Principle of Orbital Distortion

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Analysis of frontier orbital σ–π mixing in second order, induced by attacking reagents and/or substituents at π systems, leads to a comprehensive model for predicting the stereochemical course (in the absence of steric and solvation effects) of organic reactions.

Twenty-five years ago, Fukui ingeniously described the importance of the frontier molecular orbitals (energetically highest occupied and lowest unoccupied molecular orbital, HOMO and LUMO, respectively) of reactants in determining the preferred reaction path.[2] The requirement that only two interacting sets of molecular orbitals need be analyzed has allowed the rapid development of a qualitative picture for changes in electronic structure along a reaction coordinate.[3] In addition, frontier molecular orbital theory has provided the organic chemist with an immensely useful bridge between experiment and theory as well as a powerful theoretical tool for the prediction of reaction mechanisms and geometry.

For example, in reacting molecular systems where π orbitals represent these frontier levels, analysis of the π HOMO–π LUMO interactions determines the possibility of a multisite concerted reaction (from symmetry considerations) and the regiospecificity of such a process. However, in most cases, the stereospecificity of the process is not evident from such a π,π interaction approach. In order to circumvent this deficiency, Fukui proposed that inclusion of the frontier orbitals of the σ system in the analysis would provide the necessary interactions to specify the spatial extension of the developing hybrid orbitals at a π center and, thus, the stereospecificity.[4] Initially, application of this idea, in our hands, proved difficult as some of the previously specified σ-nodal properties did not agree with theoretical calculations, and the specified major σ,π interactions in many cases did not account for the experimentally observed stereochemistry.

We have reexamined this problem and describe a simple but theoretically sound principle to delineate the stereochemistry of organic reactions. Our approach involves analysis of the *major* σ,π interaction as determined by the nodal properties of the frontier σ orbitals of small molecular fragments whose ready transferability[5] into the reacting molecular system simplifies this procedure. In all cases application of these principles is straightforward, not requiring computer-derived calculations even for very complex molecules.

A molecular orbital analysis of reacting systems is based upon the following fundamental postulates.

Concerted inter- and intramolecular multicenter π interactions are defined as allowed or disallowed by the nodal properties (symmetry) of the π frontier orbital (π HOMO, π LUMO) wave functions. The *regiospecificity* of such interactions is defined by the polarization (parallel to the nodal plane) of the π orbitals which results from π,π mixing. In the absence of overriding steric effects, the *stereospecificity* of such interactions is defined by the distortion (perpendicular to the nodal plane) of the π orbitals which result from σ,π mixing. The characteristics of such σ,π mixing are a function of geometry and the one-electron eigenvectors and eigenvalues associated with the linear combination of atomic orbitals (LCAO) description of the molecule. Geometries having an unsymmetrical distribution of atomic nuclei about the nodal plane of a molecular π system allow σ,π mixing. Mixed molecular orbitals which have unsymmetrical electron probability density distributions lead to a requirement for certain geometries for maximum electron transfer or exchange (overlap) during the course of a chemical reaction. The composition of such mixed orbitals may be determined by the application of Rayleigh–Schrödinger perturbation theory.[6]

Perturbation Theory[7]

Let us consider two isolated systems A and B (Figure 1), whose *initial*, nondegenerate, unperturbed (zeroth order) eigenvectors (ψ_i, ψ_{i+1}, ψ_k) and associated eigenvalues (E_i, E_{i+1}, E_k) are known. Upon interaction of systems A and B each new eigenvector obtained (ψ') may be expanded into a series of terms representing weighted contributions or corrections from all other zeroth-order eigenvectors of both A and B (inter- and intrasystem mixing) to the zeroth-order wave function. Thus for ψ_i, this corrected wave function ψ_i' is given by eq 1, where C_1 represents the

$$\psi_i' = \psi_i^0 + C_1\psi_k^0 + C_2\psi_{i+1}^0 \qquad (1)$$

magnitude and sign of the first-order contribution from ψ_k^0 (intersystem mixing) and C_2 represents the corresponding second-order contribution from ψ_{i+1}^0 (intrasystem mixing). A similar expression may also be written for ψ_{i+1}'. The expression for the mixing of ψ_k^0 with ψ_i^0 and ψ_{i+1}^0 may be obtained by the combination of two first-order interactions: $\psi_k' = \psi_k^0 + C_1\psi_i^0 + C_1'\psi_{i+1}^0$. Neglecting overlap, the perturbation expression in our system required to define the first-order mixing coefficient, C_1, and its sign associated with ψ_k^0 for correction to ψ_i^0 are given by eq 2,

$$C_1 = H_{ik}/(E_i - E_k) \qquad (2)$$

where H_{ik} is the resonance integral between ψ_i^0 and ψ_k^0. This first-order intersystem mixing may be expressed symbolically as in Figure 2 (dotted lines). Again, neglecting overlap, the corresponding second-order coefficient, C_2, and

(1) First presented in a seminar by E.M.B. and C.L.L. at the Gordon Research Conference on Organic Reactions and Processes, 1977.

(2) K. Fukui et al., *J. Chem. Phys.*, **22**, 1433 (1954).

(3) A review has appeared: K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).

(4) K. Fukui, *Tetrahedron Lett.*, 2427 (1965); K. Fukui and H. Fujimoto, *ibid.*, 5551 (1966); *Bull. Chem. Soc. Jpn.*, **39**, 2116 (1966); **40**, 2018 (1967); K. Fukui and S. Inagaki, *Chem. Lett.*, 509 (1974); K. Fukui, "Theory of Orientation and Stereoselection", Springer-Verlag, Heidelberg, 1979; K. Fukui, H. Fujimoto, and S. Inagaki, *J. Am. Chem. Soc.*, **98**, 4054 (1976); O. Eisenstein, J. Klein, and J. M. Lefour, *Tetrahedron*, **35**, 225 (1979); C. L. Liotta, *Tetrahedron Lett.*, 519, 523 (1975).

(5) R. F. W. Bader, *Acc. Chem. Res.*, **8**, 34 (1975).

(6) An elegant application of perturbation theory to organic chemistry has been published: R. Hoffmann and L. Lebit, *J. Am. Chem. Soc.*, **96**, 1370 (1974). Much of the symbolism in the present manuscript has been taken from Hoffmann's paper.

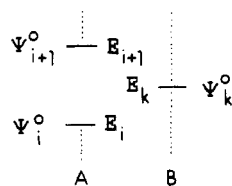(7) See, for example, H. Eyring, J. Walter, and G. E. Kimball, "Quantum Chemistry", Wiley, New York, 1944.

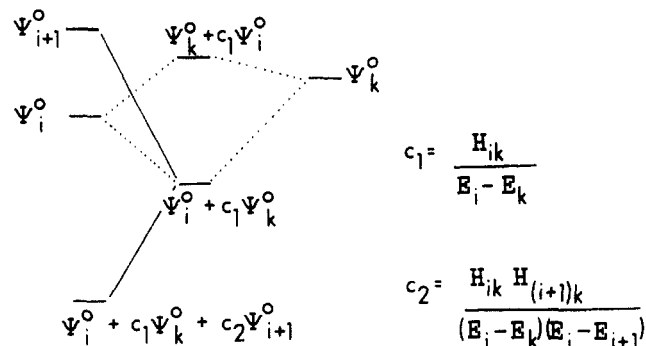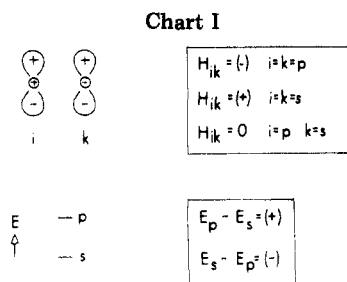**Figure 1.** Idealized three-orbital system.

Figure 2. Mixing in a three-orbital system.

$$c_1 = \frac{H_{ik}}{E_i - E_k}$$

$$c_2 = \frac{H_{ik}\, H_{(i+1)k}}{(E_i - E_k)(E_i - E_{i+1})}$$

Chart I

Figure 3. Orbital distortion at center A upon interaction with B.

Figure 4. Origin of frontier π orbital distortion.

Table I. Sign of Mixing Coefficients in Figure 3 as a Function of Energy

energy		P		S	
intrasystem	intersystem	C_1	C_2	C_1	C_2
$E_p < E_s$	$E_p < E_s < E_{p'}$	−	+	−	−
	$E_p < E_{p'} < E_s$	−	+	+	+
	$E_{p'} < E_p < E_s$	+	−	+	+
$E_s < E_p$	$E_s < E_p < E_{p'}$	−	−	−	+
	$E_s < E_{p'} < E_p$	+	+	−	+
	$E_{p'} < E_s < E_p$	+	+	+	−

its sign associated with ψ_{i+1}^0 for corrections to ψ_i^0 are given in eq 3, which is represented in Figure 2 as a solid line. For

$$C_2 = \frac{H_{ik}H_{(i+1)k}}{(E_i - E_k)(E_i - E_{i+1})} \tag{3}$$

our purposes, the sign rather than the magnitude of the second-order mixing coefficients is crucial.

Approximations[8] to the resonance integrals are by definition negative matrix elements if the overlap integral is made positive by selection of basis orbitals (s or p) which are oriented in phase (an arbitrary choice which is always possible). For an example, see Chart I. Accordingly, for such a choice, the numerator in eq 2 is negative and in eq 3 is positive, and thus the signs of the mixing coefficients C_1 and C_2 are determined by the relative eigenvalues E_i, E_{i+1}, and E_k (Figure 1), where E_i has a larger negative value than E_k which has a larger negative value than E_{i+1}. For example, consider the nondegenerate s- and p-orbital systems whose initial relative eigenvalues are shown in Figure 3, where p and s are orthogonal and located on atom A. Upon interaction with atom B, both one-center orbitals on A intermix in first-order with B according to the sign of the coefficient, C_1. The new one-center orbitals of A intramix in second order according to the sign of C_2. In general, two initially orthogonal s and p orbitals on the same center intramix in second order according to the intrasystem ordering of their eigenvalues and their energetic relationship to the intersystem perturbing orbital as shown in Table I. We will refer to such intramixe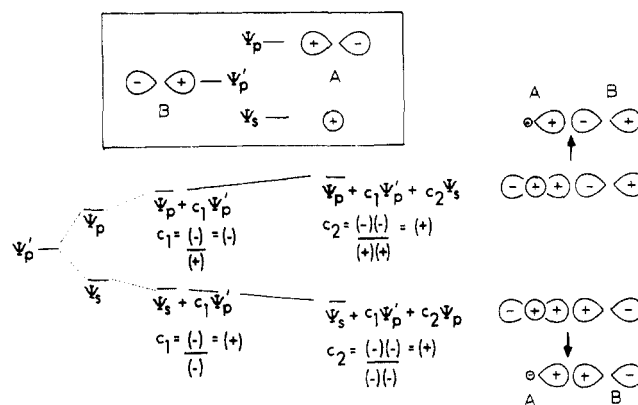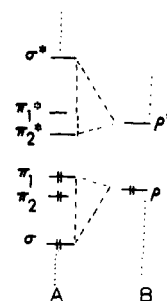d orbitals as "distorted" and represent them as nonlinear hybrids. In the organic reactants of interest where the orbital system A is composed of many bonding and antibonding σ and π levels (Figure 4), it is apparent from the inverse energy dependence of the first- and second-order perturbations of A by B that the *dominant terms in the expansion of the frontier wave functions of A are derived from the symmetry-allowed interaction of levels closest in energy.* For example, the expansion of the perturbed frontier wave function associated with π_1 and π_2^* would take the forms shown in eq 4 and 5.

$$\psi_{\pi_1}' = \psi_{\pi_1}^0 + C_1^P\psi_p^0 + C_2^\pi\psi_{\pi_2}^0 + C_2^\sigma\psi_\sigma + \ldots \tag{4}$$

$$\psi_{\pi_2}^* = \psi_{\pi_2}^{0*} + C_1^P\psi_p^0 + C_2^{\pi^*}\psi_{\pi_1^*}^0 + C_2^{\sigma^*}\psi_{\sigma^*}^0 + \ldots \tag{5}$$

The terms in $\psi_{\pi_2}^0$ and $\psi_{\pi_1^*}^0$ represent orbital polarization parallel to the π nodal plane as induced in A and B while the terms in ψ_σ^0 and $\psi_{\sigma^*}^0$ represent orbital distortion perpendicular to the π nodal plane. Thus, in the case of a reaction which is controlled by *frontier* orbital overlap, bond formation would be more advanced at site 1 (the regioselective site) and from the direction indicated relative to the nodal plane (the stereoselectivity at the regioselective site; see Scheme I).

We shall assume that the *regioselectivity* exhibited by closed-shell reactants is controlled by the symmetry (inphase orbital overlap) and magnitude of the interaction

(8) There is usually some function of the coulomb integrals (H_{ii}, H_{kk}) and overlap integral (S_{ik}) such as the Wolfberg–Helmholtz relation $H_{ik} = K[(H_{ii} + H_{kk})/2]S_{ik}$, where K is a constant.
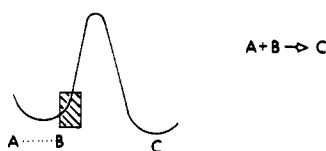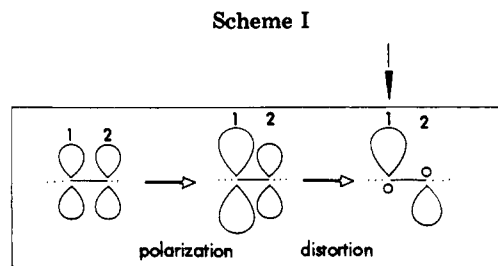
Scheme I

Figure 5. Idealized reaction coordinate vs. energy diagram for a reaction A + B → C. The boxed area designates a weak interaction between A and B for which the reactant frontier wave functions may be expanded in terms of the zero-order wave functions.

(greatest resonance integral as approximated by overlap) of the reactant HOMO-LUMO (frontier) orbitals as described by ψ'_{HOMO} and ψ'_{LUMO} which will have been corrected for polarization (i.e., in eq 4 and 5, the terms $C_2^{\pi}\psi_{\pi_2}^{0}$ and $C_2^{\pi*}\psi_{\pi_2*}^{0}$) along the nodal plane. The *stereoselectivity* experienced by the reactants at the atomic centers defined by the above HOMO-LUMO criterion will be a function of the distortion developed at these frontier orbitals as a result of $\pi-\sigma$ and $\pi*-\sigma*$ mixing (i.e., in eq 4 and 5, the terms $C_2^{\sigma}\psi_{\sigma}^{0}$ and $C_2^{\sigma*}\psi_{\sigma*}^{0}$). *Implicit in this analysis is the assumption that the initial perturbation defines a stereochemistry near the origin of the reaction coordinate which remains and increases in magnitude in the transition state* as illustrated in Figure 5.

In summary, application of these postulates to a given adiabatic reacting π system requires the following analysis.

(1) Stereochemical inspection of a reactant determines the localized group, bond, or atomic orbital geometrically out of the π nodal plane which will provide the maximum energy level splitting after mixing with the π system. This will result in a new and delocalized molecular orbital which reflects the most important electronic contribution associated with those nuclei distributed asymmetrically about this π nodal plane and will rigorously lead to asymmetric molecular orbital electron probability densities (distorted orbitals) with reference to this plane.

(2) The asymmetric character introduced into the π system as a result of the above mixing may be pictured as an orbital distortion resulting from $\sigma-\pi$ and $\sigma*-\pi*$ mixing.

(3) MO perturbation theory (neglecting isotropic electrostatic effects which in general do not provide for unique geometries) deleneates the direction and magnitude of the interaction energy during an orbitally controlled chemical reaction and will be useful in the dynamic application of these interacting distorted MO's to the prediction of both the product stereochemistry and the symmetry properties of the reaction coordinate. Only distorted MO's closest in energy (whose stabilizing interaction is largest) should be considered in arriving at the above prediction (i.e., HOMO-LUMO interaction). In systems having a single frontier HOMO-LUMO interaction[9] the predicted stere-
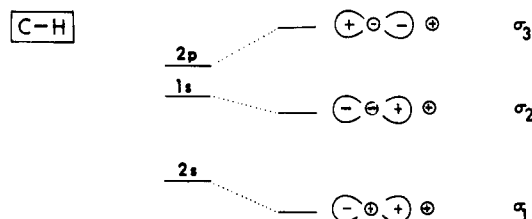

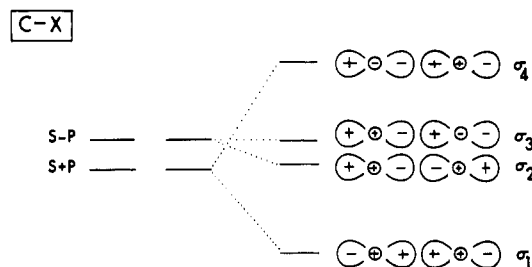**Figure 6.** σ orbitals for a C-H fragment.

Figure 7. σ orbitals for a C-X fragment.

ochemistry is simply a function of maximizing the bonding overlap (interaction energy) of the distorted HOMO-LUMO's (for electrophilic or nucleophilic attack). Two frontier concerted interactions[9] (HOMO-LUMO' and HOMO'-LUMO combinations) involving mutual perturbation of two reactants will also follow this maximum overlap rule.

Sigma Molecular Orbitals

While the nodal properties of π molecular orbitals are well-known, the corresponding σ molecular orbitals are less familiar but easily constructed by using atomic or group orbitals.[11] The σ orbital framework of most organic systems of interest may be built up from the symmetry allowed combinations of the basic fragment orbitals, C—H, C—X (X $\neq$ H), C=C, and C≡C.

The molecular orbitals of the C—H group may be easily derived from the combination of the 1s orbital of hydrogen and 2s and 2p orbitals of carbon. The relative energy levels shown in Figure 6 are based on the known ionization potentials of the atomic species in question (for carbon 2p, −11 eV, 2s, −21 eV; for hydrogen 1s, −13 eV).[6] The orthogonal 2p–2s subset on carbon mixes in first-order with the hydrogen 1s and intramixes in second-order (eq 1) to provide the three molecular orbitals shown in Figure 6. Analogously, the molecular orbitals of the C–X (X $\neq$ H) group may be derived from the combination of two s and two p atomic orbitals on adjacent atoms. Beginning with sp hybrid orbitals [$\psi^+ = 2^{-1/2}(S + P)$, $\psi^- = 2^{-1/2}(S - P)$] on each atom, first-order interaction between symmetry-related sp atomic hybrides (ψ^+ with ψ^+ and ψ^- with ψ^-) results in the four molecular orbitals shown in Figure 7.[10]

For multiply bonded fragments (C=C) there exist two sets of in-plane σ molecular orbitals, one utilizing atomic orbitals which are antisymmetric with respect to a C_2 rotation about the bond axis and the other set utilizing atomic orbitals which are symmetric with respect to a C_2 rotation about the bond axis. Since the stereochemical information is carried by the atomic s functions at each center which are always symmetric with respect to a bond axis C_2 operation, only the latter set of σ orbitals needs to be considered. The simplest example containing this

(9) G. Klopman, "Chemical Reactivity and Reaction Paths", Wiley, New York, 1974, Chapter 4, p 55.

(10) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, 1969, pp 133–135.

(11) L. Salem and W. L. Jorgenson, "The Organic Chemist's Book of Orbitals", Academic Press, New York, 1973.
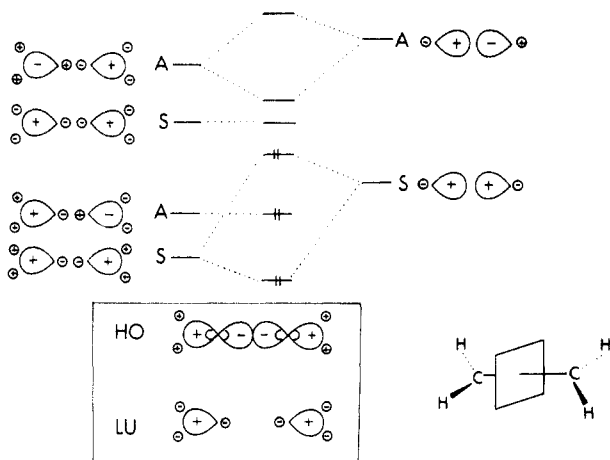
Figure 8. Pertinent ethylene σ orbitals.
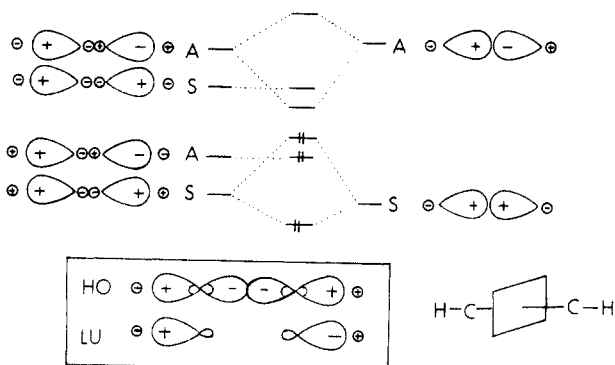
Figure 9. Pertinent acetylenic σ orbitals.

fragment is ethylene which may be constructed from two CH_2 group orbitals and one C–C bond orbital, both of C_2 symmetry with respect to the bond axis. By use of a mirror plane bisecting the C–C bond axis, the resulting four CH_2 group combinations mix in first order with the C–C bond orbital as shown in Figure 8.[11]

In a similar fashion the pertinent acetylene σ molecular orbitals evolve as shown in Figure 9.

Sample Applications

First consider the frontier orbital controlled stereochemistry for intra- and intermolecular reactions at a carbonium ion center as directed by an adjacent C–X substituent hyperconjugatively interacting with this center in a rigid system. This frontier hyperconjugative interaction may be expressed by the mixing of a σ orbital of the C–X fragment lying closest in energy (σ_2) with the s and p orbitals of the carbonium ion center (Figure 10). The direction of intermolecular attack on the carbonium ion by a nucleophile depends upon the distortion of the frontier LUMO (p′) as found by expansion of the ψ_p wave function: $\psi_p{}' = \psi_p{}^0 + C_1{}^{\sigma_2}\psi_{\sigma_2}{}^0 + C_2{}^s\psi_s{}^0$. Exercising the arbitrary choice of selection of the basis functions (σ_2, p, and s) to be initially in-phase, one finds that the second-order mixing coefficient for ψ_s is (+). This second-order correction along with the first-order negative $C_1{}^{\sigma_2}\psi_{\sigma_2}{}^0$ term provides a distorted orbital picture of the LUMO which indicates anti attack by a nucleophile. The direction of intramolecular attack (rearrangement) on the carbonium ion center by a neighboring group depends upon the distortion of the frontier HOMO ($\sigma_2{}'$) as found by two first-order mixings of σ_2 with a p and s, respectively: $\psi'\sigma_2 = \psi_{\sigma_2}{}^0 + C_1{}^P\psi_p{}^0 + C_1{}^s\psi_s{}^0$. The first-order mixing coefficients for ψ_p and ψ_s are found to be (−), indicating a distorted orbital picture of the HOMO syn to the C–X bond. The
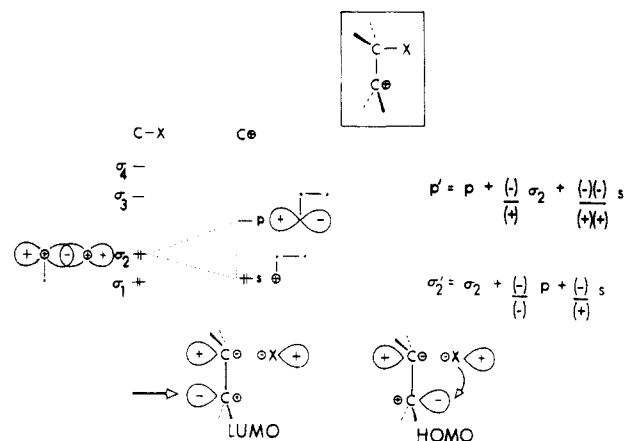

Figure 10. Analysis of a carbonium ion distorted by a C–X fragment.

$$p' = p + \frac{(-)}{(+)}\,\sigma_2 + \frac{(-)(-)}{(+)(+)}\,s$$

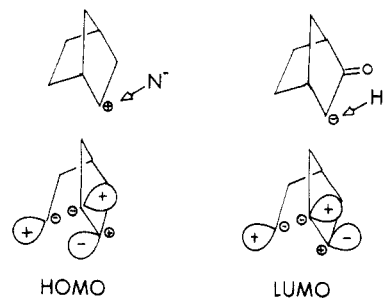$$\sigma_2' = \sigma_2 + \frac{(-)}{(-)}\,p + \frac{(-)}{(+)}\,s$$

Figure 11. Distorted frontier orbitals of the 2-norbornyl system.

nonlinear hybridization of the HOMO electron density greatly *facilitates* bonding between the β-carbon and the X-substituent during a Wagner–Meerwein rearrangement in cases where X is an alkyl group. The same argument applies to suprafacial 1,2 hydride shifts (X = H).

For application of the above to a simple system consider the stereochemistry of nucleophilic attack on the 2-norbornyl cation. The 2-norbornyl geometry indicates that it is the C(1)–C(6) σ bond, asymmetrically disposed with respect to the nodal plane of the C(2) p orbital, which will provide maximum energy level splitting when mixed with this p orbital. Figure 11 represents the HOMO and LUMO of this system. If one remembers that the LUMO of the 2-norbornyl cation also represents the HOMO of the corresponding norbornyl anion (as represented by the enolate of 2-norbornone), the preferred exo attack[12] of nucleophiles on the former and exo protonation of the latter are apparent from orbital distortion. This approach is consistent with the hyperconjugatively stabilized (vertical stabilization) model proposed for the 2-norbornyl cation.[13]

It has been shown that the π approach to the 2-norbornyl cation from the 2-(3-cyclopentenyl)ethyl cation proceeds via a symmetric transition state as indicated by the rate additivity of methyl substitution at the π bond.[14] In this transition state the controlling first-order frontier interaction is the vacant p orbital of the cationic center with the π bond of the ethylene (cyclopentene) as distorted via the second-order intragroup mixing of the σ fragment

(12) T. T. Tidwell, *J. Am. Chem. Soc.*, **92**, 1448 (1970).

(13) D. F. Eaton and T. G. Traylor, *J. Am. Chem. Soc.*, **96**, 1226 (1974); T. G. Traylor, et al., *ibid.*, **93**, 5715 (1971); F. R. Jensen and B. E. Smart, *ibid.*, **91**, 5686, 5689 (1969); P. v. R. Schleyer, *ibid.*, **89**, 699, 701 (1967).

(14) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *J. Am. Chem. Soc.*, **89**, 1288 (1965); P. D. Bartlett and G. D. Sargent, *ibid.*, **87**, 1297 (1965).
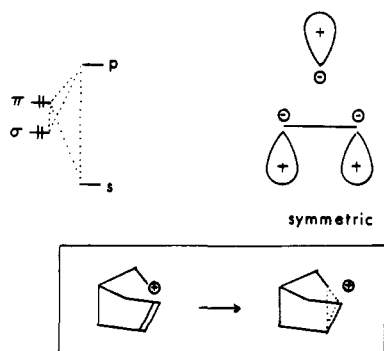
Figure 12. Distorted frontier π orbital of the symmetric (bridged) 2-norbornyl cation.
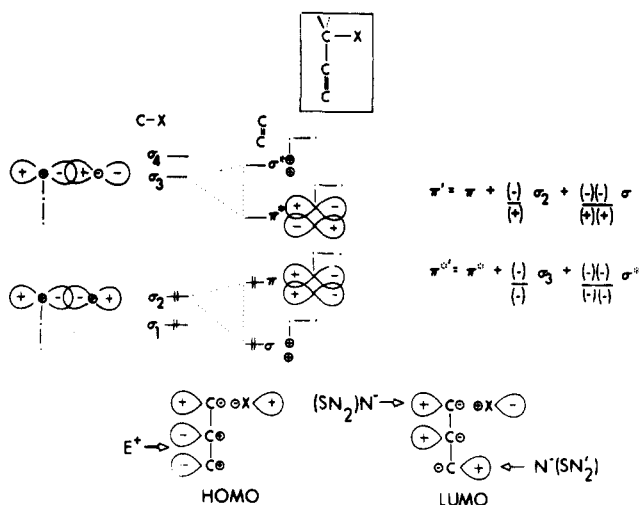

Figure 13. Analysis of a π system distorted by a C–X fragment.

at the π center (Figure 12). The resultant π-level *remains symmetric* with respect to the cationic center in agreement with the observed substituent effects.

A logical extension of the above is the hyperconjugative interaction of a C–X fragment with a π bond in a rigid system. The frontier wave functions, π' and $\pi^{*\prime}$, distorted by σ and σ^* (Figure 8) via σ_2 and σ_3 (Figure 7), respectively, are shown in Figure 13.

The two frontier orbitals of such a rigid allylic system dictate the approach of the incoming reagent according to the direction of the distortion of these critical orbitals, i.e.

position	HOMO	LUMO
1	anti	anti
3	anti	syn

Approaching reagents may be classified according to the number of energetically available frontier orbitals. *Reagents with only one frontier (monointeractive) orbital lying energetically proximate to the allylic π' and $\pi^{*\prime}$ orbitals may be differentiated from reagents having two frontier orbitals (diinteractive) within the energy span.* Monointeractive electrophilic reagents engage sites 1 and 3 of the controlling π' orbital in an anti direction while monointeractive nucleophiles are anti directed toward site 1 and syn directed toward site 3. Diinteractive nucleophiles are anti directed toward site 1 but experience a dicotomy with regard to site 3. Such diinteractive reagents with dominant (low lying) acceptor (electrophilic) orbitals attack position 3 of the distorted allylic system with anti stereochemistry while those with dominant (high lying) donor (nucleophilic) orbitals are forced into a syn approach. The juxtaposition of these two effects should
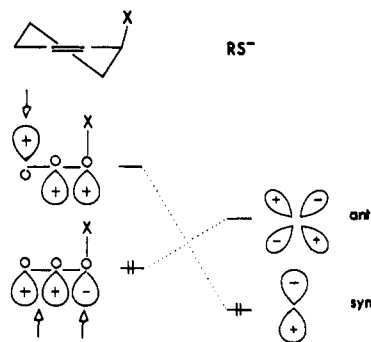

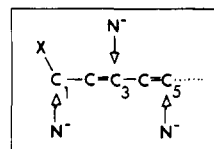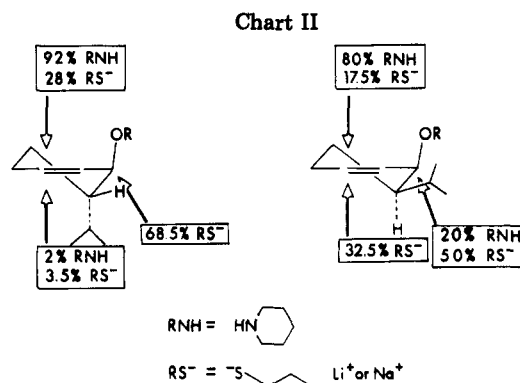**Figure 14.** Distorted frontier interaction with an α orbital diinteractive reagent in the S_N2–S_N2' reaction.

Figure 15. Stereochemistry of the S_N2–S_N2'–S_N2'' reaction.

Chart II

result in the loss of stereospecificity for certain diinteractive reagents in the S_N2' reaction. Monointeractive nucleophiles which participate in the S_N2 and S_N2' reactions are characterized by an energetically available HOMO and an unavailable (high lying) LUMO.[15] Conversely, diinteractive nucleophiles employ (geometry permitting) both the HOMO and LUMO in a frontier interaction with the substrate. In this respect, such nucleophiles truely exhibit dual donor–acceptor properties. This acceptor component may be provided by vacant low-lying p- or d-type orbitals centered at the nucleophile's reaction site and are exemplified by cyanide, substituted acetylide, pyridine, lithium dialkylcuprate,[16] dialkyl boride, thiolate,[15b,17] and phosphides. For example, in the S_N2'–

(15) (a) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4609 (1956); (b) G. Stork and A. F. Kreft, III, *ibid.*, **99**, 3850 (1977); (c) A. A. Dobbie and K. H. Overton, *J. Chem. Soc., Chem. Commun.*, 722 (1977); (d) K. H. Overton and T. Oritani, *ibid.*, 454 (1978); (e) R. M. Magid and O. S. Fruchey, *J. Am. Chem. Soc.*, **99**, 8368 (1977); (f) R. M. Magid and O. S. Fruchey, *ibid.*, **101**, 2107 (1979); (g) W. Kirmse, F. Scheidt, and H. J. Vater, *ibid.*, **100**, 3945 (1978); (h) J. Mathieu, G. Nomine, J. Martel, and E. Toromanoff, *Tetrahedron Lett.*, 1491 (1972).

(16) Dialkyl cuprates demonstrate exclusive anti stereochemistry in the S_N2' reaction: (a) J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 675 (1979); (b) J. P. Marino and D. M. Floyd, *ibid.*, 3897 (1975); (c) J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974); (d) R. J. Anderson, *ibid.*, **92**, 4978 (1970); (e) D. M. Wieland and C. R. Johnson, *ibid*, **93**, 3047 (1971); (f) J. Staroscik and B. Rickborn, *ibid.*, **93**, 3046 (1971); (g) G. Callina and P. G. Ciattini, *ibid.*, **101**, 1035 (1979); (h) H. L. Goering and V. D. Singleton, Jr., *ibid.*, **98**, 7854 (1976); (i) A. Kreft, *Tetrahedron Lett.*, 1035 (1977); (j) A. Claesson and L. I. Olsson, *J. Chem. Soc., Chem. Commun.*, 621 (1978); (k) S. L. Murashashi, *J. Am. Chem. Soc.*, **100**, 4610 (1978).

(17) G. Stork and A. F. Kreft, *J. Am. Chem. Soc.*, **99**, 3851 (1977).

Scheme II
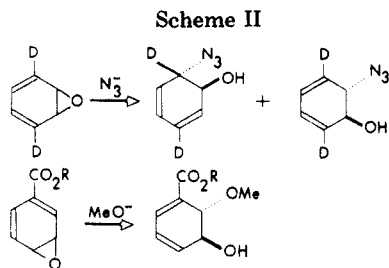
S_N2 reaction, with sulfur nucleophiles, opposite stereo-control results from this frontier interaction as shown in Figure 14. Monointeractive nucleophiles exhibit syn stereochemistry in the S_N2' pathway while diinteractive nucleophiles provide more anti product and increase the S_N2/S_N2' product ratio in a competitive reaction. This competitive behavior of nucleophiles is clearly demonstrated in the careful studies by Stork et al. on the intermolecular reaction of piperidine and propanethiolate with the 2,6-dichlorobenzoates of *cis*- and *trans*-6-isopropyl-2-cyclohexen-1-ol which provide a product distribution[15a,b,17] (Chart II). Indeed, the sterically unencumbered intramolecular S_N2' cyclization involving a thiolate nucleophile proceeds exclusively with anti stereochemistry while an intermolecular version with a secondary amine proceeded exclusively with syn stereochemistry.[15a,b]

Extension of the analysis of the hyperconjugative interaction of a C–X fragment with a conjugated trans and cis diene (Figure 15) in a rigid system dictates that a monointeractive nucleophile is directed by orbital distortion in an anti–syn–anti alternating pattern relative to the C–X fragment. Although diinteractive reagents experience a dicotomy with respect to the two frontier interactions at the 3-position, the distortions of the diene HOMO and LUMO are both anti with respect to the C–X fragment at the 5-position. The elegant work of Berchtold[18] and

Kishi[19] with an arene oxide as a cis dienoid model beautifully demonstrates the correctness of this application of the principle of orbital distortion (see Scheme II).

Finally, analysis of a C–X fragment hyperconjugated with an alkyne unit (Figure 9) gives a stereochemical result quite different from the alkene counterpart as a result of the appearance of a lowest lying antisymmetric vacant σ^* orbital. Mixing in second order of this σ^* orbital with a π^* orbital directs an incoming monointeractive reagent at the 3-position along a path anti to the bond of the C–X fragment. Diinteractive reagents take advantage of an additional interaction with the substrate highest occupied π molecular orbital, and as in the case of an alkenyl substrate, these orbitals are distorted in the anti direction. Since both substrate frontier π orbitals are distorted in concert, a high degree of stereospecificity should be demonstrated in the S_N2' reaction for alkyne substrates with both reagent types. This conclusion has been exemplified in the reaction of a number of 1-alkyn-3-ol derivatives with diinteractive and monointeractive reagents to give allenes derived from an anti reaction path.[20]

(18) G. A. Berchtold, R. M. DeMarinis, C. N. Filer, and S. M. Waraszkiewicy, *J. Am. Chem. Soc.*, **96**, 1193 (1974); G. A. Berchtold, D. M. Jerina, et al., *ibid.*, **96**, 6929 (1974).
(19) Y. Kishi, *J. Am. Chem. Soc.*, **98**, 6723 (1976).
(20) (a) W. H. Pirkle and C. D. Bolder, *J. Org. Chem.*, **43**, 1950 (1978); (b) E. J. Corey and W. T. Borden, *Tetrahedron Lett.*, 313, (1969); (c) P. Crabbie, J. L. Luche, E. Barreiro, and J. M. Dollat, *ibid.*, 4615 (1974); (d) O. J. Muscio, Jr., Y. M. Jun, and J. B. Philip, Jr., *ibid.*, 2379 (1978); (e) G. Tadema, et al., *ibid.*, 3935, (1979); (f) M. Midland, *J. Organomet. Chem.*, **156**, C5 (1978); (g) Y. Yamamoto, *ibid.*, **156**, C9 (1978).

GENOA: A Computer Program for Structure Elucidation Utilizing Overlapping and Alternative Substructures[1]

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Received September 23, 1980

An interactive computer program called GENOA, for isomer generation based on overlapping and alternative substructures, is described. This program produces an exhaustive and irredundant set of structural isomers based on these substructures and thus has direct application as a computer aid to molecular structure elucidation. The key algorithm in GENOA, constructive substructure search, solves the problem of piecing together substructures which may overlap to any extent. This algorithm provides efficient, prospective use of the often ambiguous and redundant structural information collected on an unknown structure by using a variety of complementary spectroscopic and chemical techniques. Advantages of this approach to structure elucidation are discussed, including simplicity of use and direct interface to programs for automated analysis of spectroscopic data. Examples of use of GENOA in actual structure elucidation problems are presented. Novel aspects of the algorithm for structure generation are described.

A. Introduction

In recent years several computer programs have been written to perform the structure generation task in computer-assisted structure elucidation.[2] These programs have as their common goal the construction of computer representations of all isomeric molecular structures which obey a set of constraints on desired and undesired features

(1) Part 37 of the series "Applications of Artificial Intelligence for Chemical Inference". For Part 36, see N. A. B. Gray, A. Buchs, D. H. Smith, and C. Djerassi, *Helv. Chim. Acta*, in press.

(2) "Computer-Assisted Structure Elucidation", D. H. Smith, Ed., ACS Symposium Series 54, American Chemical Society, Washington, D.C., 1977.