system (J_{AB} = 0). For each study, more than eight different temperatures were used. Log (k/T) was plotted against $1/T$ (see Figure 4) and a least-square treatment using the Eyring model gave enthalpy (ΔH^*) and entropy (ΔS^*) of activation for the observed exchanges and the free enthalpy of activation at coalescence ΔG^*_c.

$$\log (k/T) = 10.32 - \Delta H^*/4.57T + \Delta S^*/4.57$$

$$\Delta G^*_c = \Delta H^* - T_c\Delta S^*$$

For the line-shape simulation, the chemical shift difference $\Delta\nu$ between the two sites was determined for different temperatures in the low-exchange domain and this enabled us to evaluate $\Delta\nu$ at each temperature with a linear expresion: $\Delta\nu = aT + b$. The spin-spin relaxation time (T_2)

was corrected at each temperature by the line-width changes deduced from a reference peak. The populations of each site were obtained by integration of ^{1}H NMR spectra. Good fits were obtained by linear regression on the Eyring equation; nevertheless, on the basis of experimental errors and linear adjustment, maximum total errors estimated for the activation parameters are about ±1.5 kcal/mol for ΔH^* and ±3 eu for ΔS^*. However, as previously reported,[36] the errors associated with ΔG^*_c are not as important as the latter and could not exceed 0.3–0.4 kcal/mol. The reliability of ΔG^*_c values have been tested with the following approximated expression

$$\Delta G^*_c = 4.57 \times 10^{-3}T_c\left(10.32 + \log\left(T_c\sqrt{2}\big/\pi\Delta\nu\right)\right)$$

and a good agreement was obtained with the ΔG^*_c evaluated by line-shape analysis.

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Stereochemistry of Nucleophilic Addition to Cyclohexanone. The Importance of Two-Electron Stabilizing Interactions

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Abstract: A theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group by electron donors is proposed. It is postulated, using the Bell–Evans–Polanyi principle, that the feature of this transition state critical for stereoselectivity of the reaction is the existence of a low-lying vacant orbital $\sigma^*_\ddagger$ associated with the σ bond being formed in the reaction and that electron delocalization into that orbital will stabilize the transition state and may thereby enhance the reaction rate: the kinetic anomeric effect and the kinetic α effect are considered as the examples of such a stabilizing interaction. Stereochemistry of nucleophilic addition to cyclohexanone is determined by two factors according to this model: steric hindrance which favors the equatorial approach and electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the $\sigma^*_\ddagger$ orbital, which favors the axial approach since the carbon–hydrogen bonds are better electron donors. Consequently, nucleophile structure, metal cations complexing the carbonyl oxygen, solvent, and counterions or other solutes may influence stereoselectivity of the reaction by changing the $\epsilon(\sigma^*_\ddagger)$. Furthermore, it is shown that this model offers a simple and consistent way to rationalize kinetic and stereochemical effects of the so-called "remote polar substituents" which cannot be explained in terms of steric or electrostatic interactions but appear to be controlled by the overlap and energy gap between the remote electron-donor orbitals and the $\sigma^*_\ddagger$ orbital.

For an explanation of the stereochemistry of fast irreversible nucleophilic additions to cyclohexanone such as metal hydride reductions or additions of organometallic compounds, at least two different interactions must be invoked. This necessity was pointed out 2 decades ago in the first major review of the topic, which concluded in the following way.

"...Thus, the steric direction of reaction of nucleophilic addition to the carbonyl group of cyclic six-membered ketones is determined, apparently, by two competitive factors: a factor directing the entering substituent into the axial position, and a factor opposing this, depending on steric hindrance and directing the substituent into the equatorial position. It appears probable that the first factor is determined not by thermodynamic stability of the final products but is mainly connected with the orientation of the charged...attacking agent under the action of polar influences...connected for example, with the uncompensated dipole

moments of the carbon–hydrogen bonds..."[1]

The nature of the interaction, described above as the second factor, has never been questioned. It is generally agreed that if the reaction goes through an early reactant-like transition state, the steric strain between a nucleophile and the C_3 and C_5 axial hydrogen atoms destabilizes the axial transition state, thus directing a nucleophile into the equatorial position. However, after 2 decades the nature of the first interaction is still a matter of continuing discussion and in the recent reviews is described as "...some other (nonsteric) factor which provides an intrinsic preference for axial attack"[2], or as "...It is obvious that some chemical property of 4-*tert*-butylcyclohexanone directs the attack of complex metal hydrides to the axial side...".[3]

Numerous suggestions involving the arguments of thermodynamic stability, steric interactions, and frontier orbitals have been

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made to account for these observations. Of all the rationalizations, two proposals discussing transition-state stabilization and destabilization by electronic factors appear to have received the widest acceptance.[2-5]

The first hypothesis[6] suggests that the equatorial transition state is actually more destabilized than the axial one by torsional strain. In equatorial attack, the incipient bond is eclipsing the axial C_2 and C_6 carbon-hydrogen bonds, which is a destabilizing interaction.

The second hypothesis[7] postulates that the axial transition state is stabilized by the interaction with the σ^* antibonding orbitals of the axial C_2 and C_6 carbon-hydrogen bonds.

These two propositions now dominate mechanistic considerations in the field. There are, however, several general objections which in our judgment invalidate both models.

First, both hypotheses crucially depend on the postulate that a rather small difference in the angle of orbital interactions, resulting from a flattening of the cyclohexanone ring, will be preserved in the transition state and will lead to a several kilocalories difference in the enthalpy of activation between the axial and equatorial transition states. As a consequence of the flattening produced by the introduction of a trigonal carbon atom into the cyclohexane ring, the C_2C_3 and C_5C_6 carbon-carbon bonds form a larger angle with the axis normal to the carbonyl group plane than the axial C_2 and C_6 carbon-hydrogen bonds. For the description of the deviation from the perfect chair, the $\angle O-C_1-C_2-H_{eq}$ angle is normally used. This angle ranges in crystal structures from 2.5° to 12.7°,[8] whereas force-field calculations give the value of 3.3°.[9] Since even a distant interaction of a nucleophile with a carbonyl group produces a discernible pyramidalization of the trigonal carbon atom,[10] it seems that the deviation of this order of magnitude would be unlikely to impede optimization of orbital interactions during the transition state. Therefore, it appears objectionable that the authors of the transition-state stabilization hypothesis[7] disregard the stabilization of the equatorial transition state by interaction with the C_2C_3 and C_5C_6 bonds on the grounds that the axial transition state assures distinctly better antiperiplanarity. Interestingly, if the difference in the antiperiplanarity angle would be neglected, the same hypothesis would predict preference for equatorial approach in nucleophilic addition to 4-*tert*-butylcyclohexanone, because $\epsilon(\sigma^*_{CC})$ is lower than $\epsilon(\sigma^*_{CH})$.

Similarly, the authors of the destabilization hypothesis[6] disregard the eclipsing with carbon-carbon bonds in the axial transition state. However, it is rather doubtful that the factor of torsional strain, if considered as being actually a difference between the two destabilizing interactions, can account for the magnitude of the observed stereoselectivity effects.

Second, both hypotheses imply that the preference of some nucleophiles for a more hindered approach is a peculiarity of the cyclohexanone system and should not be observed in a molecule where the angles of orbital interactions would be equal during the alternative approaches. However, such a conclusion is at variance with experimental evidence.[11]

Third, there is a growing body of evidence that factors such as nucleophile structure, counterions, or solvent influence the interaction which promotes the axial approach.[12] This seems to be an important feature of this interaction and a correct model should predict such effects.

Fourth, a model of transition-state stabilization or destabilization cannot ignore a wealth of evidence about the impact of substituents and heteroatoms in the cyclohexanone ring on stereochemistry and rate constants of nucleophilic additions. None of the present hypotheses provide a tool to rationalize such effects.[13]

In conclusion, it appears that the problem still awaits its proper solution, although it should be recognized that the hitherto continuing discussion succeeded in focusing on nonbonded orbital interactions as the possible origin of stereoselectivity in nucleophilic addition to a carbonyl group. Accordingly, we wish to suggest that the preference for the axial approach in nucleophilic addition to 4-*tert*-butylcyclohexanone arises through such interactions resulting in a stabilization of the axial transition state. However, in contrast to the previous proposition of transition-state stabilization,[7] we believe that interaction with neighboring *occupied* orbitals is a dominant factor in transition-state stabilization. This article presents the theoretical basis and experimental evidence for this hypothesis.

Theory

2.1. Qualitative Model of the Transition-State Stabilization. In perturbational molecular-orbital theory of chemical reactivity, nucleophilic addition to a carbonyl group is considered as an EO_B^* reaction, that is, a reaction which obeys the Bell-Evans-Polanyi principle.[14] It means that the bond-breaking and the bond-forming processes can be regarded as independent of one another even though the reaction occurs in one step. During the addition of an anionic nucleophile Y^- to a carbonyl group, the π_{CO} bond is being broken, and the carbon-nucleophile σ_{CY} bond is being formed.
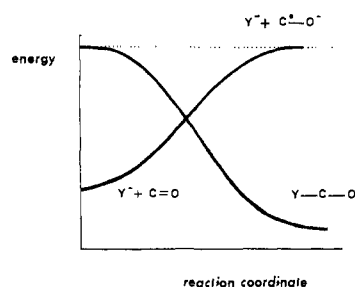
Let us now assume that the stereochemistry of the reaction is primarily determined in the bond-forming process, because in our treatment, the π_{CO} bond-breaking process may be considered symmetrical with respect to the carbonyl group nodal plane, i.e., equivalent during the two alternative approaches of a nucleophile. As a consequence, the factor which competes with steric hindrance during the axial approach originates in the nonbonded interactions of the partially formed bond with neighboring orbitals. There are three types of such interactions.[15]

The first type of interaction is the four-electron destabilizing interaction (σ_+, σ_i) with the vicinal covalent bonds; eclipsing of the incipient bond with the carbon-carbon or carbon-hydrogen bonds may lead to a destabilization of either transition state. The torsional strain model seems to invoke this possibility.[6]

The second type of interaction is the two-electron stabilizing interaction (σ_+, σ^*_i) with the adjacent antibonding orbitals, which is the content of the proposition of antiperiplanar stabilization of the axial transition state.[7]

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(12) The examples in sections 3.1.b, 3.1.c, and 3.3.

(13) The examples in sections 3.1.a and 3.2.

(14) Dewar, M. J. S.; Daugherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Press: New York, **1975**.

The third interaction is the two-electron stabilizing interaction $(\sigma_i,\sigma^*_\ast)$ of the vicinal-occupied orbitals with the antibonding orbital of the incipient bond; to the best of our knowledge, this factor has not been discussed in the literature.

While two-electron stabilizing interactions are generally more important in determining geometrical preferences than four-electron destabilizing interactions,[15] the relative importance of the two stabilizing modes of interaction cannot be determined except by a purely correlative approach. Therefore, the ultimate criterion of validity of a given model of transition–state stabilization is in success or failure of rules of thumb derived on its basis.

We postulate that the $\sigma_i,\sigma^*_\ast$ interaction is the dominant conjugative interaction in the bond-forming process because *the very definition of the incipient bond suggests that this bond is intrinsically electron deficient.* The incipient bond is to be considered as a very stretched and very polarized covalent bond, stabilized by a strong coulombic interaction. Both the elongation and the high degree of ionic character lower $\epsilon(\sigma^*)$. Thus, the kernel of our proposition consists of the following postulate: *the feature of the transition state for nucleophilic addition critical for stereoselectivity of the reaction is a low-lying orbital, $\sigma^*_\ast$, associated with the σ bond being formed in the reaction.*

This postulate leads to readily verifiable predictions based on the tenets of one-electron molecular-orbital theory. Since stereoselectivity problems involve comparisons of two systems having identical atomic constitution, two-electron stabilization resulting from the interaction of a doubly occupied MO (σ_i) with a vacant nondegenerate MO($\sigma^*_\ast$) may be approximated as being inversely proportional to the energy separation of the two MO's and directly proportional to the square of their overlap.

$$SE(\sigma_i,\sigma^*_\ast) \approx \frac{S^2\sigma_i\sigma^*_\ast}{\Delta\epsilon(\sigma_i,\sigma^*_\ast)}$$

It follows that nonequivalence of the two faces of a carbonyl group with respect to electron-donating power of the neighboring orbitals might lead to a preference for the approach which assures maximum overlap of the $\sigma^*_\ast$ orbital with the best donating orbitals. The vicinal σ,σ^* interactions which are discussed here, as well as n,σ^* interactions, display strong directional dependence, and maximum overlap is achieved in the antiperiplanar interaction of two σ bonds or of a lone pair with a σ bond.[16] It suggests two possible modes of electron-donor interaction with the $\sigma^*_\ast$ orbital, which are illustrated by the effects exerted by lone pairs interacting with the transition state of nucleophilic addition. The kinetic anomeric effect[17] can be considered as an example of transition-state stabilization by electron donation from the carbonyl side of the $\sigma^*_\ast$ orbital, while the kinetic α effect can be considered as an example of assistance through electron delocalization from the nucleophile side of this orbital.[18]
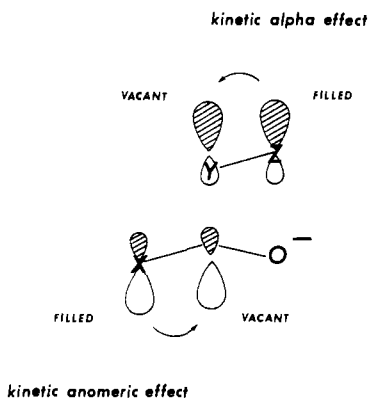
kinetic alpha effect

kinetic anomeric effect

The proposition of relative stabilization of the transition state by electron delocalization into the $\sigma^*_\ast$ orbital does not, of course, imply that an increase in the absolute reaction rate is to be observed. In terms of our model, the necessary condition would be that the $\sigma^*_\ast$ orbital energy is lower than the π^*_{CO} energy. This is not true for a three-center four-electron addition of an anion to a carbonyl group, because $\sigma^*_\ast$ arises through interaction of n_Y and π^*_{CO}. However, in reactions such as those discussed in this paper (metal hydride or organometallic addition) that proceed through *four-center* four-electron transition states, a low-lying unoccupied orbital is introduced. In particular, the lowest unoccupied orbital of the transition state for metal hydride addition should have essentially nonbonding character. Therefore, an absolute enhancement of the reaction rate due to charge-transfer stabilization cannot be a priori excluded, although transition state for these reactions is intuitively considered electron rich.

2.2. Two-Electron Stabilizing Interactions and the Properties of a Covalent Bond. The postulate described above derives from a consideration of the mechanism of charge-transfer interactions and its implications. Therefore, it seems reasonable to present here basic data and premises to infer the importance of these interactions for molecular reactivity.

The best illustration of that effect is provided by the studies of acetal and orthoester derivatives which, in defiance of the classical paradigm of conformational analysis, tend to adopt the more hindered gauche or axial conformations. The explanation for this striking preference, first recognized in the conformational equilibria of sugars and widely known as the "anomeric effect", is now well established in terms of perturbational molecular-orbital theory. There is a considerable body of evidence that a lone pair is stabilized by interaction with an antiperiplanar σ bond because of delocalization of the lone-pair electrons into the associated σ^* antibonding orbital, so the gauche or axial conformations of acetal or orthoester derivatives may be preferred because they permit such an interaction.

Theoretically, this effect of electron delocalization is distinguished and defined by an ab initio wave function based perturbational molecular-orbital treatment,[19] where it is referred to as n,σ^* conjugation. The importance of its contribution to structural equilibria of heteroatomic systems has been confirmed by numerous ab initio calculations.[20] Physical sense of the interaction is clearly implied in this definition, because conjugation of a filled and a vacant orbital results in a net charge transfer.

Experimentally, this kind of electron delocalization is to be observed as a conformationally dependent redistribution of charge density into the involved σ bond. An increase in and a shift of electron density must result in a perturbation of bond properties, and there is considerable evidence concerning the anomeric effect that parallels observations considered to be hard evidence for weak charge transfer in studies of intermolecular interactions.[21] This evidence is summarized below.

First, both X-ray crystallography and electron-diffraction studies of the cyclic or acyclic α-chloro ethers show that the electron-acceptor bond, the σ_{CCl} bond, is distinctly longer in the gauche or axial conformation.[22]

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Second, IR spectroscopy indicates a decrease in stretching frequency for the acceptor bond, which has been experimentally correlated with an increase in bond length and a decrease in bond dissociation energy.[23]

Third, a decrease of ^{35}Cl nuclear-quadrupole-resonance frequencies indicates an increase in charge density in the electron-acceptor bond in the gauche or axial conformations of the α-chloro ethers.[24]

Fourth, the direct, one-bond nuclear spin coupling constants through the electron-acceptor bond are lower in the axial conformation.[25]

It can be seen that the consequence of the described interaction, charge transfer by n,σ^* conjugation, is a reduction in bond order, i.e., weakening of the electron-acceptor σ bond.

2.3. Two-Electron Stabilizing Interactions and Molecular Reactivity. The interaction which may weaken a covalent bond is likely to have a profound impact on chemical reactivity. Indeed, acetal and orthoester derivatives which prefer strange conformations also display unusual stereoselectivity of heterolytic and homolytic bond breakdown and formation in the six-membered ring systems. The participation of a lone pair has already earlier been invoked to explain the stereoselectivity in bromine oxidation of hexoses,[26] Grignard reaction of cyclic orthoesters,[27] ozonolysis of glycosides,[28] or dithiane peracid decomposition and following radical recombination.[29] However, the well-known study of the stereochemistry of orthoester and orthoamide breakdown is regarded as the crucial demonstration of its impact.[30] The study shows that the single most important factor determining the direction of breakdown is the antiperiplanarity of the breaking σ bond with respect to the lone pairs on the adjacent heteroatoms. A similar conclusion was drawn in the investigation of acetal breakdown.[31]

These results, although important in their own right, also have an equally important consequence, imposed by microscopic reversibility. *If the hydride transfer in the aldose oxidation process and the alkoxide extrusion in orthoester breakdown are facilitated by the antiperiplanar assistance of a lone pair, the reverse reactions of nucleophilic addition to a carbonyl group, hydride reduction, and water attack on carbonyl group in ester hydrolysis should be facilitated by this assistance as well.*

Such an effect has already been postulated as the kinetic anomeric effect[16] and explored in the reactions of oxonium and imidate salts.[30] Some experimental support for the underlying argument of microscopic reversibility is provided by crystallographic studies of molecules, where close intramolecular contact of nucleophile and an amide group is believed to imitate very early stages of intermolecular reation,[10] and by stereochemical results of nucleophilic addition to a triple bond.[32] The observed antiperiplanarity preference is also reproduced in theoretical calculations.[33] Given that in this case it is a valid argument indeed,

it follows that the transition state of nucleophilic addition to a carbonyl group may be stabilized by interaction with an antiperiplanar lone pair. Generalization of this concept in terms of qualitative molecular-orbital theory directly leads to our model of transition-state stabilization.

Discussion

Nucleophilic addition and its stereochemistry in alicyclic systems have been so extensively studied that it seems possible to reach tentative conclusions about the validity of our model of the transition-state stabilization by consideration of the data available. A conceivable way to carry out such an evaluation is to select a reference ketone and change reaction parameters such as substitution, nucleophile structure, solvent, counterions, and other solutes. Then, the interpretation of these variations in terms of the two-electron stabilizing interaction should produce correct qualitative correlations with stereochemical and kinetic results.

Obviously, such a discussion requires detailed mechanistic information about the concerned reactions. The available evidence has recently been reviewed.[2-4] We believe that the transition-state features postulated or implied throughout the discussion are entirely consistent with that evidence.

3.1. Stereochemistry of Nucleophilic Addition to Cyclohexanone. The lithium aluminum hydride reduction of 4-*tert*-butylcyclohexanone in diethyl ether at 0 °C affords the product of the more hindered axial approach in 91% yield. This striking result is not
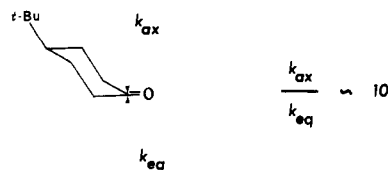
particular to cyclohexanone. The lithium aluminum hydride reduction of rigid bornanone derivatives gives an analogical predominance of the more hindered approach.[11] Thus, it can be
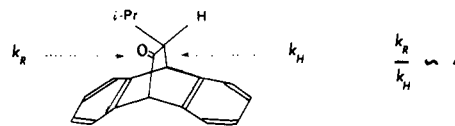
concluded that the transition state for lithium aluminum hydride reduction, which is antiperiplanar with respect to the carbon-hydrogen bonds, is generally preferred over the alternative transition state antiperiplanar with respect to the carbon–carbon bonds, in spite of the steric hindrance. This observation would fit our model if it could be shown that the carbon–hydrogen bonds are better electron donors than the carbon–carbon bonds.

The question of relative efficiency of the CH vs. CC bonds in hyperconjugative interactions was first addressed with the discovery of the Baker–Nathan effect, which led to the widely accepted tenet of the hyperconjugation theory that the CH bonds are better electron donors.[34] This tenet was subsequently questioned,[35] but the ^{13}C chemical shift study of electron-density changes upon alkyl substitution of an aromatic system unequivocally indicates the Baker–Nathan order and strongly supports the original assignment.[36]

Furthermore, if those bond properties, which were shown to be affected by electron delocalization from a lone pair (see section 2.2), are taken as the criteria, and their rotational dependence in alkyl derivatives, in particular in cyclohexane systems, is examined, all the data are again entirely consistent with the original assignment. This evidence is summarized below.

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(34) (a) Baker, J. W. "Hyperconjugation"; Oxford University Press: London, **1952**; (b) Taft, R. W.; Lewis, I. C. *Tetrahedron* **1959**, *5*, 210.

(35) (a) Dewar, M. J. S. "Hyperconjugation"; Ronald Press: New York, **1962**; (b) Glyde, E.; Taylor, R. J. *Chem. Soc., Perkin Trans 2* **1977**, 678; (c) Radom, L. *Aust. J. Chem.* **1979**, *27*, 231.

(36) Edlund, U. *Org. Magn. Res.* **1978**, *11*, 516.

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Cieplak

First, IR data on $\nu(CH)$[37] indicate that CH bonds antiperiplanar to other CH bonds are weaker than those antiperiplanar to CC bonds; in particular, the axial CH bonds in the cyclohexane ring are 2.7 kcal/mol weaker than the equatorial ones. This is corroborated by the well-known fact that the stretching frequencies of axial halogens and hydroxyl group are systematically lower than the equatorial ones.[38]

Second, [35]Cl NQR frequencies are lower for axial chorine atoms.[39]

Third, one-bond coupling constants are lower for axial bonds.[40]

Fourth, in conformational equilibria which appear to be dominated by donor–acceptor interactions of the σ bonds with low-lying vacant orbitals, the conformation which would assure electron donation from a CH bond is preferred over the one which would assure electron donation from a CC bond. For instance, the eclipsed conformation, which maximizes overlap of the σ_{CH} bond with the vacant nonbonding $2p_x$ orbital of boron, is more stable in ethyldifluoroborane.[41] On the other hand, the axial conformation, which maximizes overlap of the CH bonds with the substituents's σ^* orbital, was found to be preferred in thiane 1-oxide, thiane 1-imides, and cyclohexylmercury derivatives.[42]

Thus, on the basis of the qualitative MO model of transition state stabilization and of the data presented above, it can be concluded that the axial approach is preferred in the hydride reduction of 4-*tert*-butylcyclohexanone because the stabilization energy $SE(\sigma, \sigma^*_s)$ arising through electron delocalization from σ_{CH} bonds into the σ^*_s orbital is greater than the stabilization energy from the corresponding interaction with σ_{CC} bonds, which occurs during the equatorial approach. Consequently, two factors should
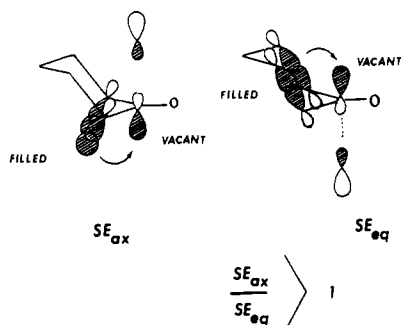
be taken into consideration as the determinants of the stereochemistry of nucleophilic addition to cyclohexanone: *steric hindrance impeding the axial approach and electron delocalization from the cyclohexanone σ bonds facilitating the axial approach because of greater electron-donating power of the σ_{CH} bonds.*

This proposition leads to readily verifiable predictions. Obviously, a change in electron-donor properties of the involved σ bonds must influence the stereochemistry of the reaction. Next, our model implies a dependence of the stereochemistry of addition

on the σ^*_s energy level. It can be seen from the following expression

$$\frac{SE_{ax}}{SE_{eq}} \approx \frac{\Delta\epsilon|\sigma_{CC}, \sigma^*_s| + \delta\epsilon}{\Delta\epsilon|\sigma_{CH}, \sigma^*_s| + \delta\epsilon}$$

where $\delta\epsilon$ represents variation in $\epsilon(\sigma^*_s)$, that when the energy gap between the σ^*_s orbital and the σ_{CC} and σ_{CH} orbitals grows ($\delta\epsilon$ tends to infinity), the absolute stabilization not only decreases but the ratio SE_{ax}:SE_{eq} tends to 1. In this case, the steric hindrance may become a dominant factor and the equatorial approach will be preferred. When the $\epsilon(\sigma^*_s)$ goes down closer to the σ orbitals, the ratio SE_{ax}:SE_{eq} increases and tends to infinity ($\delta\epsilon$ is increasingly negative), and the axial approach will be preferred.

In order to formulate expected experimental correlations, we must be able to tell how structural modifications affect energy level of localized molecular orbitals. In the case of occupied orbitals and their electron-donor properties, it is possible to find a model system and an appropriate correlation to answer this question. In the case of transition state σ^*_s orbital, however, we have to rely on a set of qualitative rules based on the rules of LUMO variation upon substitution, used in the frontier orbital theory.[43]

(I) $\epsilon(\sigma^*)$ decreases with increasing electronegativity of substituents of a given σ bond.

(II) $\epsilon(\sigma^*)$ increases in the consequence of electron donation into this bond.

(III) $\epsilon(\sigma^*)$ decreases when the atoms forming a σ bond are exchanged going down a group and to the right in a row of the Mendeleev table.[15]

We assume that the third variable from the formula describing the energy of two-electron stabilizing interaction, the orbital overlap, remains virtually unchanged in spite of the variation of substitution and other parameters. It should be pointed out, however, that the considerations and estimations concerning orbital overlap will be the weakest point of the qualitative theory.

Finally, granted that a separation of the ground- and transition-state effects would be possible for a particular reaction, an increase in the absolute rate constant might be observed due to charge-transfer stabilization.

a. Effect of Variation in $\epsilon(\sigma_{CC})$ and $\epsilon(\sigma_{CX})$. Stereochemistry of the Reduction of 3-Alkyl and 3-Heterocyclohexanones. The immediate prediction, following from the explanation of the stereochemistry of reduction given above, is that an increase in electron-donating power of the σ_{CC} bonds should result in an increase in the relative yield of the equatorial approach.

The modification which may lead to the desired increase in the case of the cyclohexanone ring without any significant changes of steric hindrance, appears to be alkyl substitution in β,β' positions. It has already been argued that alkyl substitution results in an improvement of the electron-donating power[44] of a σ_{CC} bond. Photoelectron spectroscopy of the aliphatic ketones confirms that increasing substitution by alkyl groups has an electron-releasing effect because it lowers ionization potential of the carbonyl group orbitals.[45] Accordingly, a decrease in the overall reaction rate is observed in the case of 3- and 3,5-alkylcyclohexanones compared to cyclohexanone or 4-alkylcyclohexanones.[46] On the other hand, however, the relative yield of the product of equatorial approach increases in metal hydride reductions or organometallic additions as a consequence of such a substitution (Table I). This fact suggests a selective stabilization of the equatorial transition state, in compliance with our prediction. The comparison of the relative rate constants of lithium aluminum hydride reduction in diethyl ether of the 3,5-alkylcyclohexanones and of sodium borohydride reduction of a series of steroidal ketones supports this conclusion (Table II).

(37) McKean, D. C. *Chem. Soc. Rev.* **1978**, *7*, 415.

(38) (a) Altona, C. *Tetrahedron Lett.* **1968**, 2325; (b) Awram, M.; Mateescu, Gh. "Infrared Spectroscopy", Wiley-Interscience: New York, **1972**; p 244 and pp 261–262.

(39) Lucken, E. A. C. *Adv. NQR* **1974**, *1*, 235.

(40) (a) Chertkov, V. A.; Sergeev, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 6750; (b) Kitching, W.; Praeger, D.; Doddrell, D.; Anet, F. A. L.; Krane, J. *Tetrahedron Lett.* **1975**, 759; (c) Buchanan, G. W.; Bowen, J. H. *Can. J. Chem.* **1977**, *55*, 604; (d) San Filippo, Jr., J.; Silbermann, J.; Fagan, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 4834.

(41) Odom, J. D.; Li, Y. S.; Stampf, E. J.; Durig, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 3751.

(42) (a) Lambert, J. B.; Keske, R. G. *J. Org. Chem.* **1966**, *31*, 3429; (b) Anet, F. A. L.; Krane, J.; Kitching, W.; Doddrell, D.; Praeger, D. *Tetrahedron Lett.* **1974**, 3255. (c) The possibility that donor–acceptor interactions of the σ bonds actually determine the conformational equilibrium has been suggested in the discussion on the origin of the rotation barrier in ethane: Gavezzotti, A.; Bartell, L. S. *J. Am. Chem. Soc.* **1979**, *101*, 5142; Brunck, T. K.; Weinhold, F. *J. Am. Chem. Soc.* **1979**, *101*, 1700; Kingsbury, C. A. *J. Chem. Educ.* **1979**, *56*, 431, and references cited therein. (d) It seems also worthwhile to notice that the σ_{CH}, σ^*_{CX} interactions may significantly contribute to relative stabilities of the E, Z isomers of the 1,2-disubstituted olefins, N-alkylformamides, enols of aldehydes or esters, etc.

(43) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, **1976**; p 120.

(44) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, Nye A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 5715.

(45) Hernandez, R.; Masclet, P.; Mouvier, G. *J. Electron Spectrosc. Rel. Phenom.* **1977**, *10*, 333.

(46) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

Table I. Relative Yields of Equatorial Approach in Nucleophilic Additions to 3- and 3,5-Alkylcyclohexanones and 4-*tert*-Butylcyclohexanone

	t-Bu	Me	Me–Me	*t*-Bu
LiAlH$_4$, THF, 0 °C	9–11.5[a,b]	13–15.4[b,c]	16–17[a,b]	16.5–18[b,c]
NaBH$_4$, *i*-PrOH, RT	13–14[a,d]	14[d]	20–22[a]	18[e,f]
NaC≡CH, (Li), |K|, THF–NH$_3$	12[g]	(18), 120|[h]		24[e]
CH$_3$Li, Et$_2$O	65[b]	66[b]		78.5[b]
C$_2$H$_5$MgBr, Et$_2$O (THF)	69[i]	68, (72)[h]		86[e]

[a] Eliel, E. L.; Senda, Y. *Tetrahedron* 1970, *26*, 2411. [b] Rei, M-H. *J. Org. Chem.* 1979, *44*, 2760. [c] Varma, V. J. Ph.D Thesis, Purdue University, West Lafayette, IN, 1967. [d] Wigfield, D. C.; Phelps, D. J. *J. Org. Chem.* 1976, *41*, 2396. [e] Akhrem, A. A.; Kamernitskii, A. V.; Prohoda, A. M. *Zh. Org. Khim.* 1967, *3*, 50. [f] Lemiere, G. L.; Van Osselaer, T. A.; Alderweireldt, F. C. *Bull. Soc. Chim. Belg.* 1978, *87*, 771. [g] Hennion, G. F.; O'Shea, F. X. *J. Am. Chem. Soc.* 1958, *80*, 614. [h] Rocquet, F.; Battioni, J. P.; Capmau, M.-L.; Chodkiewicz, W. *C. R. Hebd. Seances Acad. Sci., Ser. C* 1969, *268*, 1449. [i] Meakins, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* 1968, 1106.

Table II. Relative Rate Constants for Equatorial Approach in LiAlH$_4$ and NaBH$_4$ Reduction of Alkylcyclohexanones

LiAlH$_4$, Et$_2$O	k_{rel}[a]	NaBH$_4$, *i*-PrOH	k_{rel}[b]
	1.0		1.0
	1.8		2.0
	4.0		5.7
	3.7		

[a] Eliel, E. L.; Senda, Y. *Tetrahedron*, 1970, *26*, 2411. [b] Kirk, D. N.; Hartshorn, M. P. "Steroid Reaction Mechanisms"; Elsevier: Amsterdam/London/New York, 1968; pp 142–43.

The second opportunity to verify our predictions is offered by heterocyclohexanones, where one or both of the β,β' methylene groups are replaced by a heteroatom. Electron-donating power of a few typical σ bonds increases in the following order:[15] $\sigma_{CO} < \sigma_{CN} < \sigma_{CC} < \sigma_{CS}$. Therefore, it is expected that the relative yield of equatorial approach of a nucleophile will be smaller in the case of oxa and aza analogues and greater in the case of thia derivative than that for a carbocyclic ketone.[47] The supporting evidence is summarized below.

i. σ_{CC} **vs.** σ_{CO} **Replacement.** A dramatic reversal of stereoselectivity has been found in the case of Grignard reactions of 2-phenyl-1,3-dioxan-5-one (Table III).

The ^{35}Cl NQR data on 5-chloro-1,3-dioxanes corroborate the expectation that the difference in electron donation from σ_{CH} bonds vs. σ_{CO} bonds[48] is greater than that between the σ_{CH} and σ_{CC} electron donation.

ii. σ_{CC} **vs.** σ_{CN} **Replacement.** The stereochemical results of sodium borohydride reduction of 1,5-dialkyl-3-piperidones display both the impact of σ bond properties and the influence of alkyl substitution; both effects appear to be accentuated in the case of the corresponding methyl iodides (Table IV). The relative greater impact of alkyl substitution on the reduction stereochemistry in the case of 3-piperidones complies with the fact that alkyl substitution of the σ_{CN} bond on the nitrogen atom has a greater weakening effect on this bond than similar substitution of the σ_{CC} bond, both in absolute and relative terms.[49]

iii. σ_{CC} **vs.** σ_{CS} **Replacement.** The introduction of sulfur into the cyclohexanone ring in the β position results in a reversal of the usual preference of metal hydrides for the axial approach.[50]

(47) We assume that the contribution of transannular electron delocalization from the heteroatom lone pair is small due to poor overlap in the equatorial transition state.

(48) Cazaux, L.; Jugie, G. *J. Mol. Struct.* 1977, *39*, 219.

(49) Egger, K. W.; Cooks, A. T. *Helv. Chim. Acta* 1973, *56*, 1516, 1537.

Table III. Relative Yields of Axial Approach of Grignard Compounds to 2-Phenyl-1,3-dioxan-5-one and 4-*tert*-Butylcyclohexanone

	t-Bu	Ph (dioxan)
CH$_3$MgI	45	98
CH$_3$CH$_2$MgI	31	98
(CH$_3$)$_2$CHMgI	18	96
(CH$_3$)$_3$CMgCl	0	no addition

[a] Jochims, J. C.; Kobayashi, Y.; Skrzelewski, E. *Tetrahedron Lett.* 1974, 571. [b] Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* 1978, *111*, 3442.

Table IV. Relative Yields of the Equatorial Approach in NaBH$_4$ Reduction of 1,5-Dialkyl-3-piperidones

	R: Me R': Me	Et Me	*i*-Pr Me	*t*-Bu Me	*t*-Bu *t*-Bu
NaBH$_4$, MeOH/H$_2$O	10	26	27	28	33
NaBH$_4$, H$_2$O	15	49	60	63	70

[a] Katvalyan, G. T.; Semenova, N. A.; Mistryukov, E. A. *Izv. Akad. Nauk SSSR*, 1976, 129. [b] Katvalyan, G. T.; Mistryukov, E. A. *Ibid.* 1976, 220. [c] Katvalyan, G. T.; Mistryukov, E. A. *Ibid.* 1976, 1335.

Thus, a good qualitative agreement of the experimental data with the model predictions can indeed be obtained.
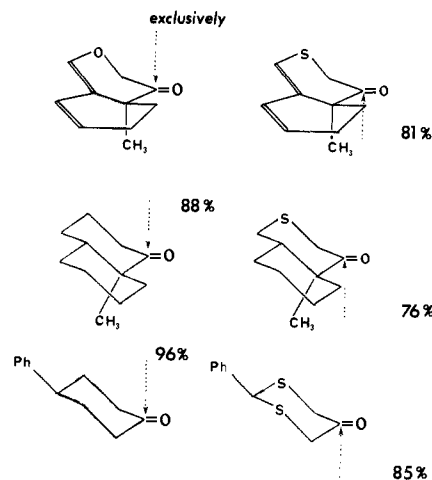
exclusively

88%

96%

81%

76%

85%

Table V. Relative Yields of the Axial Approach in the Addition of Substituted Methyl Carbanions to 4-*tert*-Butylcyclohexanone

nucleophile ⁻CH₂R	%	counterion	solvent	Hammett–Taft[p] constants of R		^{35}Cl NQR[q] of RCH₂Cl, ν, MHz
				σ_I	σ_R	
⁻CH₂NO₂[a]	≥90	Na	EtOH	0.65	0.15	37.64
⁻CH₂S⁺(CH₃)₂[b]	83	Na	Me₂SO	0.90		
⁻CH₂CN[c,d]	75, (85), 65	Li, (Na, K), Li	THF, pentane-Et₂O, benzene-Me₂SO	0.56	0.13	38.13
	67, (72)	ZnBr	THF, (THF-HMPT)			
⁻CH₂COOSi(CH₃)₃[c,e,f]	56, (72)	Li, (Mg)	THF	0.30	0.14	36.28
-CH₂CH₃	54, (68)	Li, (ZnBr)	pentane-HMPT, (DMM-HMPT)			
-C(CH₃)₃	62, (81)	MgBr	Et₂O-HMPT, (HMPT)			
	53, (82)	ZnBr	DMM-Me₂SO, (Me₂SO)			
	65		THF			
⁻CH₂CH≐CH₂ ⁻⁺Li[g]	45	ZnBr	DMM-HMPT	0.27	0.09	34.88
⁻CH₂CON(CH₃)₂[c]	45, (68)	ZnBr	DMM (DMM-HMPT)			
-(CH₂CH₃)₂	50, (33)	Li, (Na)	Me₂SO			
⁻CH₂S(=NTs)C₆H₅[h]	35	Li	Et₂O		0.00	34.03
⁻CH₂H[i-k]	41, (40)	MgCl, (Br)	Et₂O			
	47, (51)	MgI, (ZnI)	Et₂O			
⁻CH₂CH₂CH₃[l]	32, (33)	MgBr, (I)	Et₂O		-0.15	32.97
⁻CH₂CH₃[l,m]	29	MgBr	Et₂O		-0.17	32.70
⁻CH₂SC₆H₅[n]	20	Li	THF	0.30	-0.22	
⁻CH₂C₆H₅[i]	20	MgCl	Et₂O	0.10	-0.11	33.63
⁻CH(CH₃)₂[i]	18	MgBr	Et₂O			
⁻CH₂CH=CH₂[g,o]	15, (16)	ZnBr, (Zn₁/₂)	THF (Et₂O)	0.09	-0.11	33.45

[a] Favre, H.; Gravel, D. *Can. J. Chem.* 1961, *39*, 1548. [b] Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* 1965, *87*, 1353. [c] Bellassoued, M.; Dardoize, F.; Gaudemar-Bardone, F.; Gaudemar, M.; Goasdoue, N. *Tetrahedron* 1976, *32*, 2713. [d] Idriss, N.; Perry, M.; Maroni-Barnaud, Y.; Roux-Schmitt, M.-C.; Seyden-Penne, J. *J. Chem. Res., Synop.* 1978, 128. [e] Idriss, N.; Perry, M.; Maroni-Barnaud, Y. *Tetrahedron Lett.* 1973, 4447. [f] Pansard, J.; Gaudemar, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* 1970, *271*, 159; metalloorganic derivatives of esters and amides appear to exist preferentially as C-metallated monomeric species in the media, containing large amounts of polar solvents; see also footnotes c and e. Their stereochemical preferences in the nonpolar, weakly solvating solvents are different, presumably due to association of O- or O- and C-metallated species, and should thus be more properly considered as the example of solute effects on the reaction stereoselectivity. See section 3.3. [g] Gaudemar, M. *Tetrahedron* 1976, *32*, 1689. In contrast to diallylzinc or allylzinc bromide (the last entry), metal bonding in allyllithium is much less ionic due to the less electropositive character of the metal: Wilke, G. et al. *Angew. Chem.* 1966, *78*, 157; Thiele, K.-H.; Zdunneck, P. *J. Organomet. Chem.*, 1965, *4*, 10. [h] Johnson, C. R.; Mori, K.; Nakanishi, A. *J. Org. Chem.*, 1979, *44*, 2065. [i] Meakins, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* 1968, 1106. [j] Houlihan, W. J. *J. Org. Chem.* 1962, *27*, 3860. [k] Jones, P. R.; Goller, E. J.; Kauffman, W. J. *J. Org. Chem.* 1969, *34*, 3566. [l] Jones, P. R.; Kauffman, W. J.; Goller, E. J. *J. Org. Chem.* 1971, *36*, 186. [m] Hennion, G. F.; O'Shea, F. X. *J. Am. Chem. Soc.* 1958, *80*, 614. [n] Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* 1973, *95*, 7424. [o] Abenhaim, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* 1969, 4038. [p] Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Progr. Phys. Org. Chem.* 1973, *10*, 1; Charton, M. *Ibid.* 1973, *10*, 81, and references cited therein. [q] Biryukov, I. P.; Voronkov, M. G. *Collect. Czech. Chem. Commun.* 1967, *32*, 830; Allen Jr., H. C. *J. Phys. Chem.* 1953, *57*, 501; Okhlobystina, L. V. et al. *Izv. Akad. Nauk SSSR Ser. Khim.* 1970, 1899.

A third possibility to modify the electron-donating power of the ring σ bonds is an electron-withdrawing substitution of the β,β' positions. A resulting lowering of ε(σ_CC) and, as a consequence, a decrease in SE_eq should increase the usual preference for the axial approach. This might explain, for instance, the opposite effects of 1β-methyl and 1β-cyano substitution on stereochemistry of lithium tri-*tert*-butoxyaluminum hydride reduction of 3-decalones.[51] Unfortunately a more systematic investigation

CH₃ =O 15%

CH₃ =O 9%

CH₃ C≡N =O 3%
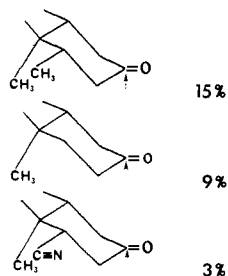
of the impact of electron-withdrawing β,β' substituents on stereoselectivity of the discussed reactions is lacking.

[Note Added in Proof: Interesting results concerning the impact of β-halogen substitution on the stereoselectivity of LiAl(O-t-Bu)₃H reduction of adamantanone were published since this

(50) (a) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* 1978, 1252; (b) Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* 1978, *111*, 3442.
(51) Agami, C.; Fadlallah, M.; Kazakos, A.; Levisalles, J. *Tetrahedron* 1979, *35*, 969.

manuscript was accepted: Giddings, M. R.; Hudec, J. *Can. J. Chem.* 1981, *59*, 459. According to our model, a change in the

syn

X =O

anti
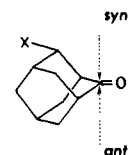
reaction stereoselectivity should correlate with a net change of charge density in the σ_CC bond resulting from substitution. Assuming that the latter is reflected in ^{35}Cl NQR frequency of the corresponding halochloromethanes, the expected correlation is found. The frequency difference ($\nu_{XCH_2Cl} - \nu_{CH_3Cl}$) increases in the following order: F, -0.23, Cl, 1.96; Br, 2.05; I, 2.35 (Livingston, R. *J. Chem. Phys.* 1953, *57*, 496; Tsvetkov, E. N. et al. *Dokl. Akad. Nauk SSSR* 1965, *161*, 1102), and so does the difference between relative yields of the syn and anti approaches (% syn - % anti): F, -6; Cl, 10; Br, 14; I, 32.]

b. Effect of Variation in ε(σ*ₜ). Dependence of the Addition Stereochemistry on Nucleophile Structure. Another important consequence of the model discussed is that the stereochemistry of nucleophilic addition to cyclohexanone will depend strongly on the substitution of the bond formed in the reaction, which is determined by the structure of a nucleophile. Electron-withdrawing substitution, which lowers ε(σ*ₜ) according to our rules, may produce a predominance of the axial approach, overriding nucleophile's steric demand. In contrast, electron-donating substitution may produce a predominance of the equatorial approach even in the case of a relatively small nucleophile. This relationship can be demonstrated with the examples of carbanion and metal

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hydride addition to 4-*tert*-butylcyclohexanone.

(i) Sulfonium ylide and nitromethane anion may be considered as methyl carbanion substituted by strongly electron-withdrawing groups, and they indeed prefer the axial approach. On the other hand, benzyl carbanion may be considered as a methyl carbanion substituted by a $2p_\pi$ electron-donating substituent (hyperconjugative electron donation from the phenyl ring is indicated, for instance, by [35]Cl NQR of benzyl chlorides[52] and will be more pronounced in the interaction with a lower-lying σ^* orbital), and, in fact, it adds like the bulky isopropyl carbanion, although its steric demand is closer to that of methyl carbanion[53] (see Table V).
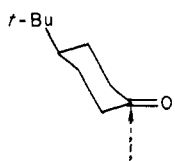
(ii) Similar effects are observed in metal hydride reductions and can be explained in the same way if the reaction is assumed to proceed through a linear transition state with a three-center $\sigma^*_{\mathring{s}}$ orbital, extended on carbon, hydrogen, and metal nuclei. For instance, there is little difference between the stereoselectivity of unsubstituted hydrides and the stereoselectivity of the hydrides substituted by the large *alkoxy* groups. In contrast, *alkyl* substitution almost immediately leads to a reversal of reduction stereochemistry. This observation can be readily explained by the difference of electronegativity between alkyl and alkoxy substituents. A lowering of the $\epsilon(\sigma^*_{\mathring{s}})$ due to inductive effect is expected to be greater in the case of alkoxy substitution, and, therefore, an increase in SE_{ax} may offset the increase in unfavorable steric interactions, whereas in the case of trialkylboro-hydrides the steric bulk remains the dominant factor (Table VI).

The mesomeric donation from an alkoxy group, due to electron delocalization from the oxygen lone pair into the $\sigma^*_{\mathring{s}}$ orbital, cannot be realized in the case of a bulky phenoxy or *tert*-butoxy substitution, because if all the three substituents would adopt the necessary conformation, the hydride approach to a substrate would be entirely hindered.[54] However, this effect is to be observed with monosubstituted hydrides, and the alkoxy- and aminomagnesium hydrides indeed prefer the equatorial approach.[55]

Finally, the third rule concerning electron-acceptor properties of the σ bonds leads to the prediction that the relative yield of axial approach will increase in the case of typical metal hydrides in the order: beryllium < magnesium < boron < aluminum, and so forth. This could explain the observation that the small chloroberyllium hydride affords the axial and equatorial alcohols in the reduction of 4-*tert*-butylcyclohexanone in ratio of 1:1[56] and could resolve the old controversy about "why does the BH_4^- anion behave like a larger ion than AlH_4^-, although it is smaller".[57]

c. Effect of Variation in $\epsilon(\sigma^*_{\mathring{s}})$. Impact of Metal Cations. Stereochemistry of the Reduction of Cyclohexanone Iminium Salts by Hantzsch Ester. The lone pair which develops on the carbonyl oxygen along the reaction pathway is also involved in an anti-

Table VI. Relative Yields of the Equatorial Approach in the Reduction of 4-*tert*-Butylcyclohexanone by Complex Metal Hydrides


hydride	R	%
LiAlR₃H	H	10[a,b]
	O-*t*-Bu	11[a,b]
	OC₆H₄-Cl	8[b]
	OC₆H₄-*t*-Bu	7[b]
NaBR₃H	H	14[a]
	O-*i*-Pr	23[a]
LiBR₃H	H	9[b]
	Et	22[c]
	n-Bu	38[c]
	i-Bu	86[c]

[a] Eliel, E. L.; Senda, Y. *Tetrahedron* 1970, *26*, 2411. [b] Ashby, E. C.; Boone, J. R. *J. Org. Chem.* 1976, *41*, 2890. [c] Brown, H. C.; Krishnamurthy, S. personal communication.

periplanar interaction with the bond being formed in the reaction. The extent of delocalization of this lone pair into the $\sigma^*_{\mathring{s}}$ orbital is likely to depend on metal cations which complex the carbonyl group during the transition state of metal hydride reduction in ethereal solvents[58] and stabilize its surplus negative charge. Thus, our model implies that the impact of a metal cation on reduction stereochemistry should be correlated with its capability to stabilize that negative charge. For instance, the presence of lithium cation, which complexes oxygen bases more efficiently than larger alkaline metal cations of sodium or potassium, should result in a greater proportion of the axial approach of a hydride anion due to the lower $\epsilon(\sigma^*_{\mathring{s}})$. On the other hand, reduction in the presence of quarternary ammonium ion, which probably does not complex the carbonyl group at all, should afford a greater yield of the equatorial approach, since the carbonyl oxygen negative charge will raise the $\epsilon(\sigma^*_{\mathring{s}})$. This effect has indeed been noticed:[56] the relative yield of the equatorial approach of AlH_4^- is 10% in the presence of Li^+ and 15% in the presence of tri-*n*-octyl-*n*-propylammonium ion. The difference, although small, has even some commercial significance, since the potassium salt of the tri-*sec*-butylhydroborate, sold as K-Selectride, is slightly more selective than the lithium salt, L-Selectride: they afford 88% and 80.5% of the axial alcohol, respectively, in the reduction of 4-methylcyclohexanone.[59]

A good model for this phenomenon is provided by the reduction of 4-*tert*-butylcyclohexanone iminium salts. A dihydropyridine derivative, the so-called "Hantzsch ester", reduces such salts in boiling acetonitrile in a reaction which may be considered a model for NADH enzymic reductions.[60] The stereochemistry of this
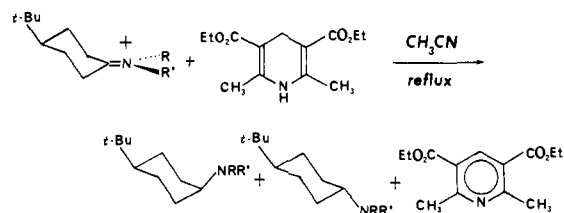

reaction markedly changes with variation of the alkyl moieties on the iminium nitrogen atom. On the basis of our model it is expected that the alkyl substitution of this nitrogen atom will influence the reaction stereochemistry by affecting the capability

(52) Dewar, M. J. S.; Herr, M. L. *Tetrahedron* 1971, *27*, 2377.

(53) Conformational energy of the alkyl groups: CH₃ = 1.70, ≈ CH₂C₆H₅ = 1.81, ≪ CH(CH₃)₂ = 2.15 (Anderson, J. E., *J. Chem. Soc., Perkin Trans. 2* 1974, 10).

(54) It is tempting to point out that the proposed interpretation can indeed be useful in the discussion of the α effect. The same impact of steric hindrance is observed in the case of cyclic hydrazines and hydroxylamines (Brass, H. J.; Edwards, J. O.; Fina, N. J. *J. Chem. Soc., Perkin Trans. 2* 1972, 726); in piperidazine for instance, the proper interaction requires, according to the model, the transdiaxial conformation of the two lone pairs and the attack on a carbonyl group with the hindered axial side, so the stabilization effect is not observed. On the other hand, the impact of variation in electrophile structure should be explicable in terms of $\epsilon(\sigma^*_{\mathring{s}})$ variation, and indeed, the increase of the α effect for carbon electrophiles in the order sp³ < sp² < sp complies with this expectation (Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* 1973, *5*, 1).
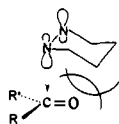
(55) (a) Ashby, E. C.; Noding, S. A.; Goel, A. B. *J. Org. Chem.* 1980, *45*, 1028; (b) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* 1978, *43*, 1560, 1564.

(56) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* 1976, *41*, 2890.

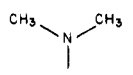(57) Wheeler, D. M. S.; Huffman, J. W. *Experientia* 1960, *16*, 516.

(58) (a) Pierre, J.-L.; Handel, H. *Tetrahedron Lett.* 1974, 2317; (b) Pierre, J.-L.; Handel, H.; Perraud, R. *Tetrahedron* 1975, *31*, 2795.

(59) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* 1972, *94*, 7159; (b) Brown, C. A. *J. Am. Chem. Soc.* 1973, *95*, 4100.

(60) de Nie-Sarink, M. J.; Pandit, U. K. *Tetrahedron Lett.* 1978, 1335.
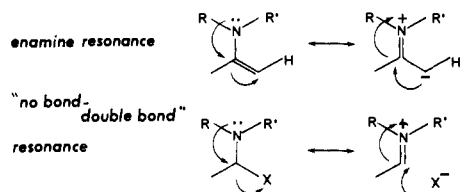
Table VII. Correlation between Relative Yields of Equatorial Approach in Hantzsch Reduction of 4-*tert*-Butylcyclohexanone Iminium Salts and Chemical Shifts of Olefinic Carbon and Vinyl Proton of the Corresponding Enamines

R, R'	^{13}C, ppm^a	^{1}H, ppm^a	%^{b}
	93.8	4.18	95
			88
	98.8^c	4.37	75
	100.0	4.57	73
	100.1	4.58	81

^{a} Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* 1967, *32*, 3289; Tourwe, D.; Van Binst, G.; De Graaf, S. A. G.; Pandit, U. K. *Org. Magn. Res.* 1975, *7*, 433. ^{b} de Nie-Sarink, M. J.; Pandit, U. K. *Tetrahedron Lett.* 1978, 1335. ^{c} R = R' = ethyl.

of the nitrogen lone pair to interact with the $\sigma^*_\ddagger$ orbital. The more effective (n,$\sigma^*_\ddagger$) conjugation, the higher the $\epsilon(\sigma^*_\ddagger)$, and, in turn, the more product of the equatorial approach should be obtained.

For assignment of the delocalization capability for various alkyl derivatives, the corresponding enamines can be taken as models. The extent of lone-pair delocalization into a double bond of an enamine also depends on alkyl substitution and can be measured by ^{13}C and ^{1}H chemical shifts of the C_2 olefinic carbon atom and of the vinyl proton, respectively.[61] Thus, the greater the upfield shift in the enamine, the more product of equatorial approach should be observed in reduction of the corresponding iminium compound. It follows from Table VII that the expected corre-

lation is found, with one exception of morpholine derivative. The discrepancy is readily explained as the result of transannular electron delocalization from the oxygen lone pair, as is argued in the forthcoming sections.

d. Conformational Equilibria of Cyclohexyl Derivatives as a Model of Two-Electron Stabilizing Interactions in Nucleophilic Addition to Cyclohexanone. Another important implication of the discussed model is that the correlations proposed in previous sections should be found in conformational equilibria of cyclohexyl derivatives, since the SE_{ax}:SE_{eq} ratio for transition-state interactions should differ only in order of magnitude from the SE_{ax}:SE_{eq} ratio for ground-state interactions. The evidence summarized below appears to corroborate this expectation.

First, the variation in $\epsilon(\sigma_{CX})$ of the ring σ bonds, which interact with antibonding orbitals of cyclohexyl substituents in the equatorial conformation, results in changes of their conformational energies. For instance, 3- and 3,5-alkyl substitution of cyclohexanols increases the equatorial preference of the hydroxyl group;[62] introduction of the β,β' σ_{CO} bond increases the axial preference;[63] and introduction of the β,β' σ_{CS} bond increases the

equatorial preference of a number of substituents.[64]

Second, the variation in $\epsilon(\sigma^*)$ of the σ bond attaching the substituent to the ring results in expected changes of conformational energy as well: an interesting illustration is provided by N-substituted thiane 1-imides, where the conformational equilibrium can be shifted from the axial preference in the case of electron-withdrawing N-acyl substitution to the equatorial preference in the case of electron-donating N-phenyl substitution.[65] A decrease in conformational energy upon electron-withdrawing substitution of acyl moiety has also been noticed for a number of esters.[66]

Thus, it can be seen that indeed the effects which increase the relative yield of axial approach in nucleophilic addition to cyclohexanone also increase molar fraction of the axial conformer in equilibria of cyclohexyl derivatives.

3.2. Transannular Electron Delocalization in Nucleophilic Addition to Cyclohexanone and Heterocyclic Analogues. Nucleophilic additions to cyclohexanones provide many examples of kinetic and stereochemical effects exerted by substituents which are too remote to interfere sterically with the transition state. There is a tendency to consider these effects in terms of electrostatic models, which parallels the way the interaction of two remote polar bonds is often interpreted. This approach is, however, burdened with a basic disadvantage, because models based on macroscopic molecular properties such as dipole moments, polarizabilities, and dielectric constants do not account for energy contributions involving changes of the kinetic energy of electrons, which may be substantial if the system retains a significant degree of orbital overlap.

This seems to be the case for intramolecular interactions between atoms even as distant as their van der Waals radii would require. Namely, the dipole–dipole interaction model indeed fails to explain the classic example of a distant interaction of two polar bonds, manifested in conformational equilibria of 1,4-disubstituted cyclohexanes.[67] Therefore, it is tempting to believe that the orbital overlap at the distances between those 1,4-substituents is still sufficient to allow a discernible two-electron stabilizing interaction. Consequently, it seems reasonable to assume that a significant contribution to the effects exerted by remote substituents may come from charge-transfer stabilization due to $\pi,\sigma^*_\ddagger$ or n,$\sigma^*_\ddagger$ conjugation. If this is the case, we should find these effects to be controlled by the overlap and energy gap between the $\sigma^*_\ddagger$ and donating π or n orbitals.

a. Reaction Rate Control by Orbital Overlap and $\Delta\epsilon$ in Nucleophilic Addition to β,γ-Unsaturated Ketones. The introduction of a β,γ double bond into the cyclohexanone ring results in an increase of the rate constant of its sodium borohydride reduction.[68] Examples of bicyclic and tricyclic β,γ-unsaturated ketones show that the facilitation of hydride addition depends on the $\pi,\sigma^*_\ddagger$ overlap and the $\Delta\epsilon(\pi,\sigma^*_\ddagger)$ separation.

i. Orbital Overlap Control. In the situation when two sides of a carbonyl group are equivalent with respect to alicyclic framework but not with respect to an olefinic bond, stereoselectivity of nucleophilic addition will be a result, due to the requirement of maximum overlap, of a competition between two-electron stabilization, and steric destabilization. The examples of metal

(61) (a) Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* 1967, *32*, 3289; (b) Tourwe, D.; Van Binst, G.; De Graaf, S. A. G.; Pandit, U. K. *Org. Magn. Res.* 1975, *7*, 433.

(62) Eliel, E. L.; Schroeter, S. H.; Brett, T. J.; Biros, F. J.; Richer, J.-C. *J. Am. Chem. Soc.* 1966, *88*, 3327.

(63) (a) Borremans, F.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* 1976, *85*, 673, 681, and references, in particular to the work by E. L. Eliel et al.; (b) Carey, F. A.; Smith, P. M.; Maher, R. J.; Bryan, R. F. *J. Org. Chem.* 1977, *42*, 961.

(64) (a) Evans, S. A.; Goldsmith, B.; Merill, R. L.; Williams, R. E. *J. Org. Chem.* 1977, *42*, 438; (b) Lambert, J. B.; Vulgaris, E.; Featherman, S. I.; Majchrzak, M. *J. Am. Chem. Soc.* 1978, *100*, 3269.

(65) Claus, P. K.; Vierhapper, F. W.; Willer, R. L. *J. Org. Chem.* 1979, *44*, 2863.

(66) (a) Borsdorf, R.; Kleinpeter, E.; Meinel, Ch.; Lenk, D. *Z. Chem.* 1978, *18*, 185; (b) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* 1978, *43*, 3866.

(67) (a) Stolow, R. D., "Conformational Analysis, International Symposium Brussels 1969"; Chiurdoglu, G., Ed., Academic Press: New York, 1971; p 251; (b) Zefirov, N. S. *Tetrahedron Lett.*, 1975, 1087; (c) Zefirov, N. S.; Samoshin, V. V.; Nikulin, A. V.; Zyk, N. V. *Zh. Org. Khim.* 1978, *14*, 2617; (d) Abraham, R. J.; Rossetti, Z. L. *J. Chem. Soc., Perkin Trans. 2* 1973, 582; (e) Collins, L. J.; Kirk, D. N. *Tetrahedron Lett.* 1970, 1547; (f) Borsdorf, R.; Arnold, M.; Kleinpeter, E. *Z. Chem.* 1977, *17*, 378.

(68) Wheeler, O. H.; Mateos, J. L. *Can. J. Chem.* 1958, *36*, 1049.

Table VIII. Stereoselectivity in Organolithium Addition to Norbornen-7-one

R	rel yields, %[a] R—OH (exo)	rel yields, %[a] HO—R (endo)
CH_3	77	23
$C(CH_3)_3$	67	33
$CH=CH_2$	30	70
C_6H_5	28	72
C_6H_4-p-OCH_3[b]	76	24

[a] Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* 1975, 75, 521.
[b] Kleinfelter, D. C.; Sanzero, G. *J. Org. Chem.* 1977, 42, 1944.

hydride reductions in Scheme I demonstrate the predominance of the more hindered approach in such systems.[69,11] The comparison of absolute rate constants for borohydride reduction of saturated and unsaturated bornane and norbornane ketones confirms that only the exo approach, which is anti to the double bond, is being facilitated.[70]

	$k_{UNSAT/SAT}$
exo	2.5
endo	0.8
anti	2.6
syn	0.6
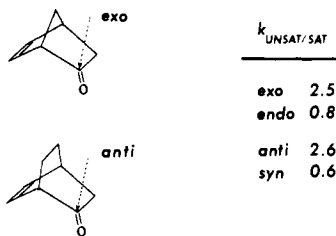
ii. $\Delta\epsilon(\pi,\sigma^*_\ast)$ Separation Control. The results of carbanion addition to norbornen-7-one demonstrate the impact of a variation in $\epsilon(\sigma^*_\ast)$ with nucleophile structure on reaction stereoselectivity (Table VIII). The difference of stereoselectivity between phenyllithium and p-methoxyphenyllithium is of particular interest. According to our model, the addition of phenyllithium occurs from the more hindered side, because the corresponding anti transition state is stabilized by $\pi,\sigma^*_\ast$ interaction. In the case of p-methoxyphenyllithium addition, where the $\epsilon(\sigma^*_\ast)$ is higher due to electron donation from the methoxy group, the stabilization effect is too small to overcome steric repulsion, and approach from the less hindered side predominates.

Similar effects, although less accentuated, are observed in additions of Grignard compounds to norbornen-7-one.[71]

b. Reaction Rate Control by Orbital Overlap and $\Delta\epsilon$ in Nucleophilic Addition to 4-Heterocyclohexanones. It has recently been proposed that the reaction rate increase observed upon the introduction of a nitrogen or sulfur atom in the place of C_4 in the cyclohexanone ring may be attributed to a "through-space effect" of dipole–dipole interaction.[72] It seems worthwhile to examine the nature of this transannular effect in the light of our model.
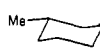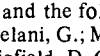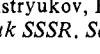
i. Orbital Overlap Control. Since in the case of the axial approach to a 4-heterocyclohexanone the overlap $n_{heteroat}$, $\sigma^*_\ast$ may be expected to be better during the whole reaction pathway, the

$S_{ax} \rangle S_{eq}$

Table IX. Relative Yields of Equatorial Approach in Metal Hydride Reduction of Alkyl-Substituted Tetrahydropyran-4-ones, 4-Piperidones, and Corresponding Cyclohexanones

hydride	ketone, %		ketone, %	
$LiAlH_4$[a]	(tetrahydropyranone)	21	(cyclohexanone)	15
$LiAlH_4$ NaBH_4 L-selectride	(Me-tetrahydropyranone)	15 14 88, 94.5	(Me-tetrahydropyranone)	5 7.5 70, 76
$LiAlH_4$ NaBH_4	(t-Bu-tetrahydropyranone)	18 24	(t-Bu-tetrahydropyranone)	5.5 10.3
$NaBH_4$	(cyclohexanone)	27[b]	(t-Bu-piperidone)	10[c]
$NaBH_4$	(cyclohexanone)	38[b]	(t-Bu-piperidone)	22[c]

[a] This result and the following concerning tetrahydropyranone reactions: Catelani, G.; Monti, L.; Ugazio, M. *J. Org. Chem.* 1980, 45, 919. [b] Wigfield, D. C.; Phelps, D. J. *J. Am. Chem. Soc.* 1974, 96, 543. [c] Mistryukov, E. A.; Katvalyan, G. T.; Smirnova, G. N. *Izv. Akad. Nauk SSSR. Ser. Khim.* 1970, 1131.

Table X. Rate Constants for Nucleophilic Addition to 4-Heterocyclohexanones

X	$NaBH_4$,[a] k_{rel}	H_2O,[b] k_{rel}
acetone	0.1[c]	1.0
CH_2	1.0	5.6
O		14.0
NC_2H_5	9.7	19.0
S	11.2	20.0

[a] Reduction in dioxane-water at 25 °C; Geneste, P.; Durand, R.; Hugon, I.; Reminiac, C. *J. Org. Chem.* 1979, 44, 1971. [b] Measured as the rate of ^{17}O exchange in dioxane-water, acetate buffer, pH 5 at 28 °C; Dahn, H.; Schlunke, H.-P.; Temler, J. *Helv. Chim. Acta* 1972, 55, 907. [c] The approximate extrapolation from the rate constants for the reaction in isopropyl alcohol; Brown, H. C.; Ichikawa, K. *Tetrahedron* 1957, 1, 221.

Table XI. Rate Constants of $NaBH_4$ Reduction of N-Alkyl-4-piperidones[a]

R	k, L· $mol^{-1}·min^{-1}$
cyclohexanone	8.9
H	55
CH_3	88
CH_2CH_3	87
$C(CH_3)_3$	49

[a] Geneste, P.; Durand, R.; Hugon, I.; Reminiac, C. *J. Org. Chem.* 1979, 44, 1971.

transition-state stabilization by electron donation from the heteroatom lone pair should lead to a shift in stereoselectivity of nucleophilic addition in favor of this approach. The relative yields of equatorial approach are indeed lowered in the case of metal hydride reduction of alkyl-substituted 4-piperidones and tetrahydro-4H-pyran-4-ones; but the difference is rather small (see Table IX). Moreover, the lack of a systematic study of the reduction stereochemistry in the case of tetrahydrothiopyran-4-ones does not allow exclusion of a decrease in $\epsilon(\sigma_{CC})$ of the ring σ bonds (see section 3.1.a, β,β' electron-withdrawing substitution) as the major factor leading to the observed shift in reduction stereochemistry.

ii. $\Delta\epsilon(n,\sigma^*_\ast)$ Separation Control. The absolute rate constants of nucleophilic additions to 4-heterocyclohexanones are expected to increase in the order of increasing electron-donor abilities of the heteroatom lone pair, which would oppose the order of increasing electronegativity for these heteroatoms. The examples of hydride and water addition indeed suggest such a correlation (see Table X). Furthermore, modification of the electron-donating power of the nitrogen lone pair by nitrogen substitution also results

(69) Yano, K.; Isobe, M.; Yoshida, K. *J. Am. Chem. Soc.* 1978, 100, 6166.
(70) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* 1966, 88, 2811.
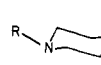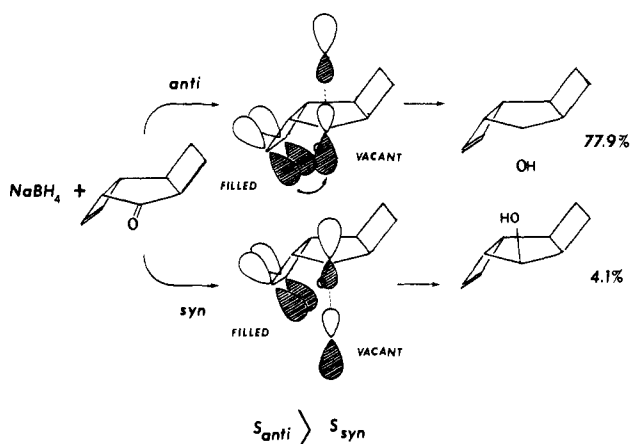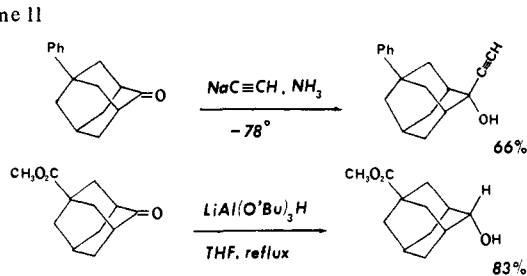(71) The reason for this difference is not apparent. See ref 4.
(72) Geneste, P.; Durand, R.; Hugon, I.; Reminiac, C. *J. Org. Chem.* 1979, 44, 1971.

Scheme I

$S_{anti} \rangle S_{syn}$

$\sim 70\%$

Scheme II

Table XII. Relative Yields of Equatorial Approach in Reduction of 3,3,5-Trimethylcyclohexanone in Various Solvents

hydride	solvent	%	hydride	solvent	%
NaBH$_4$[a]	*t*-BuOH	55	LiAl(O-*t*-Bu)$_3$H[b]	benzene	60, 63
	i-PrOH	55.2–56		Et$_2$O	73
	EtOH	63–67		THF	88
	MeOH	80			
			LiAlH$_4$[c]	Et$_2$O	68
				THF	82
			NR$_4$AlH$_4$[c,d]	benzene	47
				THF	55

[a] Haubenstock, H.; Eliel, E. L. *J. Am. Chem. Soc.* 1962, *84*, 2368. [b] Haubenstock, H.; Hong, S.-J. *Tetrahedron* 1978, *34*, 2445. [c] Ashby, E. C.; Boone, J. R. *J. Org. Chem.* 1976, *41*, 2890. [d] R$_4$ = tri-*n*-octyl-*n*-propyl.

stituted piperidines, thianes, etc., which can be considered as the model systems for the postulated donor–acceptor interactions (compare section 3.1.e).

c. Effect of Polar Substituents on C$_4$ on the Rate and Stereochemistry of Nucleophilic Addition to Cyclohexanone. Let us consider as a last example the impact of C$_4$ substituents in cyclohexanone on the rate and stereochemistry of nucleophilic addition. If this impact is to be controlled by n,$\sigma^*$$_{\#}$ orbital overlap, the predominance of axial approach should be observed for both axial and equatorial C$_4$ substituents. This expectation is confirmed

$S_{eq,ax} \rangle S_{eq,eq}$ $S_{ax,ax} \rangle S_{ax,eq}$

in predictable change of the reduction rate constants (see Table XI). N-Methylation increases the reduction rate because N-alkylation significantly lowers ionization potential of aliphatic amines,[73] and the resulting decrease in energy separation between n$_N$ and $\sigma^*$$_{\#}$ improves two-electron stabilization of the transition state. Further branching of *N*-alkyl group, however, may reverse this effect because it allows delocalization of the lone pair into carbon–carbon bonds, leading in the consequence to a less efficient two-electron stabilizing interaction with the transition state.[74]

Thus, the transannular electron delocalization appears to play an important role in determining the reactivity of 4-heterocyclohexanones toward nucleophiles. This conclusion is corroborated by the available data on conformational equilibria[75] of C$_4$-sub-

by the results of investigations of the following rigid systems: 2-*tert*-butylcyclohexanone, 3-*tert*-butylcyclohexanone, 1-decalone, 2-decalone, and adamantanone; two examples are given in Scheme II.[76] Since the C$_4$ substituents enhance the absolute reaction rate of sodium borohydride reduction,[77] and we assume the ground-state effect of such remote substituents to be negligible, it seems that this stereochemical effect indeed results from selective transition-state stabilization.

The available data are not sufficient to constitute conclusive evidence that the impact of the C$_4$ substituents on the reaction rate is also controlled by the energy gap between the donating n or π orbitals and the $\sigma^*$$_{\#}$ orbital.[78]

3.3. Solvent and Solute Effects on the Stereochemistry of Nucleophilic Addition to Cyclohexanone. In the light of our conclusions from the previous discussion, it seems reasonable to predict that solvents or solutes may modify the stereoselectivity of nucleophilic addition to cyclohexane through interaction with the transition state $\sigma^*$$_{\#}$ orbital. *Electron donation from the molecules solvating the transition state would raise* $\epsilon(\sigma^*$$_{\#})$, *and*

(73) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* 1976, *98*, 311.

(74) Further branching of alkyl group still lowers the first ionization potential. However, it seems reasonable to assume, by analogy to aliphatic ketones (ref 45) and alcohols (Peel, J. B.; Willett, G. D. *Aust. J. Chem.* 1975, *28*, 2357), that the nitrogen coefficient of the highest occupied MO decreases at the same time, which we describe here as a delocalization of the lone pair into CC bonds. The example of enamine–iminium salt series (section 3.1.c) demonstrates that, indeed, the ionization potential of a parent amine and the extent of resonance in enamine show opposite trends.

(75) For instance, the equilibrium of 4-piperidinol acetate is shifted in favor of the axial conformer as compared to cyclohexyl acetate (Terui, Y.; Tori, K. *J. Chem. Soc., Perkin Trans. 2* 1975, 127), while there is no or little stabilization of the axial conformer of 4-piperidinol, where the $\epsilon(\sigma^*$$_{CO})$ is higher. The change of the ring σ bond properties (due to the electron-withdrawing effect of a heteroatom) cannot be the sole factor involved here, since the effect of sulfur on conformational energies of the C$_4$ substituents in the six-membered ring is greater than the impact of oxygen or nitrogen (Remane, H.; Borsdorf, R.; Nord, G.; Pfestorf, U. *J. Prakt. Chem.* 1980, *322*, 638; Borsdorf, R.; Remane, H.; Ziegler, U.; Kohler, H.-J.; Scholz, M. *Ibid.* 1974, *316*, 773). In the case of *N*-*p*-chlorophenyl thiane 1-imide, introduction of sulfur increases the molar fraction of the axial isomer from 18% to 60%, whereas introduction of oxygen increases its molar fraction to 54% (see ref 65).
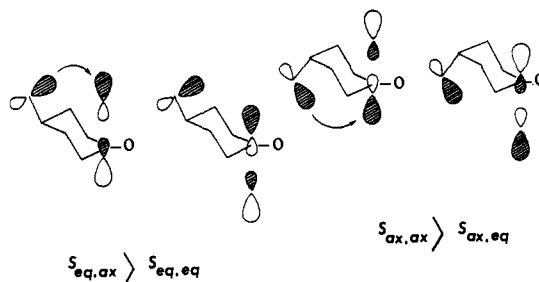
(76) (a) Moreau, G. *Bull. Soc. Chim. Fr.* 1972, 2814; (b) Akhrem, A. A.; Kamernitskii, A. V.; Prohoda, A. M. *Zh. Org. Khim.* 1967, *3*, 57; (c) Monson, R. S.; Przybycien, D.; Baraze, A. *J. Org. Chem.* 1970, *35*, 1700; (d) Lantvoev, V. I. *Zh. Org. Khim.* 1976, *12*, 2361; (e) le Noble, W. J.; Chiou, Der-Ming; Okaya, Y. *J. Am. Chem. Soc.* 1979, *101*, 3244. Several examples of "anomalous" behavior suggest, however, that our qualitative assessment of the overlap magnitudes does not provide sufficient criterion to predict stereoselectivity of the reaction in this system.

(77) Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* 1962, *84*, 2833.

(78) Some examples of the model donor–acceptor systems, such as 4,4-disubstituted cyclohexanols (Stolow, R. D.; Groom, T.; McMasters, P. D. *Tetrahedron Lett.* 1968, 5781; Stolow, R. D.; Giants, T. W.; Roberts, J. D. *Ibid.* 1968, 5777) or *trans*-1,4-dihalocyclohexanes (Remisov, A. B.; Butenko, G. G. *Zh. Prikl. Spektr.* 1973, *18*, 865; and ref 67d) suggest that the extra stabilization of the axial or diaxial conformation does not diminish, but rather increases, going down a group of the Mendeleev table.

*the relative yield of the product of equatorial approach should increase.*

Both reduction with sodium borohydride in hydroxylic solvents as well as with lithium aluminum hydride and its alkoxy derivatives in aprotic solvents display solvent effects on the reaction stereochemistry, which are less or more pronounced depending on the ketone structure,[79] and which are well illustrated by the results for 3,3,5-trimethylcyclohexanone (see Table XII). It follows from these data that if the order of increasing electron-donor power adopted for amines (see sections 3.1.c and 3.2.b) is applied to alcohols and ethers, the relative yield of the equatorial approach indeed increases in the same order.

The composition and solvation of metal hydrides in reaction medium and the role of metal cation in these reactions have been extensively studied,[2,3] and the elaborated models of transition-state solvation allow closer interpretation of the mechanism of electron donation from solvent molecules into the σ^*_+ orbital.

In the case of sodium borohydride reduction of cyclohexanone in isopropyl alcohol, the transition state was proposed to be solvated by two alcohol molecules: one complexed with the carbonyl oxygen, and the second, an ionized molecule, coordinated with boron.[80] Thus, it can be seen that the lone pairs of both alcohol molecules may interact with the σ^*_+ orbital, which corroborates our interpretation if this model applies to the reduction of 3,3,5-trimethylcyclohexanone in other alcohols as well.
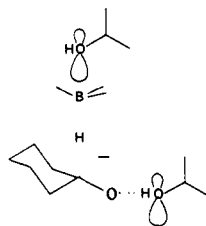
In the case of lithium aluminum hydride reduction in tetrahydrofuran, where the hydride exists predominantly as solvent-separated ion pairs, the picture of transition-state solvation is similar. It was proposed that during the reaction ketone replaces one of the four THF molecules in the coordination sphere of lithium cation and is subsequently attacked by AlH_4^- ion.[3]
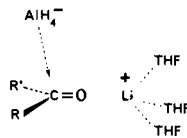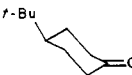

Furthermore, it was pointed out that specific solvation of metal cation is necessary for the solvent effect to occur,[56] and it was suggested that the difference in reaction stereochemistry in Et_2O vs. THF originates in the presumed difference in stereoselectivity of contact ion pairs, predominant in Et_2O vs. solvent-separated ion pairs. This would also explain decrease of solvent effect for a series of cations of decreasing capability to complex oxygen bases $Li^+ > Na^+ > K^+ > NR_4^+$, but is inconsistent with the decrease of solvent effect produced by addition of crown ethers or polyamine.[56] In our interpretation the lithium cation mediates the greatest THF effect on reduction stereochemistry because it is most efficient in bringing solvent molecules into the immediate vicinity of the transition state and the σ^*_+ orbital.

It follows that the addition of a stoichiometric amount of lithium salt of an electron-donating anion to lithium aluminum hydride reduction in diethyl ether, where both salts would exist predominantly as contact ion pairs, should nevertheless produce a similar shift of reaction stereochemistry toward higher yield of axial alcohol as the addition of tetrahydrofuran. This was in fact

Table XIII. Nucleophilic Addition to Cyclohexanones in the Presence of Lithium Salts in Diethyl Ether

reagent	salt	molar ratio	rel yields of equatorial approach	
			t-Bu	Me,Me
LiAlH₄[a]	LiBr	0	10	57
		1	11.5	66.5
		5	11.5	68
CH₃Li[b]			65	
	LiO-*t*-Bu	1	75	
	LiBr	1	76	
	LiI	1	81	
	LiClO₄	1	92	

[a] Guyon, R.; Villa, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* 1976, *283*, 541. [b] Ashby, E. C.; Noding, S. A. *J. Org. Chem.* 1979, *44*, 4371.

observed in the case of lithium bromide,[81] and an analogous effect was reported for the addition of lithium salts to methyllithium reaction in diethyl ether[82] (see Table XIII). In tetrahydrofuran, the inorganic anion cannot be brought into the immediate vicinity of the transition state and, indeed, no effect of the salt addition is observed in this solvent.

Conclusions

The growing knowledge about nucleophilic additions to cyclohexanone has already produced some prehension of the limits of a theory based solely on the concept of steric interactions. In the last few years several proposals were advanced in order to define some nonsteric determinants of stereoselectivity in the nucleophilic addition to cyclohexanone.[2-4] However, none of these attempts to produce a comprehensive and consistent theory succeeded.

In this paper, we have proposed an approach based on the premise that numerous stereochemical effects in nucleophilic addition to cyclohexanone arise through interactions resulting in *transition-state stabilization* rather than through transition-state destabilization by steric hindrance; in other words, a particular direction of nucleophile approach may be predominant because it is facilitated and not because the opposite one is hindered. Thus, one has to look for stabilizing interactions relevant to the transition state of nucleophilic addition, which would compete with steric destabilization.

Our hypothesis answering the above problem is based on the assumption that the stereochemistry of reaction is primarily determined in the bond-forming process, treated independently according to the Bell–Evans–Polanyi principle, through nonbonded orbital interactions with the vicinal σ bonds. We postulate, in contrast to the previous proposition of transition-state stabilization,[7] that the dominant conjugative interaction in the bond-forming process is electron donation from the σ bonds because the very definition of the incipient bond suggests that this bond is intrinsically electron deficient. Thus, the kernel of our model consists in the postulate that the feature of the transition state of nucleophilic addition critical for stereoselectivity of the reaction is a low-lying vacant orbital, σ^*_+, associated with σ bond being formed in the reaction.

Consequently, the stereochemistry of nucleophilic addition to 4-*tert*-butylcyclohexanone is proposed to result from a superposition of two effects: *steric hindrance which favors the equatorial approach, and electron donation from the cyclohexanone σ_{CC} and σ_{CH} bonds into the σ^*_+ orbital, which favors the axial approach because the carbon–hydrogen bonds are better electron donors.*

This model has numerous consequences which can be clearly spelled out and readily verified.

(79) In addition to the references to Table XII, see Haller, R.; Ebersberg, J. *Arch. Pharm.* 1970, *303*, 53; and Combe, M. G.; Henbest, H. B. *Tetrahedron Lett.* 1961, 404. A slight shift toward equatorial approach in more polar solvents is also observed in organometallic additions to cyclohexanones (see ref 4).

(80) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* 1977, *42*, 1108.

(81) Guyon, R.; Villa, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* 1976, *283*, 541.

(82) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* 1979, *44*, 4371.

First, a variation in electron-donating power of the cyclohexanone σ bonds will result in corresponding changes of stereoselectivity: this prediction is corroborated by the data on metal hydride reductions or organometallic additions on 3- and 3,5-alkylcyclohexanones, N-alkyl-5-alkylpiperidin-3-ones, 2-phenyl-1,3-dioxan-5-one, and steroidal thian-3-ones.

Second, a variation in transition-state electron affinity, i.e., in $\epsilon(\sigma^*_\ddagger)$, will result in corresponding changes in stereoselectivity of the reaction. Thus, electron-withdrawing substitution of a nucleophilic reagent, which lowers $\epsilon(\sigma^*_\ddagger)$, may produce a predominance of the axial approach overriding the nucleophile's steric demand. In contrast, electron-donating substitution may produce a predominance of the equatorial approach even in the case of relatively small nucleophiles. The stereochemistry of addition of substituted methyl carbanions and alkyl and alkoxy metal hydrides indeed follows this simple relation.

Since $\epsilon(\sigma^*_\ddagger)$ can also be influenced by electron donation from the lone pair which develops on the carbonyl oxygen along the reaction pathway, we expect that metal cations which complex the carbonyl group during the transition state and efficiently stabilize its surplus negative charge will increase the relative yield of axial approach in metal hydride reduction. The observed trends for alkaline metal cations in AlH_4^- or Selectride reductions confirm this expectation, and a good model for this phenomenon is provided by the Hantzsch reduction of the iminium salts derived from 4-*tert*-butylcyclohexanone.

The other important implication of our model is that the same trends due to variation of $\epsilon(\sigma)$ and $\epsilon(\sigma^*)$ should be observed in the ground-state conformational equilibria of cyclohexyl derivatives. The examples of 3- and 3,5-alkylcyclohexanols, oxathiane and dithiane S-oxides, and N-substituted thiane imides illustrate the same relationships listed above as observed in the reactions of nucleophilic addition. Thus, our model seems not only to be rather successful in qualitative treatment of various parameters of the reaction, but also lead to a consistent picture of the dominant interactions determining cyclohexane conformational equilibria, because *the effect of even the weakest two-electron stabilizing interaction (σ,σ^*) between the σ bonds apparently may be comparable to that of steric hindrance, i.e., in the range of a few tenths of a kilocalorie to a few kilocalories per mol.*

For further exploration of the scope of the discussed effect, lower limits to the relevant overlap magnitudes should be established, since in general all the overlaps will be different from zero. The subsequent discussion of data on organometallic addition and metal hydride reduction of β,γ-unsaturated ketones, 4-heterocyclohexanones, and C_4-substituted cyclohexanones demonstrates that our model offers a consistent way to rationalize kinetic and stereochemical effects off the so-called remote polar substituents. The available evidence, although only tentative, suggests that these effects, inexplicable in steric or electrostatic terms, depend on the energy gap and the overlap between the interacting orbitals of the transition state and the electron-donating substituents.

Consequently, in the last part of the discussion, solvent and solute effects on the stereochemistry of 3,3,4-trimethylcyclohexanone reduction and of methyllithium addition to 4-*tert*-bu-

tylcyclohexanone were analyzed in terms of our model. The expectation that electron donation from a solvent or a solute such as an inorganic anion will increase the $\sigma^*_\ddagger$ energy level and should thus lead to an increase in the relative yield of the product of equatorial approach is corroborated by experimental evidence. This result implies that solvent effects might be considered as exerted by individual molecules participating in the transition state as its inherent and ordered element.

Thus, two-electron stabilization of the transition state appears to be relevant even at the distances of intermolecular interactions.

In this paper, the existence of a low-lying vacant orbital $\sigma^*_\ddagger$ is considered as the feature of the transition state, which is critical for stereoselectivity of nucleophilic addition to a carbonyl group. However, it should not escape our attention that our postulate reveals a mechanism of facilitation of the bond-forming process which appears to be of broad relevance;[83] the discussed model readily embraces the kinetic α effect and the kinetic anomeric effect as well. It seems that in spite of the purely correlative character of our approach, the proposed model correctly identifies *electron deficiency as an important and general cause of the energetic elevation during the process of bond translation.* Obviously, this would be important for the interpretation of catalytic effects in solution reactions, particularly for elucidation of the mechanism of enzyme action. The last possibility will be pursued in a separate article which shows that the stereochemistry of the active site of pancreatic serine proteases may be rationalized in terms of $n,\sigma^*_\ddagger$ and $\pi,\sigma^*_\ddagger$ interactions of the enzyme and transition-state orbitals. Two classical propositions concerning the mechanism of enzyme catalytic action would thereby be unified.[84]

(83) It is tempting to mention a few examples of other reactions, such as alkylation of piperidines (Duke, R. P.; Jones, R. A. Y.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1553), oxidation of thianes (Van Acker, L.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 299 and references cited therein), peracid epoxidation of methylenecyclohexanes (Sevin, A.; Cense, J. M. *Bull. Soc. Chim. Fr.* **1974**, 963), chlorination of 7-azabenzonorbornenes (Malpass, J. R.; Walker, M. P. *Chem. Commun.* **1979**, 585), or electrophilic additions to 7-isopropylidenebenzonorbornenes (Hertel, L. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 7620, and references cited therein), which could be controlled by the same nonbonded orbital interactions as nucleophilic additions to cyclohexanones and norbornen-7-ones.

(84) (a) Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375; (b) Suard, M.; Berthier, G.; Pullman, B. *Biochim. Biophys. Acta* **1961**, *52*, 254; (c) Szent-Gyorgyi, A. *Nature (London)* **1941**, *148*, 157.