathrm{mn}}' + \Delta \mathrm{solv}_{\mathrm{mn}}$$

where $\Delta E_{\mathrm{mn}}'$ has the value derived in Appendix I and $\Delta\mathrm{solv}_{\mathrm{mn}}$ that of eq 5. The variational treatment applied to this expression leads to the following equation for the perturbational energy

$$\Delta E_{\mathrm{mn}} = M(\mathrm{m,m}) + M(\mathrm{n,n}) + \sqrt{[M(\mathrm{m,m}) - M(\mathrm{n,n})]^2 + 4M(\mathrm{m,n})^2}$$

where the matrix elements M are

$$M(\mathrm{m,m}) = 0$$

$$M(\mathrm{n,m}) = c_{\mathrm{r}}^{\mathrm{m}}c_{\mathrm{s}}^{\mathrm{n}}\beta$$

$$\begin{aligned}M(\mathrm{n,n}) = {} & \mathrm{IP_n} - \mathrm{EA_m} + (c_{\mathrm{s}}^{\mathrm{n}})^2(q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2)\frac{\Gamma}{\epsilon} - \\ & (c_{\mathrm{r}}^{\mathrm{m}})^2 q_{\mathrm{s}}\frac{\Gamma}{\epsilon} - (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right) - b^2\left[\mathrm{IP_n} - \mathrm{EA_n} + \right. \\ & \left.\mathrm{IP_m} - \mathrm{EA_m} - 2(c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right] - \\ & \sum_{\mathrm{s}}\frac{x_{\mathrm{s}}(c_{\mathrm{s}}^{\mathrm{n}})^2}{R_{\mathrm{s}}}\left(1 - \frac{1}{\epsilon}\right)[q_{\mathrm{s}} - 2b^2x_{\mathrm{s}}(c_{\mathrm{s}}^{\mathrm{n}})^2] + \\ & \sum_{\mathrm{r}}\frac{x_{\mathrm{r}}(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{r}}}\left(1 - \frac{1}{\epsilon}\right)[q_{\mathrm{r}} + 2b^2x_{\mathrm{r}}(c_{\mathrm{r}}^{\mathrm{m}})^2]\end{aligned}$$

and with the following transformations

$$\begin{aligned}E_{\mathrm{m}}^* = {} & \mathrm{IP_m} + q_{\mathrm{s}}(c_{\mathrm{r}}^{\mathrm{m}})^2\frac{\Gamma}{\epsilon} - \\ & a^2\left[\mathrm{IP_m} - \mathrm{EA_m} - (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right] - \\ & \sum_{\mathrm{r}}\frac{x_{\mathrm{r}}(c_{\mathrm{r}}^{\mathrm{m}})^2}{R_{\mathrm{r}}}\left(1 - \frac{1}{\epsilon}\right)[q_{\mathrm{r}} + 2b^2x_{\mathrm{r}}(c_{\mathrm{r}}^{\mathrm{m}})^2] \\ E_{\mathrm{n}}^* = {} & \mathrm{IP_n} + [q_{\mathrm{r}} + 2(c_{\mathrm{r}}^{\mathrm{m}})^2](c_{\mathrm{s}}^{\mathrm{n}})^2\frac{\Gamma}{\epsilon} - \\ & b^2\left[\mathrm{IP_n} - \mathrm{EA_n} - (c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\Gamma\left(\frac{2}{\epsilon} - 1\right)\right] - \\ & \sum_{\mathrm{s}}\frac{x_{\mathrm{s}}(c_{\mathrm{s}}^{\mathrm{n}})^2}{R_{\mathrm{s}}}\left(1 - \frac{1}{\epsilon}\right)[q_{\mathrm{s}} - 2b^2x_{\mathrm{s}}(c_{\mathrm{s}}^{\mathrm{n}})^2]\end{aligned} \quad \text{(A2)}$$

The final perturbation energy becomes (after correction for double account of electron–electron interaction)

$$\begin{aligned}\Delta E_{\mathrm{mn}} = {} & E_{\mathrm{n}}^* - E_{\mathrm{m}}^* + \\ & b^2[(E_{\mathrm{m}}^* - E_{\mathrm{n}}^*)_{\mathrm{b^2}} - (E_{\mathrm{m}}^* - E_{\mathrm{n}}^*)_{\mathrm{b^2=0}}] + \\ & \sqrt{(E_{\mathrm{m}}^* - E_{\mathrm{n}}^*)^2 + 4(c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\beta^2}\end{aligned} \quad \text{(A3)}$$

When the perturbation is small, *i.e.*, $4\beta^2 << (E_{\mathrm{m}} - E_{\mathrm{n}})^2$ and therefore $b^2 \rightarrow 0$, then this expression can be further reduced and approximated by

$$\Delta E_{\mathrm{mn}} = \frac{2(c_{\mathrm{r}}^{\mathrm{m}})^2(c_{\mathrm{s}}^{\mathrm{n}})^2\beta^2}{E_{\mathrm{m}}^* - E_{\mathrm{n}}^*} \quad \text{(A4)}$$

Proton Magnetic Resonance Studies of Water as Hydrogen Donor to Tributyl Phosphate[1]

Sanji Nishimura, Charles H. Ke, and Norman C. Li

Contribution from the Department of Chemistry, Duquesne University, Pittsburgh, Pennsylvania.

Received September 12, 1967

Abstract: Proton magnetic resonance studies are reported of hydrogen bonding between water protons and tributyl phosphate (TBP) in carbon tetrachloride medium in the range 10–45°. When the mole fraction of water is below 2.0×10^{-3}, self-association of water is negligible, and the data are treated in a manner which permits the determination of the equilibrium constants K_1 and K_2 of the reactions $\mathrm{OH_2 + TPB = OH_2 \cdot TBP}$ and $\mathrm{OH_2 \cdot TBP + TBP = OH_2 \cdot (TBP)_2}$, respectively. The ratio of K_1 to K_2 increases with decrease in temperature, the ratios being 7 and 10 at 45 and 10°, respectively. The enthalpy changes on the hydrogen-bond formation are: $\Delta H_1 = -4.1 \pm 0.2$ kcal/mole and $\Delta H_2 = -2.0 \pm 0.3$ kcal/mole. The $\mathrm{H_2O}$ proton magnetic resonance of the $\mathrm{OH_2 \cdot (TBP)_2}$ species appears to move to lower field with decrease in temperature.

Because of the predominance of water as a medium in living systems, the hydrogen-bonding properties of water have been of particular interest to chemists and biologists. As part of an extensive program in this laboratory on the use of the proton magnetic resonance

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