

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/11680621>

Parabolic Relationship between the Basicity of the Nucleophile and π -Face Selection in Addition of the Substituted Acetylide Ions to Cyclohexanone and Cyclohexanethione

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MARCH 1998

Impact Factor: 4.72 · DOI: 10.1021/jo9713722 · Source: PubMed

CITATIONS

12

READS

9

1 AUTHOR:



Andrzej Cieplak

10 PUBLICATIONS 878 CITATIONS

SEE PROFILE

Parabolic Relationship between the Basicity of the Nucleophile and π -Face Selection in Addition of the Substituted Acetylide Ions to Cyclohexanone and Cyclohexanethione

Andrzej Stanislaw Cieplak

Department of Chemistry, Yale University, New Haven, Connecticut 06520, and Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

Received July 25, 1997[®]

Energy changes, structural variation, and electron density shifts during nucleophilic addition to cyclohexanone and cyclohexanethione were examined by means of the *ab initio* calculations at the HF/6-31G* level. The atomic charge on the carbonyl C was found to become more positive upon approach of the nucleophile; the density deformation maps suggest that the charge polarization occurs to a large extent in the π bond. Since this effect is not compensated for by charge transfer until in the late stage of addition, the reaction site is considerably electron deficient (more so than the carbonyl C in the substrate) for most of the reaction path, and its interactions with the ligands are dominated by hyperconjugation with the vicinal C–H and C–C bonds. Relative stabilities of the axial and equatorial transition-state structures were examined in the series $\text{HN}=\text{C}$, $\text{ON}=\text{C}^-$, $\text{N}=\text{C}^-$, $\text{FC}=\text{C}^-$, $\text{HC}=\text{C}^-$, $\text{SBeC}=\text{C}^{2-}$, $\text{O}_3\text{SC}=\text{C}^{2-}$, $\text{H}_3\text{AlC}=\text{C}^{2-}$, $\text{SC}=\text{C}^{2-}$, $\text{H}_3\text{BC}=\text{C}^{2-}$, and $\text{C}=\text{C}^{2-}$ and found to depend on polarization of the electrophiles, $\text{C}=\text{O}$ vs $\text{C}=\text{S}$, and basicity of the nucleophiles. The latter dependence is parabolic: the axial preference reaches a maximum for the moderately basic anions, and it is diminished or even reversed for the most and least basic nucleophiles, i.e., in the case of reactions proceeding through the very early or very late transition states. Thus, the stereoelectronic effect is largest in the region of the reaction coordinate where the electron deficiency at the reaction site reaches a maximum. These findings corroborate the premises of the hypothesis of hyperconjugative assistance to bond formation and are consistent with major trends in the experimental data if the stereochemistry of alkylation of 4-*tert*-butylcyclohexanone is correlated with Pauling electronegativity of metals in the case of methylmetals, methylmetal ate complexes, allylmetals and arylmetals, and with the $\text{p}K_a$ of conjugated acids in the case of sulfur-, carbonyl-, and nitrile-stabilized carbanions.

The intense practical and theoretical interest in controlling the stereochemistry of nucleophilic addition to carbonyls through the properties of the organometallic or hydride-transfer reagents has generated an extraordinary wealth of experimental data.¹ This evidence often suggests that besides the steric demand of the nucleophile² and Lewis acid,^{2,3} bonding properties of metals and their ligands might have a considerable effect on the stereoselectivity of carbonyl additions.

One such property is the nucleophilicity of the carbon or hydrogen ligand to be transferred to the carbonyl.³ Its importance was first emphasized by the hypothesis of hyperconjugative assistance to bond formation,^{4,5} which posulated that the axial preference in additions to cyclohexanones should increase in a series of isosteric nucleophiles as their basicity decreases. The major trend in the data available by the end of the 1970s was indeed consistent with a linear Hammett relationship,^{4a} and the early inferences were supported by the study of the sulfur-stabilized primary carbanions.^{4b} However, the subsequent studies of the stereochemistry of addition of

the carbonyl- and nitrile-stabilized secondary and tertiary carbanions did not confirm a linear relationship between the face preference and basicity.⁶ Similarly, a simple extension of this concept to organometallics such as alkyl and allylmetals, and to the alkoxy and phenoxy metal hydrides, was not supported by the available data, *vide infra*, and the trends found in Ir^{I} , Rh^{I} , and Zr^{IV} -catalyzed Meerwein–Ponndorf–Verley reductions also seemed difficult to explain.⁷ Apparently, either the early model, while capturing a significant trend in the data, is still inadequate, or some other factors overshadow the effect of nucleophilicity of the alkylating and reducing agents in the actual processes in solution.

To address this question, we decided to study a series of gas-phase additions of carbanions to cyclohexanone by means of the *ab initio* MO theory. The nucleophile chosen for the study was the acetylide ion. The stereochemistry of ethynylation of unhindered cyclohexanones

[®] Abstract published in *Advance ACS Abstracts*, December 15, 1997.

(1) Presented in part at the 118th Annual Symposium of the Pharmaceutical Society of Japan, March 1995, Tohoku University, Sendai.

(2) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

(3) Doyle, M. P.; McOsler, C. C.; Ball, N.; West, C. T. *J. Org. Chem.* **1977**, *42*, 1922.

(4) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(5) In an earlier attempt to relate electronic properties of alkylating agents to face selectivity, hard nucleophiles were proposed to prefer the axial approach to cyclohexanone and soft nucleophiles the equatorial one: Maroni-Barnaud, Y.; Roux-Schmitt, M. C.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, 4447. For the more recent discussion of this concept see: Mladenova, M.; Gaudemar-Bardone, F. *Phosphorus, Sulfur Silicon* **1990**, *47*, 191.

(6) Dobrev, A.; Ivanov, Ch.; Lattes, A.; Bon, M. *Bull. Soc. Chim. Fr.* **1987**, 1084.

(7) Vinzi, F.; Zassinovich, G.; Mestroni, G. *J. Mol. Catal.* **1983**, *18*, 359. Mestroni, G.; Zassinovich, G.; Alessio, E.; Tornatore, M. *J. Mol. Catal.* **1989**, *49*, 175. Krohn, K.; Knauer, B. *Liebigs Ann.* **1995**, 1347. Knauer, B.; Krohn, K. *Liebigs Ann.* **1995**, 677.

is remarkably independent of the counterion and solvent properties.⁸ The naked ion (THF, $n\text{-Bu}_4\text{N}^+$) displays the axial preference in addition to 4-*tert*-butylcyclohexanone, which is very similar to that observed for metals salts in liquid NH_3 (Li^+ , Na^+) and in THF (K^+ , MgBr^+).^{8c} Ethynylation resembles in this regard some metal hydride reductions of cyclohexanones, e.g., with AlH_4^- and BH_4^- , where the changes in the counterion (Li^+ , Na^+ , MgCl^+ , $n\text{-Bu}_4\text{N}^+$, Ce^{3+}) or the solvent (Et_2O , THF, 50% H_2O –50% dioxane, *i*-PrOH, MeOH) have little effect on face selection,⁹ and some alkylations, e.g., with acetonitrile metal salts, where the stereochemistry of addition (64–85% axial) is also only moderately affected by the cation (Li^+ , Na^+ , K^+ , Mg^{2+} , Zn^{2+} , Ce^{3+}) and the solvent (Et_2O , THF, HMPT, DMSO, NH_3).¹⁰ This suggests that the axial preference observed in these reactions is an inherent characteristic of the corresponding anions and as such ought to be reproduced in the gas phase both in experiment and in theory. Thus, it seemed reasonable to expect that the effect of basicity of the acetylide ions on the stereochemistry of their additions would also be reproduced in the gas phase.

Computational Methods

Ab initio calculations were carried out with the Gaussian-92 and Gaussian-93 systems of programs¹¹ and were run on Multiflow Trace 14/2000, DEC-GPX, Sun 330, and IBM RS6000/350 computers. Initially, the transition states for additions of the cyanide ion were located at the HF/3-21G level, taking the previously reported transition structures for LiH additions as the departure point¹² and using the Gaussian option Opt = (TS,calcFC) (Berny optimization); this protocol was then employed repeatedly, taking each newly located pair of structures as the starting point of the next search and gradually changing the basicity of the nucleophiles. Given the default convergence criteria, the initial and the final structure in the last step of the Opt = (TS,calcFC) procedure were in each case indistinguishable in terms of the geometry and energy. Reoptimization with the 6-31G* basis set was achieved in every case except for the axial addition of $\text{O}_3\text{SC}\equiv\text{C}^{2-}$, when the search for the transition structure turned out to be too time-consuming and was not completed. No attempt was made to go beyond the HF/6-31G* level of the theory, since

the study focuses on the *relative* change in the *relative* transition-state energies, which in the present case appear to depend little on the basis set and electron correlation.¹³ The analysis of electron density was carried out with the CASGEN system of programs developed in this laboratory,¹⁴ running on a DEC-GPX computer.

Results

The energies, dipole moments, and selected geometry parameters and atomic populations of the transition structures for additions of a series of the acetylide- and cyanide-like nucleophiles to cyclohexanone and cyclohexanethione are listed in Table 1. In terms of the C(1)···C(7) separation (see Table 1 for the numbering system), the reaction paths mapped out by these structures extend between ~ 1.5 and ~ 4.8 Å. Following the cyclohexanone/acetylide ion entries, the transition structures for additions of other nucleophiles are listed in the order of the decreasing protonation energies. The incipient bonds shorten in the same order; reasonable linear correlations were obtained for the protonation energies and the mean values of the axial and equatorial incipient bond distances ($r^2 = 0.93$ (C=O) and $r^2 = 0.96$ (C=S)). To widen the range of basicity of the acetylides and allow for fine-tuning of the charges on C(7), several dianions are employed as models for the very basic nucleophiles. Except for the parent dianion $\text{C}\equiv\text{C}^{2-}$, the examined species incorporate as the acetylide substituent either a conjugate base of a Brønsted acid or an ate ion and are likely to be stable in solution; one of the most basic ions, $\text{SC}\equiv\text{C}^{2-}$, has actually been reported to exist.¹⁵ The cyclohexanone entries are followed in Table 1 by a series of transition structures for additions of the same series of nucleophiles to cyclohexanethione (occurring at the thiocarbonyl C).

Basicity of the Nucleophile and π -Face Selection.

The differences in the potential energy of the equatorial and axial transition structures are plotted against the mean values of the axial and equatorial incipient bond distances in Figure 1. The plots indicate that in a series of isosteric anions the axial preference initially increases with the increase in electronegativity of the substitution at the nucleophilic C, in accord with the original hypothesis.⁴ The trend then reverses in the mid-region of the reaction coordinate. As expected, the resulting parabolic relationship is independent of the basis set, except that the axial preference is greater at the higher level of theory for most of the reaction path, Figure 1a.

The stereochemistry of addition also depends on the polarization of the electrophile, Figure 1b. This effect is most striking in the case of the four most basic nucleophiles, which display the axial preference in additions to cyclohexanone, and the equatorial preference in ad-

(8) (a) Hennion, G. F.; O'Shea, F. X. *J. Am. Chem. Soc.* **1958**, *80*, 614. (b) Rocquet, F.; Battioni, J. P.; Capmau, M.; Chodkiewicz, W. C. *R. Acad. Sci. Ser. C* **1969**, *268*, 1449. (c) Battioni, J. P.; Chodkiewicz, W. C. *R. Acad. Sci. Ser. C* **1970**, *271*, 1390. (d) Fleming, I.; Terret, N. K. *J. Organomet. Chem.* **1984**, *264*, 99. (e) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975.

(9) (a) Guyon, R.; Villa, P. *Bull. Soc. Chim. Fr.* **1977**, 145. (b) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (c) Handel, H.; Pierre, J.-L. *Tetrahedron Lett.* **1976**, 2029. (d) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(10) Cf. Table 3.

(11) (a) Frisch, M.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, G.; Schlegel, H. B.; Robb, M. A.; Repogle, E. S.; Gomperts, R.; Andres, J. L.; Ragavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*; Gaussian, Inc.: Pittsburgh, PA, 1992. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Foresman, J. B.; Robb, M. A.; Cheesman, J. R.; Keith, T.; Ayala, P. Y.; Wong, M. W.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 93*, Development Version (Revision E.2); Gaussian, Inc., Pittsburgh, PA, 1993.

(12) (a) At the HF/3-21G level, the incipient bond distances and the ring conformations turned out to be quite similar in the LiH and the cyanide structures: Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) At the B3LYP/6-31G* level, the transition structures for LiH additions are considerably less advanced (the incipient bond distances increase from 2.057 and 2.029 Å to 2.542 and 2.403 Å), while the difference in the transition-state energy remains the same: Senju, T.; Tomoda, S. *Chem. Lett.* **1997**, 431.

(13) E.g., the effect of the diffuse functions on the relative energies of the transition states for the cyanide addition to substituted acetaldehydes is very small: Me 1.42, 0.0, 0.62 and 0.97, 0.0, 0.39 (at the HF/6-31G*//HF/6-31G* and HF/6-31+G*//HF/6-31+G* levels, respectively, in the order +sc, -sc, app, cf. ref 18b); F 0.49, 3.67, 0.0 and 0.73, 3.96, 0.0; SiH₃ 3.26, 0.0, 0.85 and 2.25, 0.0, 0.33; CN 1.41, 2.53, 0.0 and 1.15, 2.61, 0.0 (Cieplak, A. S.; Wiberg, K. B.; Ochterski, J. W. Unpublished results.). See also: Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456; **1991**, 327, and ref 12b. Let us also add that the 6-31G* Mulliken charges were found to be linearly related to other measures of atomic charge for this basis set. This is not true for the 6-31+G* and other basis sets: Wiberg, K. B.; Rablen, P. *J. Comput. Chem.* **1993**, *14*, 1504.

(14) Rablen, P. R.; Hadad, C. M. Yale University.

(15) Brandsma, L.; Bos, H. J. T.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 307.

Table 1. Energies, Selected Geometry Parameters, and Atomic Charges of Structures along Reaction Paths for Additions of Cyanide and Acetylide-like Nucleophiles to Cyclohexanone and Cyclohexanethione (6-31G*)

| | d_1^a | E | θ_c | d_4 | d_5 | d_6 | α_5 | α_6 | ω_1 | ω_2 | atomic charges C(1) | μ |
|------------------------------------|---------------------|------------|------------|--------|--------|--------|------------|------------|------------|------------|---------------------|-------|
| cyclohexanone | | | | | | | | | | | | |
| HC≡C ⁻ | | | | | | | | | | | | |
| 1 | 4.8534 | -384.1018 | 3.6 | 1.0925 | 1.0841 | 1.5365 | 106.2 | 108.1 | -21.5 | 43.8 | 0.556 | 11.6 |
| 2 | 4.50 | -384.1005 | 4.7 | 1.0929 | 1.0838 | 1.5351 | 106.0 | 108.0 | -30.1 | 42.8 | 0.565 | 20.3 |
| 3 | 3.90 | -384.0996 | 7.4 | 1.0934 | 1.0832 | 1.5327 | 105.4 | 107.8 | -43.2 | 38.0 | 0.584 | 10.9 |
| 4 | 3.30 | -384.0997 | 10.3 | 1.0931 | 1.0823 | 1.5303 | 104.7 | 107.2 | -56.2 | 26.7 | 0.604 | 9.7 |
| 5 | 3.00 | -384.0996 | 11.4 | 1.0928 | 1.0815 | 1.5301 | 104.6 | 107.0 | -61.8 | 21.9 | 0.615 | 8.9 |
| 6 | 2.70 | -384.0975 | 17.6 | 1.0936 | 1.0811 | 1.5295 | 104.5 | 107.3 | -62.9 | 25.4 | 0.627 | 8.3 |
| 7 | 2.0777 | -384.0895 | 39.9 | 1.0933 | 1.0830 | 1.5296 | 104.7 | 108.0 | -61.7 | 39.3 | 0.597 | 6.9 |
| 8 | 1.5429 | -384.1052 | 59.0 | 1.0889 | 1.0869 | 1.5329 | 105.2 | 108.0 | -63.6 | 49.7 | 0.485 | 7.3 |
| 9 | 4.50 | -384.1066 | -0.7 | 1.0879 | 1.0847 | 1.5399 | 107.9 | 109.0 | 90.8 | 55.2 | 0.533 | 10.2 |
| 10 | 3.9425 | -384.1096 | 0.1 | 1.0890 | 1.0851 | 1.5388 | 106.9 | 108.8 | 97.9 | 52.8 | 0.540 | 9.2 |
| 11 | 3.90 | -384.1096 | 0.2 | 1.0874 | 1.0850 | 1.5382 | 107.1 | 108.7 | 97.3 | 52.3 | 0.542 | 9.1 |
| 12 | 3.60 | -384.1082 | 0.6 | 1.0865 | 1.0852 | 1.5367 | 106.3 | 108.3 | 100.7 | 47.3 | 0.555 | 9.0 |
| 13 | 3.30 | -384.1045 | 0.3 | 1.0845 | 1.0854 | 1.5352 | 105.4 | 107.8 | 103.9 | 39.9 | 0.575 | 9.3 |
| 14 | 3.00 | -384.0990 | 4.9 | 1.0819 | 1.0852 | 1.5352 | 105.5 | 107.6 | 115.1 | 39.3 | 0.605 | 10.0 |
| 15 | 2.85 | -384.0960 | -14.1 | 1.0804 | 1.0839 | 1.5390 | 108.2 | 108.4 | 137.9 | 55.9 | 0.623 | 10.8 |
| 16 | 2.70 | -384.0934 | -20.2 | 1.0797 | 1.0833 | 1.5401 | 109.1 | 108.7 | 147.5 | 59.5 | 0.626 | 10.7 |
| 17 | 2.1654 | -384.0872 | -40.1 | 1.0838 | 1.0832 | 1.5386 | 111.1 | 108.7 | 163.0 | 63.7 | 0.590 | 8.1 |
| 18 | 1.5325 | -384.1089 | -59.9 | 1.0932 | 1.0867 | 1.5290 | 112.1 | 107.8 | 175.5 | 62.5 | 0.437 | 5.3 |
| C≡C ²⁻ | | | | | | | | | | | | |
| 19 | 3.9066 ^b | -383.2301 | 9.6 | 1.0977 | 1.0850 | 1.5322 | 104.4 | 107.6 | -39.1 | 37.4 | 0.600 | 21.0 |
| 20 | 2.7002 | -383.2286 | -24.3 | 1.0835 | 1.0861 | 1.5423 | 106.6 | 108.6 | 140.5 | 59.0 | 0.630 | 20.7 |
| H ₃ BC≡C ²⁻ | | | | | | | | | | | | |
| 21 | 3.8444 | -409.7937 | 9.1 | 1.0959 | 1.0840 | 1.5321 | 104.6 | 107.5 | -42.2 | 34.3 | 0.597 | 24.1 |
| 22 | 2.5808 | -409.7892 | -28.1 | 1.0788 | 1.0839 | 1.5423 | 109.2 | 108.8 | 148.6 | 62.1 | 0.652 | 24.0 |
| SC≡C ²⁻ | | | | | | | | | | | | |
| 23 | 3.8270 | -780.9059 | 9.1 | 1.0958 | 1.0839 | 1.5319 | 104.7 | 107.5 | -42.2 | 34.1 | 0.597 | 20.9 |
| 24 | 2.5641 | -780.9011 | -28.6 | 1.0787 | 1.0836 | 1.5423 | 109.4 | 108.8 | 149.7 | 62.4 | 0.651 | 20.5 |
| H ₃ AlC≡C ²⁻ | | | | | | | | | | | | |
| 25 | 3.8136 | -627.0694 | 8.9 | 1.0951 | 1.0836 | 1.5319 | 104.7 | 107.5 | -44.6 | 32.9 | 0.594 | 24.5 |
| 26 | 2.4595 | -627.0628 | -32.1 | 1.0794 | 1.0831 | 1.5418 | 110.2 | 108.8 | 154.0 | 63.3 | 0.643 | 24.4 |
| SBeC≡C ²⁻ | | | | | | | | | | | | |
| 27 | 2.2805 | -795.6757 | 33.2 | 1.0961 | 1.0817 | 1.5290 | 104.6 | 107.8 | -61.1 | 34.7 | 0.630 | 20.9 |
| 28 | 2.3853 | -795.6707 | -34.3 | 1.0803 | 1.0829 | 1.5413 | 110.6 | 108.9 | 156.6 | 63.6 | 0.634 | 25.5 |
| FC≡C ⁻ | | | | | | | | | | | | |
| 29 | 2.0257 | -482.9206 | 40.6 | 1.0929 | 1.0832 | 1.5297 | 104.7 | 108.1 | -62.0 | 40.1 | 0.596 | 6.2 |
| 30 | 2.1054 | -482.9191 | -41.8 | 1.0845 | 1.0833 | 1.5381 | 111.3 | 108.7 | 174.7 | 63.7 | 0.584 | 6.6 |
| N≡C ⁻ | | | | | | | | | | | | |
| 31 | 1.9076 | -400.1853 | 44.2 | 1.0912 | 1.0841 | 1.5308 | 104.6 | 108.2 | -61.6 | 42.2 | 0.537 | 8.4 |
| 32 | 1.9721 | -400.1853 | -45.3 | 1.0866 | 1.0837 | 1.5360 | 111.5 | 108.6 | 166.4 | 63.7 | 0.508 | 9.5 |
| 33 | 1.8648 ^c | -400.1967 | 45.6 | 1.0901 | 1.0855 | 1.5314 | 104.4 | 108.4 | -63.9 | 42.8 | 0.525 | 10.1 |
| 34 | 1.8481 ^c | -400.1990 | -48.4 | 1.0866 | 1.0856 | 1.5353 | 111.4 | 108.5 | 169.0 | 62.3 | 0.481 | 10.7 |
| 35 | 1.5704 | -400.1904 | 56.5 | 1.0884 | 1.0864 | 1.5327 | 104.8 | 108.1 | -63.1 | 48.8 | 0.478 | 8.0 |
| 36 | 1.5570 | -400.1937 | -57.8 | 1.0924 | 1.0861 | 1.5292 | 112.0 | 108.0 | 174.7 | 62.8 | 0.427 | 7.3 |
| ON≡C ⁻ | | | | | | | | | | | | |
| 37 | 1.725 | -747.9550 | 50.3 | 1.0894 | 1.0851 | 1.5315 | 104.6 | 108.2 | -62.6 | 45.7 | 0.528 | 8.3 |
| 38 | 1.7907 | -747.9568 | -50.2 | 1.0891 | 1.0845 | 1.5331 | 111.7 | 108.4 | 169.8 | 63.3 | 0.492 | 8.8 |
| cyclohexanethione | | | | | | | | | | | | |
| C≡C ²⁻ | | | | | | | | | | | | |
| 39 | 3.9912 | -705.8696 | 11.6 | 1.0970 | 1.0827 | 1.5342 | 103.6 | 109.2 | -35.8 | 40.1 | 0.090 | 21.3 |
| 40 | 2.7629 | -705.8769 | -17.7 | 1.0816 | 1.0857 | 1.5356 | 103.6 | 108.7 | 108.8 | 31.5 | 0.124 | 16.8 |
| H ₃ BC≡C ²⁻ | | | | | | | | | | | | |
| 41 | 3.7014 | -732.4286 | 11.4 | 1.0954 | 1.0817 | 1.5325 | 103.8 | 108.8 | -42.6 | 35.4 | 0.104 | 24.7 |
| 42 | 2.7996 | -732.4319 | -21.4 | 1.0813 | 1.0821 | 1.5409 | 106.7 | 109.9 | 137.4 | 57.9 | 0.144 | 22.5 |
| SC≡C ²⁻ | | | | | | | | | | | | |
| 43 | 3.6736 | -1103.5407 | 11.5 | 1.0953 | 1.0816 | 1.5323 | 103.9 | 108.7 | -43.1 | 35.1 | 0.104 | 21.5 |
| 44 | 2.7719 | -1103.5434 | -25.4 | 1.0789 | 1.0820 | 1.5430 | 108.5 | 109.9 | 147.6 | 59.7 | 0.129 | 15.9 |
| H ₃ AlC≡C ²⁻ | | | | | | | | | | | | |
| 45 | 3.6153 | -949.7032 | 11.3 | 1.0945 | 1.0814 | 1.5321 | 104.0 | 108.6 | -46.4 | 32.9 | 0.100 | 25.2 |
| 46 | 2.7546 | -949.7047 | -22.9 | 1.0798 | 1.0815 | 1.5415 | 107.7 | 110.0 | 141.8 | 59.7 | 0.139 | 23.6 |
| HC≡C ⁻ | | | | | | | | | | | | |
| 47 | 3.2614 | -706.7314 | 12.0 | 1.0923 | 1.0809 | 1.5312 | 104.4 | 108.3 | -54.6 | 28.3 | 0.095 | 9.5 |
| 48 | 2.6263 | -706.7289 | -26.4 | 1.0800 | 1.0808 | 1.5415 | 108.8 | 110.1 | 150.1 | 61.4 | 0.119 | 9.9 |
| FC≡C ⁻ | | | | | | | | | | | | |
| 49 | 2.7351 | -805.5643 | 19.2 | 1.0916 | 1.0799 | 1.5300 | 104.3 | 108.1 | -61.1 | 26.9 | 0.114 | 7.4 |
| 50 | 2.5636 | -805.5618 | -27.7 | 1.0801 | 1.0807 | 1.5416 | 108.9 | 110.1 | 152.2 | 61.4 | 0.116 | 8.8 |
| N≡C ⁻ | | | | | | | | | | | | |
| 51 | 2.4672 | -722.8336 | 26.3 | 1.0909 | 1.0802 | 1.5306 | 104.1 | 108.5 | -60.9 | 31.5 | 0.086 | 9.7 |
| 52 | 2.4190 | -722.8312 | -31.6 | 1.0815 | 1.0806 | 1.5410 | 109.5 | 110.1 | 155.3 | 62.0 | 0.078 | 11.6 |
| 53 | 1.4864 | -722.8908 | 58.3 | 1.0855 | 1.0839 | 1.5345 | 106.3 | 109.0 | -64.8 | 51.9 | -0.184 | 9.2 |
| 54 | 1.4832 | -722.8902 | -56.9 | 1.0926 | 1.0833 | 1.5292 | 109.3 | 108.8 | 171.0 | 56.3 | -0.181 | 8.4 |
| ON≡C ⁻ | | | | | | | | | | | | |
| 55 | 2.2513 | -797.6101 | 32.2 | 1.0899 | 1.0805 | 1.5305 | 104.0 | 108.7 | -61.9 | 35.3 | 0.062 | 10.1 |
| 56 | 2.2321 | -797.6082 | -36.3 | 1.0831 | 1.0806 | 1.5398 | 109.8 | 110.0 | 159.0 | 61.8 | 0.054 | 11.5 |

Table 1 (Continued)

| | d_1^a | E | θ_C | d_4 | d_5 | d_6 | α_5 | α_6 | ω_1 | ω_2 | atomic charges C(1) | μ |
|------|---------|-----------|------------|--------|--------|--------|------------|------------|------------|------------|---------------------|-------|
| HN=C | | | | | | | | | | | | |
| 57 | 1.8677 | -723.3490 | 38.9 | 1.0867 | 1.0823 | 1.5315 | 103.9 | 109.4 | -65.2 | 42.9 | -0.082 | 6.9 |
| 58 | 1.8566 | -723.3476 | -40.9 | 1.0880 | 1.0817 | 1.5364 | 110.0 | 109.9 | 167.8 | 60.8 | -0.095 | 6.5 |

^a The geometry parameters are defined as follows: d_1 C(1)–C(7), d_4 C(2)–H_{ax}, d_5 C(2)–H_{eq}, d_6 C(2)–C(3), α_5 C(1)–C(2)–H_{ax}, α_6 C(1)–C(2)–H_{eq}, ω_1 C(3)–C(2)–C(1)–C(7), ω_2 C(3)–C(2)–C(1)–C(6), θ_C C(2)–C(1)–O–C(6). The ring C atoms are numbered beginning with the carbonyl C, counterclockwise when looking at the axial face (therefore, $\omega_2 > 0$), the nucleophile C is C(7). Thus, during the axial approach $\omega_1 < 0$, $\theta_C > 0$, during the equatorial approach $\omega_1 > 0$, θ_C usually but not always < 0 . ^b The ions are listed in the order of the decreasing energies of protonation (au): C≡C²⁻ -0.9201, H₃BC≡C²⁻ -0.8304, SC≡C²⁻ -0.8248, H₃AlC≡C²⁻ -0.7898, SBeC≡C²⁻ -0.7893, HC≡C⁻ -0.7636, FC≡C⁻ -0.6324, ON≡C⁻ -0.5572, HN≡C -0.3037. ^c In a polar solvent (scrfl model, see text): dielectric constant = 78.5, $\epsilon_0 = 4.32$ (ax TS) and 4.33 (eq TS).

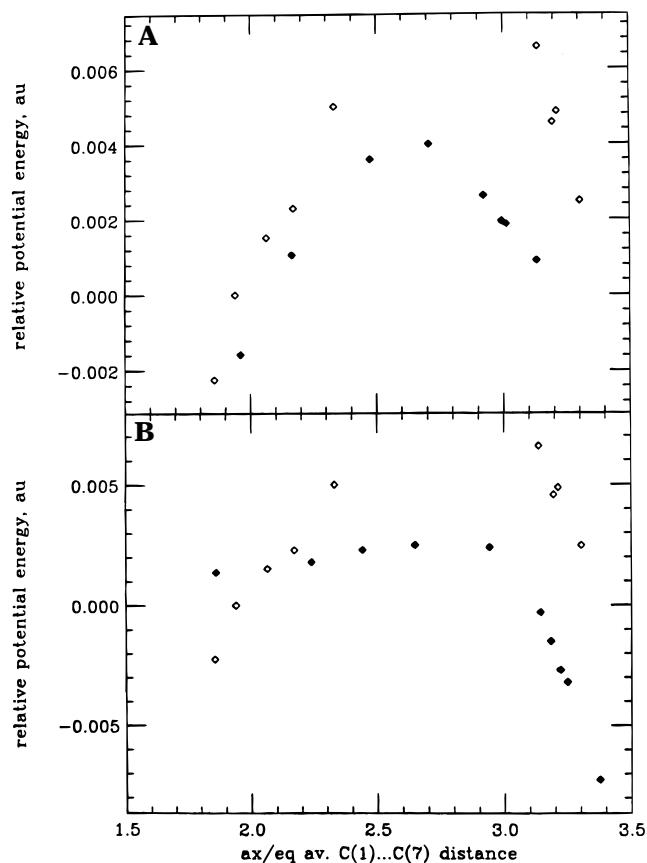


Figure 1. Basicity of the nucleophiles and π -face selectivity in additions to cyclohexanone and cyclohexanethione: the plots of the difference in the total potential energies of the equatorial and axial transition-state structures vs the mean of the equatorial and axial C(1)···C(7) distances. The top panel (A) compares the 3-21G (◆) and 6-31G* (◇) results for cyclohexanone, and the bottom panel (B) compares the 6-31G* results for cyclohexanone (◇) and cyclohexanethione (◆).

ditions to cyclohexanethione, Table 1, entries 19–26 and 39–46. The relative stabilities differ on average by 6 kcal mol⁻¹, even though the transition-structure geometries are essentially identical.

Structural Variation at C(2) and C(6). The geometry changes accompanying the progress in C(1)···C(7) bonding and rehybridization of C(1) are consistent with expectations and will not be analyzed here.¹⁶ The second source of the structural variation along the reaction coordinate turns out to be the rotation of the cyclohexanone ring and the concomitant rehybridization of C(2) and C(6). To examine this variation, the path of the

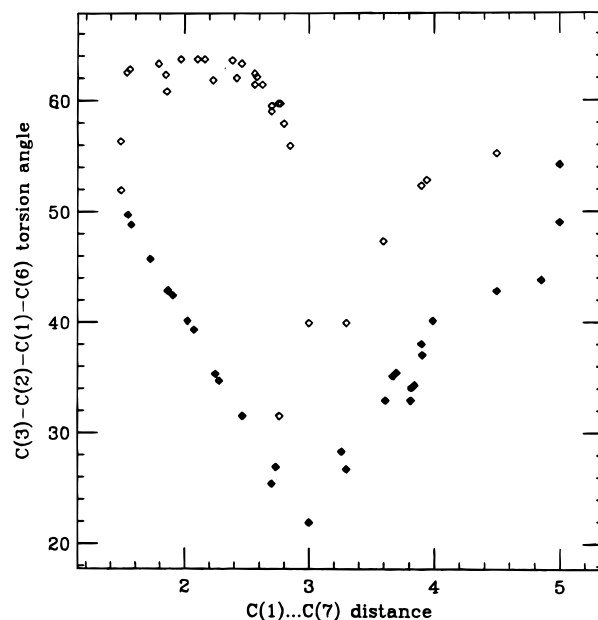


Figure 2. Changes in the chair conformation of the cyclohexanone and cyclohexanethione ring during the axial (◆) and equatorial (◇) approach of the nucleophiles illustrated by the plot of the torsional angle ω_2 against the C(1)···C(7) distance. The abscissa values for the data sets of cyclohexanone and cyclohexanethione are arbitrarily chosen to be 5.0 Å (all the transition structures included as well as the fixed-incipient bond structures of the acetylide additions).

acetylide addition to cyclohexanone was mapped out by the energy and geometry optimizations at the fixed C(1)···C(7) distances. The changes in the ring geometry along the axial and equatorial reaction paths are illustrated by the plots of the endocyclic torsion angle ω_2 C(3)–C(2)–C(1)–C(6) against the incipient bond distances, Figure 2. Along both paths, the ω_2 angle reaches the minimum values of $\sim 22^\circ$, Figure 3, and $\sim 39^\circ$, Figure 4, at the C(1)···C(7) distance of ~ 3.0 Å. Thus, in the mid-region of the reaction coordinate, the ring is severely flattened during the equatorial approach as well as during the axial approach. In the early and late stages of the equatorial addition, on the other hand, the ring folds (ω_2 increases); see Figure 5.

The folding and flattening of the ring result from the rotation about the C(1)–C(2) and C(1)–C(6) bonds. This rotation is accompanied by the distortion of the C(2) and C(6) methylene groups. During the axial approach, the antiperiplanar C(2)–H_{ax} and C(6)–H_{ax} bonds tilt toward the reaction site, i.e., the α_5 angle decreases; the dependence of α_5 on the incipient bond length is parabolic, with the minimum reached at the C(1)···C(7) distance of ~ 2.7 – 3.0 Å, entries 1–8 in Table 1. The bond distances at C(2) and C(6) undergo subtle changes during this

(16) Cieplak, A. S. In *Structure Correlation*; Dunitz, J. D., Bürgi, H. B., Eds.; Verlag Chemie: Weinheim, 1994; Vol. 1, p 207.

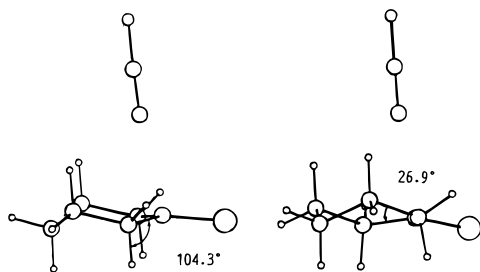


Figure 3. Flattening of the cyclohexanone ring in the axial transition structures that occur in the mid-region of the reaction coordinate during the additions of nucleophiles to cyclohexanone and cyclohexanethione. The diagram on the right shows the Newman-type projection along the C(1)–C(2) bond.

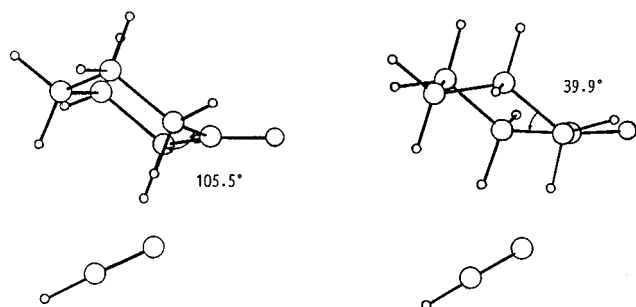


Figure 4. Flattening of the cyclohexanone ring in the mid-region of the reaction path during the equatorial addition of the acetylide ion. The diagram on the right shows the Newman-type projection along the C(1)–C(2) bond and reveals a nearly perfect eclipsing of the incipient bond and the C(2)–H_{ax} bond.

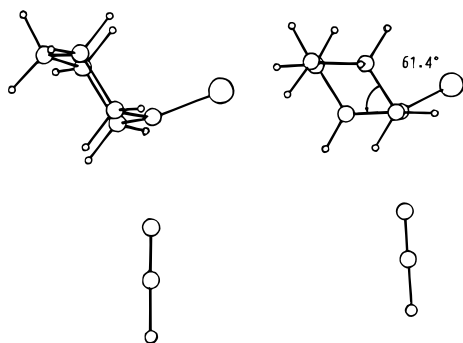


Figure 5. Folding of the cyclohexanone ring in the transition structures and the late stages of the equatorial additions of nucleophiles. The diagram on the right shows the Newman-type projection along the C(1)–C(2) bond.

approach as well, with the same parabolic dependence: d_4 (ax C–H) reaches maximum and the d_5 (eq C–H) and d_6 (C–C) distances reach their minima in the mid-region of the reaction path. This trend is also recognizable in the variation of the C(2) and C(6) geometry mapped out by the transition structures, although d_4 , and to a lesser extent d_5 , are affected by the anion field.¹⁷

During the equatorial approach, the course of the variation in α_5 , d_4 , d_5 , and d_6 is more complex, since the ring first slightly folds, then flattens, and then folds

(17) The anion field causes lengthening of the C–H bonds pointing away and shortening the ones pointing toward the anion. The increase in d_4 is largest in the case of the axial $\text{C}\equiv\text{C}^{2-}$ additions, entries 19 and 43, and for the four most basic dianions it correlates with the C(7) rather than C(1) atomic charges.

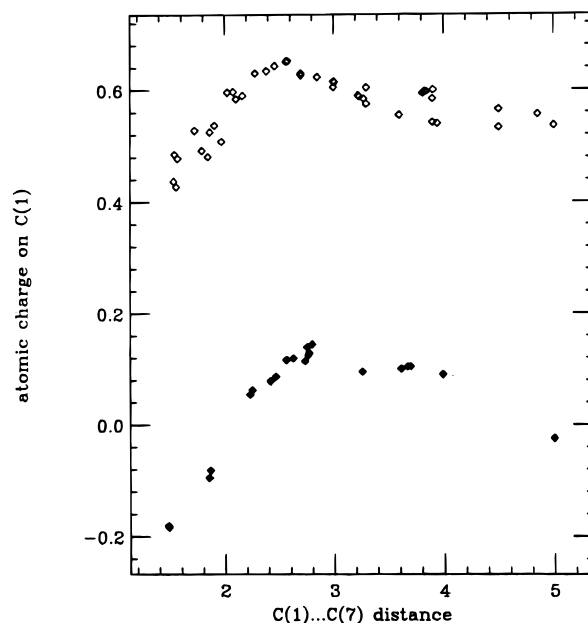


Figure 6. Change in Mulliken charges at C(1) along the paths of the additions to cyclohexanone (\diamond) and cyclohexanethione (\blacklozenge). The abscissa for the data set of the isolated reactants is arbitrarily chosen to be 5.0 Å.

again. Most interestingly, however, the flattening of the ring, which leads here to the *eclipsing* about the C(1)–C(2) and C(1)–C(6) bonds, is accompanied by a surprising decrease in the α_5 angle, cf. entries 13 and 14 of Table 1. Such tilting is also observed in a number of the early equatorial transition structures where the axial C–H bonds and the incipient bond eclipse to some degree, cf. α_5 in the cyclohexanone entry 20 (Table 1) and cyclohexanethione entries 44 and 46 (Table 1).

Electron Density at the Carbonyl C. Examination of the atomic populations reveals that the charges on the carbonyl and thiocarbonyl C initially become more positive upon the approach of the nucleophile. The overall dependence on the C(1)···C(7) separation is parabolic, with a maximum in both cases at ~ 2.7 Å, Figure 6. Even in the late transition structures, C(1) is still more electron deficient than it is in the reactants. The charge density difference maps, Figure 7, suggest that the charge polarization of the C=O and C=S occurs to a large extent in the π bonds: the isodensity lines form contours of the 2p and 3p orbitals on the electron-deficient C and the electron-rich O and S.

Solvent Effect. The effect of a dielectric continuum on the transition states for nucleophilic additions to cyclohexanone has been examined using the Onsager reaction field model as incorporated recently into *ab initio* theory using a spherical cavity for the solute^{18a} and applied in the studies of solvent effects on the transition states for nucleophilic additions to substituted acetaldehydes.^{18b} The results of reoptimizations of the transition structures for the cyanide additions in a polar solvent are consistent with the trends observed so far. Both transition structures are slightly more advanced in the solvent, cf. entries 33 and 34, Table 1.

(18) (a) Wong, M. W.; Frisch, M.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (b) Cieplak, A. S.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 9226.

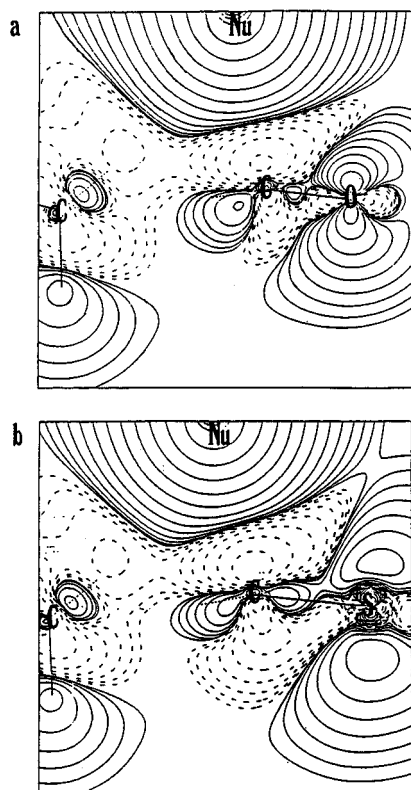


Figure 7. Electron density shifts upon approach of a nucleophile to: (a) cyclohexanone (axial approach of the acetylide ion, the C(1)···C(7) distance of 2.7 Å); and (b) cyclohexanethione (transition-state structure for the axial addition of the fluoroacetylide ion). In both cases, the ρ function is plotted in the C_s plane of the fragment, x size: 10.0 B, x increment: 0.1 B; y size: 10.0 B, y increment: 0.1 B; outermost contour = 10^{-4} e/B³, each successive contour represents a factor of 2.0 increase.

Discussion

Stereoelectronic Control Is Most Effective in the Mid-Region of the Reaction Coordinate. The puzzle of the stereochemistry of addition to cyclohexanones is often defined in terms of the reagent's size: small nucleophiles prefer axial attack, the bulky ones prefer equatorial attack. Consequently, there is a tendency to attribute the effects such as the opposite face preferences of *n*-hexyllithium (75% equatorial)^{19a} and (perfluoro-*n*-hexyl)lithium (85% axial)^{19b} to the differences in the steric demand related to the degree of oligomerization. Our calculations suggest, however, that a change in electronegativity of the nucleophile's substitution may be sufficient to reverse its face preference. For instance, $H_3B-C\equiv C^-$ prefers the equatorial approach to cyclohexanethione by ~ 1.5 kcal mol⁻¹, while $FC\equiv C^-$ prefers the axial approach by ~ 2.0 kcal mol⁻¹. In general, the predicted relationship is parabolic: in a series of isosteric nucleophiles, the decrease in basicity is expected to increase the axial preference for the most reactive ones and to increase the equatorial preference for the least reactive ones. Thus, while our results support the notion that the basicity of the nucleophile plays a major role in π -face selection, we have to abandon the original hypothesis that the Hammett relationship should be linear.

Does the new model fare better in rationalization of the experimental results? The patterns of stereoselection in organometallic alkylations are shown in Tables 2 and 3. Table 2 lists the results of alkylations of 4-*tert*-butylcyclohexanone with the carbanions stabilized by sulfur, carbonyl, cyano group, etc., i.e., with pK_a 's of the conjugated carbon acid < 35 . Since metal bonding in these reagents is highly ionic (metal bonded to heteroatom²⁰), pK_a 's of the conjugated carbon acids should be an adequate measure of nucleophilicity of such reagents. The data in Table 2a (primary carbanions) suggest that in the nonsolvating media (the first column, ethers and hydrocarbons, alkali metals, cerium, magnesium, zinc, and iron halides as counterions), the dependence of face selection on pK_a is parabolic with the maximum at $pK_a \approx 31.3$. In the cation-solvating media (the second column, liquid NH_3 , HMPT, and DMSO, neat or used as a cosolvent), reactivity of the stabilized carbanions increases due to depolymerization or extrusion from the aggregate nucleus.^{20c} One would expect then the shift of the maximum toward lower pK_a values, but the position of this maximum and even its existence are uncertain because of the conflicting results for the least basic nucleophiles.²¹ In the series of secondary anions (Table 2b, liquid NH_3 , Na^+), a maximum was obtained for the ester derivatives: in the series of the tertiary anions it apparently shifted to the higher pK_a values. In the series of the cyclic tertiary anions (Table 2c, liquid NH_3 , Na^+), the results also suggest a parabolic dependence, assuming that the pK_a values reflect the ring-size effect on the delocalization of the unshared electron pair.²²

Table 3 lists relative yields of the axial approach for the organometallic reagents containing alkyl and aryl groups with pK_a 's of the conjugated carbon acids > 40 (for the sake of comparison, metal salts of acetonitrile are also included). For want of a better measure of nucleophilicity of the carbon-metal bonds, the reagents are listed according to the Pauling electronegativity of the metals. To gauge the effect of nucleophilicity of the σ_{C-M} bonds in the methylmetal alkylations (the first column), it is crucial to separate the roles of the metal as the electron donor (activating the nucleophile) and the electron acceptor (activating the carbonyl). Therefore, all the methylmetal reactions included involve dimers or occur in the presence of Lewis acid catalysts. The alkylations by methylmetalates (the second column) occur in the presence of Li^+ as the counterion. These data suggest that the relationship between the axial preference and the ionicity of the C-M bond is parabolic. The third column lists methylmetals with the halogen (left) or oxygen (right) substituents on the metal; the observed change in the face preference might be related to the decrease

(20) (a) Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501. (b) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(21) The ρ values for the $(CH_3)_2S^+CH_2^-$ and $(CH_3)_2S(=O)^+CH_2^-$ additions to 4-substituted cyclohexanones (Migneco, L. M.; Vecchi, E. *Gazz. Chim. Ital.* **1997**, *127*, 19) suggest that in the case of equatorial TS's, the one for the $(CH_3)_2S(=O)^+CH_2^-$ addition is more advanced, but the order of progression is opposite in the case of axial TS's. This may be due to the increased steric strain during axial addition of the reagents with tetracoordinated S caused by the *trans*-orientation requirement for O and S. For the same reason, the epoxide would form exclusively via equatorial attack of $(CH_3)_2S(=O)^+CH_2^-$ if the first addition step was reversible.

(22) Cf. the corresponding delocalization in enamines (Table 7 in ref 4a) and the barriers to inversion in cyclic amines: Cieplak, A. S. *Struct. Chem.* **1994**, *5*, 89.

(19) (a) Ashby, E. C.; Laemmle, J. T. *J. Org. Chem.* **1975**, *40*, 1469. (b) Uno, H.; Okada, S.; Ono, T.; Shiraishi, Y.; Suzuki, H. *J. Org. Chem.* **1992**, *57*, 1504.

Table 2. Relative Yield of the Axial Approach in Alkylations of 4-*tert*-Butylcyclohexanone by Sulfur, Carbonyl, Thiocarbonyl, Nitro, and Cyano Group-Stabilized Carbanions and pK_a of the Conjugated Acid

| (a) | ZCH ₃ | p <i>K</i> _a ^a | solvent DN ^b < 20 | solvent DN > 25 | |
|-----|---|--------------------------------------|--|---|-----------------------------------|
| | C ₆ H ₅ SeCH ₃ | | 0 ^e | | |
| | C ₆ H ₅ SCH ₃ | 37.0 ^c | 17, ^f 20 ^g | | |
| | LiOC(=O)CH ₃ | | 30, 41 ^h | | |
| | (CH ₃) ₂ NC(=O)CH ₃ | | 35 ^h | 45 ^h | |
| | (C ₂ H ₅) ₂ NC(=O)CH ₃ | 34.5 | 38, 58, 45 ^h | 68 ^h | |
| | C ₆ H ₅ S(=O)(=NCH ₃)CH ₃ | 33.0 | 60 ⁱ | | |
| | CH ₆ H ₅ S(=NTs)CH ₃ | 31.7 ^c | | 33, ^s 50 ^t | |
| | N≡CCH ₃ | 31.3 | 84, ^j 80, 85 ^k | 65, ^h 71, ^u 72 ^h | |
| | | | 85, ^k 65, ^h 75, ^k 84 ^j | | |
| | | | 66, ^l 64, ^j 67, ^h 71 ^j | | |
| | (CH ₃) ₂ NS(=O) ₂ CH ₃ | 31.1 ^d | 62, 62, 61, ^m 65 ⁿ | 62 ^m | |
| | | | 28, 32 ⁿ | | |
| | (CH ₃) ₃ SiOC(=O)CH ₃ | | 56, 72 ^h | | |
| | C ₂ H ₅ OC(=O)CH ₃ | 30.5 | 37, 43 ^h | 54, 67, 68 ^h | |
| | | | | 69, 69 ^h | |
| | (CH ₃) ₃ COC(=O)CH ₃ | | 4, 10, 15 ^o | 81, ^o 82 ^{o,v} | |
| | | | 25, 40, 53 ^o | | |
| | C ₆ H ₅ S(=O)(=NTs)CH ₃ | 27.7 | | 0 ^t | |
| | (CH ₃) ₃ CC(=O)CH ₃ | 26.5 | 5 ^p | | |
| | | | 20, 21 ^q | | |
| | (CH ₃) ₂ NC(=S)CH ₃ | 25.7 | 25 ^r | | |
| | (CH ₃) ₂ S ⁺ CH ₃ | 18.2 | | 45, ⁱ 55, ^w 83 ^x | |
| | | | | 67, 65, 62 ^z | |
| | O ₂ NCH ₃ | 17.2 | | ~90 ^z | |
| | (CH ₃) ₂ S ⁺ (=O)CH ₃ | | | 0, ^x 14, 10, 8 ^y | |
| | C ₆ H ₅ ((CH ₃) ₂ N)S ⁺ (=O)CH ₃ | 14.4 | | 0 ^{aa} | |
| (b) | ZCHRR' | p <i>K</i> _a ^a | C ₆ H ₅ , H | CH ₃ , H | CH ₃ , CH ₃ |
| | (CH ₂) ₄ NC(=O)– | 26.6 ^{bb} | 25 ^u | 53 | 100 |
| | (CH ₃) ₃ COC(=O)– | 23.6 | 46 | 59 | 59 |
| | N≡C– | 21.9 | 17 | 33 | 0 |
| (c) | (CH ₂) _n CH–Z | p <i>K</i> _a ^a | –C(=O)OC(CH ₃) ₃ | –C≡N | |
| | 2 | 28.2 ^{bb} | | 23 | |
| | 5 | | 46 ^u | 100 | |
| | CH ₃ , CH ₃ | 26.2 | 59 | 0 | |
| | 4 | | 36 | 0 | |

^a In DMSO: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. ^b DN is Gutmann's donor number of a solvent or cosolvent: Gutmann, V. *The Donor–Acceptor Approach to Molecular Interactions*, Plenum Press: New York, 1978; pp 19–21. ^c In DMSO: estimated assuming ΔpK_a S(=O) 4.0, cf. footnote a. ^d In DMSO: pK_a of CH₃S(=O)₂CH₃. ^e Uemura, S.; Ohe, K.; Sugita, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1697. ^f Hannaby, M.; Warren, S. *Tetrahedron Lett.* **1985**, *26*, 3133. ^g Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424. ^h Bellasoued, M.; Dardoize, F.; Gaudemar-Bardone, F.; Gaudemar, M.; Goasdoue, N. *Tetrahedron* **1976**, *32*, 2713. ⁱ Extrapolated: Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447; Table 1. ^j Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. ^k Idriss, N.; Perry, M.; Maroni-Barnaud, Y.; Roux-Schmitt, M.-C.; Seyden-Penne, J. *J. Chem. Res., Synop.* **1978**, 128. ^l Lin, H.-J.; Al-said, N. H. *Tetrahedron Lett.* **1991**, *32*, 5473. ^m Mladenova, M.; Gaudemar-Bardone, F. *Phosphorus, Sulfur Silicon* **1990**, *47*, 191. ⁿ Stanchev, S.; Christov, R.; Simova, S.; Mladenova, M.; Linden, A. *Phosphorus, Sulfur Silicon* **1995**, *104*, 123. ^o Idriss, N.; Perry, M.; Maroni-Barnaud, Y. *Tetrahedron Lett.* **1973**, 4447. ^p Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302. ^q Koudsi, Y.; Maroni-Barnaud, Y. *Tetrahedron Lett.* **1973**, 4451. ^r Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1981**, *208*, 279. ^s Tamura, Y.; Matsushima, H.; Ikeda, M.; Sumoto, K. *Synthesis* **1976**, 35. ^t Johnson, C. R.; Mori, K.; Nakamishi, A. *J. Org. Chem.* **1979**, *44*, 2065. ^u Dobrev, A.; Ivanov, Ch.; Lattes, A.; Bon, M. *Bull. Soc. Chim. Fr.* **1987**, 1084. ^v Pansard, J.; Gaudemar, M. *C. R. Acad. Sci.* **1970**, *271C*, 159. ^w Davies, R.; Kluge, A. F.; Maddox, M. L.; Sparacino, M. L. *J. Org. Chem.* **1983**, *48*, 255. ^x Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. ^y Migneco, L. M.; Vecchi, E. *Gazz. Chim. Ital.* **1997**, *127*, 19. ^z Favre, H.; Gravel, D. *Can. J. Chem.* **1961**, *39*, 1548. ^{aa} Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. ^{bb} pK_a values in part b of the table are those for R = C₆H₅, R' = H; the *N,N*-diethylamide pK_a is used for acylpyrrolidines; in part c, pK_a values for the corresponding phenyl ketones.

in reactivity. The π -face selectivity of the allylmetal reagents (the fourth column), save the allyl alkali metal and the allylboron entries, still conforms to the picture of the parabolic dependence, although these reagents are quite diverse in terms of the C–M bonding, solution structure, and properties of the metal ligands. When the C–M bonds are more ionic, cf. phenylmetals (the fifth column) the differences in electronegativity of the metal are less important.

The stereochemistry of the metal hydride additions also seems related to the nucleophilicity of the σ_{M-H} bonds. The best such evidence comes from the alkoxyborohydride reductions of cyclohexanones. Here, the nucleophilicity of the B–H bond should depend on the extent of the O-back-donation, which can be assumed to

correlate with the B–O bond order and, therefore, with the B–O stretching frequencies. As shown in Table 4, the relative yield of the axial reduction generally increases with the decrease in the B–O bond order, but when the range of the substituents is sufficiently wide (i.e., C₆F₅O is included), or the reaction is slower (e.g., with HMgOR or with 3,3,5-trimethylcyclohexanone), the parabolic dependence is revealed.

Thus, the experimental evidence supports the *ab initio* model and suggests that the original hypothesis⁴ fails to account for the stereochemistry of additions of the least basic reagents because of the limitations of its premises and not because the effect of the basicity of the nucleophile is obscured in solution by other factors. In fact,

Table 3. Relative Yield of the Axial Approach in Organometallic Alkylations of 4-*tert*-Butylcyclohexanone and Pauling Electronegativities of Metals

| M | χ^a | (CH ₃) _n M | CH ₃ ML _n ⁻ | CH ₃ ML _n | (C ₃ H ₅)ML _n | C ₆ H ₅ ML _n | (CH ₂ CN)ML _n |
|----|----------|---|---|--|--|---|--|
| K | 0.82 | | | | 63 ^v | | 84, ^{ll} 80 ^{mm} |
| Na | 0.93 | | | | 65 ^v | | 85 ^{mm} |
| Li | 0.98 | 6, ^b 8 ^c 16, ^d 21 ^b 35 ^e | | | 65 ^v | 42 ⁱⁱ | 65, ⁿⁿ 71 ^{oo} 75, ^{mm} 84 ^{ll} |
| Ce | 1.12 | | 29, 29 ^k | 33 ^m 42 ^m | | 40, ^m 42 ^k 44, 50 ^k 50, ^m 61 ^k | 66 ^{pp} |
| Sm | 1.17 | | | 30 ⁿ 18 ^o | 13, ^w 50 ^x | | |
| Yb | | | | | | | |
| Mg | 1.31 | 35, ^f 41 ^e | 31 ^l | 41 ^q 21 ^p 44 ^q 24 ^q 47 ^{e,i,r,s} 47 ^q | 55, ^v 56 ^y | 15, 27 ^{jj} 51 ^s | 64 ^{ll} |
| Zr | 1.33 | | | 20 ^t | | | |
| Ti | 1.54 | 62 ^g | 67 ^g | 18 ^g 6 ^g 24 ^g 14 ^{g,u} 19 ^k 8 ^k | 77, 80 ^z 57 ^z 31, 43 ^{aa} 32 ^v | 50 ^{kk} 47, 50 ^k 73, 92 ^h 56 ^h | |
| Mn | 1.55 | | | | | | |
| Al | 1.61 | 83, 88 ^h | 69, 82 ^j 58 ^l 36 ^j | | 15, ^{v,bb} 16 ^y 23 ^v 12, 19 ^{cc} 22 ^{y,dd} 18 ^{ee} | | 67, 72 ⁿⁿ 71 ^{ll} |
| Zn | 1.65 | 54 ⁱ 62 ⁱ | | | | | |
| Cr | 1.66 | | | | | | |
| Cd | 1.69 | 48, 59 ⁱ | | | | | |
| In | 1.78 | | | | | | |
| Fe | 1.83 | 1 ^j | | | | 7, 18 ^j | |
| Cu | 1.90 | 32 ^d | | | | | |
| Si | 1.90 | | | | 13 ^{ff} | | |
| Sn | 1.96 | | | | 8, 15 ^{gg} | | |
| B | 2.04 | | 30 ^l | | 45 ^{hh} | | |

^a Huheey, J. E. *Inorganic Chemistry*, 2nd ed.; Harper & Row: New York, 1978; p 162. ^b Macdonald, T. L.; Clark Still, W. J. *J. Am. Chem. Soc.* **1975**, *97*, 5280. ^c Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. ^d Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. ^e Houlihan, W. J. *J. Org. Chem.* **1962**, *27*, 3860. ^f House, H. O.; Respass, W. J. *J. Org. Chem.* **1965**, *30*, 301. ^g Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. ^h Laemmle, J. T.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526. ⁱ Jones, P. R.; Goller, E. J.; Kauffman, W. J. *J. Org. Chem.* **1969**, *34*, 3566. ^j Reetz, M. T.; Stanchev, S. *J. Chem. Soc., Chem. Commun.* **1993**, 328. ^k Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **1992**, *33*, 6963. ^l Ashby, E. C.; Chao, L.-C.; Laemmle, J. T. *J. Org. Chem.* **1974**, *39*, 3258. ^m Greeves, N.; Lyford, L.; Pease, J. E. *Tetrahedron Lett.* **1994**, *35*, 285. ⁿ Curran, D. P.; Tottleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050. ^o Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990. ^p Warkentin, J. *Can. J. Chem.* **1970**, *48*, 1391. ^q Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. ^r Ficini, J.; Maujean, A. *Bull. Soc. Chim. Fr.* **1971**, 219. ^s Meakins, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* **1968**, 1106. ^t Weidman, B.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1552. ^u Weidman, B.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2451. ^v Gaudemar, M. *Tetrahedron* **1976**, *32*, 1689. ^w Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. ^x Collin, J.; Bied, C.; Kagan, H. B. *Tetrahedron Lett.* **1991**, *32*, 629. ^y Abenham, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* **1969**, 4038. ^z Reetz, M. T.; Steibach, R.; Westerman, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. ^{aa} Hiyama, T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237. ^{bb} Shono, T.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, 449. ^{cc} Okuda, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. ^{dd} Hiyama, T.; Obayashi, M.; Nakamura, A. *Organometallics* **1982**, *1*, 1249. ^{ee} Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1833. ^{ff} Kawai, M.; Onaka, M.; Izumu, Y. *Chem. Lett.* **1986**, 381. ^{gg} Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979**, 919. ^{hh} Kramer, G. W.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2292. ⁱⁱ Mertens, M. P.; Ramsey, A. A.; Hama, P. E.; Miller, D. D. *J. Med. Chem.* **1970**, *13*, 789. ^{jj} Reetz, M. T.; Harmat, N.; Mahrwald, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 342. ^{kk} Weidmann, B.; Widler, L.; Oliver, A. G.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357. ^{ll} Trost, B. M.; Flores, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. ^{mm} Idris, N.; Perry, M.; Maroni-Barnaud, Y.; Roux-Schmitt, M.-C.; Seyden-Penne, J. *J. Chem. Res., Synop.* **1978**, 128. ⁿⁿ Bellasoued, M.; Dardoize, F.; Gaudemar-Bardone, F.; Gaudemar, M.; Goasdoue, N. *Tetrahedron* **1976**, *32*, 2713. ^{oo} Dobrev, A.; Ivanov, Ch.; Lattes, A.; Bon, M. *Bull. Soc. Chim. Fr.* **1987**, 1084. ^{pp} Lin, H.-J.; Al-said, N. H. *Tetrahedron Lett.* **1991**, *32*, 5473.

the basicity appears to be at least as important as the nucleophile's steric demand, cf. Table 2b,c.

The observed parabolic relationship between π -face selection and nucleophile basicity hints at the origin of the stereoelectronic effect. This effect is largest for the moderately basic nucleophiles, i.e., in the mid-region of the reaction coordinate. To understand its nature, we need to understand what happens there in terms of the interactions between the incipient bond and the C(2) and C(6) methylene groups; in particular, what brings about the flattening of the chair that occurs in this region regardless of the direction of the nucleophile approach.

Ring Flattening in the Mid-Region of the Reaction Coordinate Is Driven by Hyperconjugation. The rotation of the cyclohexanone ring was first observed in the transition structures for the LiH addition, which are relatively late.^{12a} It was proposed that the folding

(an increase in ω_2) and flattening (a decrease in ω_2) occur to release the strain due to the eclipsing of the incipient bond by the C–H and C–C bonds at C(2) and C(6). There are several reasons, however, to suggest that the interactions of the incipient bond and the C(2) and C(6) methylene groups are dominated by the C–H hyperconjugation and that the rotation about the C(1)–C(2) and C(1)–C(6) bonds occurs in the mid-region of the reaction coordinate to improve the overlap of the C–H bonds with the reaction site.

(1) The addition site is considerably electron deficient in this region (more so than in the reactants or in the less and more advanced transition states), and the distortions of the C(2) and C(6) bond angles and bond distances, maximized here,²³ are identical to the structural manifestation of hyperconjugation in carbonium

Table 4. Relative Yield of the Axial Approach in Reductions of Cyclohexanones by Alkoxy-metal Hydrides and the Metal–Oxygen Bond Order

| R | ν_{BO}^a (cm ⁻¹) | 4- <i>tert</i> -butylcyclohexanone | | | | KB(OR) ₃ H ^a | | | |
|---|---|-------------------------------------|--------------------------|--------------------------------------|--------------------|------------------------------------|-----------------------|-----------------------|------------------------------|
| | | KB-(OR) ₃ H ^a | LiAl-(OR) ₃ H | LiMg-(OR)H ₂ ^e | HMgOR ^f | 4-methylcyclohexanone | 3-methylcyclohexanone | 2-methylcyclohexanone | 3,3,5-trimethylcyclohexanone |
| <i>sec</i> -C ₄ H ₉ – | 1385 | 29.5 | | | | 30.0 | 17.5 | 7.0 | 2.5 ^g |
| (CH ₃) ₂ CH– | 1375 | 47.0 | | 30 | 85 | 33.5 | 26.0 | 9.0 | 4.5 |
| (CH ₃) ₃ C– | 1365 | 66.0 | 90 ^c | 41 | 31 | 67.0 | 54.0 | 38.0 | 12.5 |
| (CH ₂) ₄ CH– | 1365 | 77.0 | | | | 72.5 | 66.5 | 60.5 | 29.5 |
| C ₆ H ₅ – | 1330 | 85.0 | 93 ^d | 72 | 24 | 85.0 | 79.0 | 65.0 | 19.0 |
| <i>p</i> -ClC ₆ H ₄ – | | | 92 ^d | | | | | | |
| C ₆ F ₅ – | | 0.0 ^b | | | | | | | |

^a Brown, H. C.; Cha, J. S.; Nazer, B. *Inorg. Chem.* **1984**, *23*, 2929. ^b Na⁺ salt: Fuller, J. C.; Karpinski, M. L.; Williamson, S. M.; Singaram, B. *J. Fluorine Chem.* **1994**, *66*, 123. ^c Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. LiAl(OCH₃)₃H: 59% axial approach. ^d Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. ^e Ashby, E. C.; Noding, S. A.; Goel, A. B. *J. Org. Chem.* **1980**, *45*, 1028. LiMg(OCH₃)H₂: 40% axial approach. ^f Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1560. HMgOCH₃: 24% axial approach. ^g For the LiAl(OR)₃H reductions of 3,3,5-trimethylcyclohexanone see: Houbenstock, H.; Eliel, E. L. *J. Am. Chem. Soc.* **1962**, *84*, 2363.

ions,²⁴ ketones,²⁵ and boranes.²⁶ These distortions are consistent with the sp³ → sp² rehybridization of C(2) and C(6).

(2) The interaction with the reaction site is stabilizing, i.e., hyperconjugative, since it leads to the eclipsing about the C(1)–C(2) and C(1)–C(6) bonds during the equatorial approach, when the ring flattens.

(3) The NBO analysis of the B3LYP/6-31G* transition structures for the LiH addition to cyclohexanone suggests that the electron population of the incipient bond orbital is very low,^{12b} so the strain due to the eclipsing of this bond is unlikely to be significant. Indeed, there is no indication (e.g., increased α_5 angle) of any repulsion between the incipient bond and the eclipsing C–H bonds in the structures examined in our study.

(4) The presence of the nucleophile is not necessary for the flattening and folding of the ring to occur since the same distortions are found in the cyclohexyl cation.²⁷

Consequently, the variation in the ω_2 angle in Figure 2 can be explained as follows. During the axial approach, the flattening of the ring is driven by the C–H hyperconjugation (improved overlap), which is countered by the increase in the ring strain (bond angle and eclipsing strain). The ring is most flattened when the C(1) is most electron deficient. During the equatorial approach, the folding of the ring is driven by the C–C hyperconjugation and by the decrease in the ring strain (return to the cyclohexane bond angles and nearly perfect staggering). However, when the C(1) is more electron-deficient, as in the mid-region of the reaction coordinate, those two factors and the strain of the ring flattening are offset by the advantage of the C–H hyperconjugation.

The last point is consistent with the C–H > C–C order of the electron-donor ability found whenever the inductive and hyperconjugative effects of the alkyl groups are

effectively separated, either (1) by comparing the charge distribution and stability of rotamers in which the C–H and C–C bonds compete to interact with an electron acceptor (cf. high-level examination of the C₃H₇⁺ potential energy surface,^{24b} and the study of the *tert*-pentyl cation,^{24c,28} ESR data on conformations of the ethyl- and isopropylbenzene radical cations,²⁹ structure correlation analysis of the isopropyl rotation in carbonyls,²⁵ the effect of Lewis acid complexation on the conformational preferences of the β -alkyl groups in α,β -unsaturated aldehydes and esters,³⁰ and the data on spectroscopy and conformational equilibria of cyclohexyl derivatives where the electron acceptors are σ bonds^{4,31}), or (2) by comparing the distribution of charge in the alkyl-substituted π -acceptors where the alkyl donor and the probe acceptor sites are separated by an aromatic nucleus (cf. NMR studies of 2-alkylindenes,^{32a} *p*-alkylbenzyl cations,^{32b} and *p*-alkyl- α,α -difluorostyrenes^{32c}).

Electronegative Substitution Can Slow Down Nucleophilic Addition to Carbonyls. The finding that the electron demand at the reaction site considerably changes along the reaction coordinate, and at some point actually exceeds that of the reactant, implies that the Hammett ρ constants correlate with the nucleophile reactivity and may reach negative values. The latter claim contradicts the widely held belief that the electron-withdrawing groups always accelerate nucleophilic additions to carbonyls. There is, however, some evidence to support this claim. Thus, the α -OR substitution of carbonyls was reported to slow down (CH₃)₂Mg and CH₃–

(23) Coxon was first to point out that the elongation of the vicinal bonds which are antiperiplanar to the incipient bond suggests hyperconjugation, see: Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651. Coxon, J. M.; Luihrand, R. T. *Tetrahedron Lett.* **1993**, *34*, 7097. Coxon, J. M.; Houk, K. N.; Luihrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.

(24) (a) Schleyer, P. v. R.; Koch, W.; Liu, B.; Fleischer, U. *J. Chem. Soc., Chem. Commun.* **1989**, 1098. (b) Koch, W.; Liu, B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 3479. (c) Schleyer, P. v. R.; de M. Carneiro, J. W.; Koch, W.; Forsyth, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 3990.

(25) Laube, T.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 5511.

(26) Boese, R.; Blaesser, D.; Niederpruem, N.; Nuesse, M.; Brett, W. A.; Schleyer, P. v. R.; Buehl, M.; van Eikema Hommes, N. J. R. *Angew. Chem.* **1992**, *104*, 356.

(27) Rauk, A.; Sorensen, T. S.; Maerker, C.; de M. Carneiro, J. W.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1996**, *118*, 3761.

(28) Consider the conformers of the classical 1-propyl **1** and 2-(2-methylbutyl) **2** cation (A) CH₃ out-of-plane of the cation and (B) CH₃ in the plane of the cation. At the MP2/6-311G** and MP4(fc)/6-311G** (including ZP vibrational energies from the MP2 frequencies) levels, see ref 24b, the more sterically strained conformer **B** has lower energy than the strain-free conformer **A** in **1**, while in **2** the two conformers have the same energy. In a recent review (Gung, B. W. *Tetrahedron* **1996**, *52*, 5263), the results for **1** are mistakenly attributed to Houk et al., and the order of stability of **A** and **B** related by Gung (*op. cit.*), and Houk (in ref 12a) is opposite to that given in ref 24b.

(29) Ramakrishna Rao, D. N.; Chandra, H.; Symons, M. C. R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1201. Boon, P. J.; Harris, L.; Olm, M. T.; Wyatt, J. L.; Symons, M. C. R. *Chem. Phys. Lett.* **1984**, *106*, 408.

(30) Gung, B. W.; Yanik, M. *J. Org. Chem.* **1996**, *61*, 947.

(31) Kirby, A.; Williams, N. H. *J. Chem. Soc., Chem. Commun.* **1992**, 1285. Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 627.

(32) (a) Edlund, U. *Org. Magn. Reson.* **1978**, *11*, 516. (b) Brown, H. C.; Periasamy, M.; Perumal, P. T. *J. Org. Chem.* **1984**, *49*, 2754. (c) Coney, B. T.; Happer, D. A. R. *Aust. J. Chem.* **1987**, *40*, 1537.

Ti(*i*-Pr)₃ additions in the absence of chelation,³³ and the β -COOEt group was found to accelerate the equatorial addition of (CH₃)₂Zn to 2-decalone ($k_{\text{COOEt}}/k_{\text{H}} = 7.2$) but to have no effect on CH₃Li ($k_{\text{COOEt}}/k_{\text{H}} = 1.0, 1.1$) and to slow down the addition of CH₃Li/(CH₃)₂CuLi ($k_{\text{COOEt}}/k_{\text{H}} = 0.6$).³⁴ The expected positive Hammett ρ constants were found for the reactions of lithium enolate of pinacolone with ketones.³⁵ As for the metal hydride additions, the α -OCH₃ group was recently reported to slow down LiAlH₄ reduction of cyclohexanone.³⁶ This is consistent with the earlier observations that β -F and Cl slow down the equatorial reduction by LiAl(O-*t*-Bu)₃H,³⁷ while β, β' -CH₃'s accelerate the equatorial LiAlH₄ reduction.³⁸ No such anomalies were reported for the NaBH₄ reductions.

The studies of the secondary kinetic isotope effect in nucleophilic additions to carbonyls also support the conclusion that the reaction site of a nucleophilic addition can be more electron-deficient than the reactant carbonyl. The C–D bonds are poorer hyperconjugative donors than the C–H bonds. Consequently, reactions with the negative or very small ρ (electron-deficient TS) should display normal KIE in additions to cyclohexanones-2,2,6,6-*d*₄ (β -deuterium kinetic isotope effect), and the ones with the greater positive ρ (electron-rich TS) should display inverse KIE. A trend consistent with this prediction is indeed apparent in the available data (KIE's NH₂OH 1.054, 1.048; SO₃²⁻ 0.918; BH₄⁻ 0.890, 0.883;³⁹ and the ρ values reported for the additions to aromatic carbonyls: NH₂OH 0.32, SO₃²⁻ 1.27, BH₄⁻ 2.81, 3.06⁴⁰).

Conclusions

The computational and experimental evidence suggest that the basicity of the nucleophile plays a major role in π -face selection in nucleophilic addition to carbonyls. For the additions of the substituted acetylide ions to cyclohexanone and cyclohexanethione, the *ab initio* predicted dependence is parabolic; that is, the highest axial preference is displayed by the moderately basic ions, whose transition structures are located in the mid region of the reaction coordinate. Due to the charge polarization of the carbonyl by the approaching nucleophile, these

transition structures are considerably electron deficient at the carbonyl reaction site (more so than the reactants or the less and more advanced transition states), and the interactions between their incipient bonds and the adjacent methylene groups are dominated by the C–H and C–C hyperconjugation.

Thus, the stereoelectronic effect that promotes the axial approach in these additions appears to result from the stabilization of the electron-deficient reaction site by the $\sigma_{\text{C-H}}$ hyperconjugation. Indeed, the axial preferences are for the most part greater in the additions to cyclohexanone than to cyclohexanethione; the reaction site is more electron deficient (the incipient bond more ionic) in the case of the more polarized electrophile (C=O) and, thereby, more sensitive to the advantage of the $\sigma_{\text{C-H}}$ hyperconjugation.

These findings are consistent with the hypothesis that the stereochemistry of nucleophilic additions to cyclohexanone results from the competition between the steric strain and hyperconjugative assistance to bond formation;⁴ the latter promotes the axial approach because the $\sigma_{\text{C-H}}$, $\sigma^*_{\text{C-H}}$ hyperconjugation is more effective than the $\sigma_{\text{C-C}}$, $\sigma^*_{\text{C-C}}$ hyperconjugation. In contrast, it seems difficult to explain the parabolic relationship between the basicity of the nucleophile and π -face selection using the hypotheses of the $\sigma_{\text{C-H}}$, $\sigma^*_{\text{C-H}}$ and $\sigma_{\text{C-H}}$, $\sigma^*_{\text{C-H}}$ repulsion⁴¹ or the $\sigma_{\text{C-H}}$, $\sigma^*_{\text{C-H}}$ and $\sigma_{\text{C-H}}$, $\sigma^*_{\text{C-H}}$ donation.⁴² A highly ionic incipient bond cannot be effectively involved in such interactions,^{12b} and indeed, there is no structural evidence of either one along the reaction path. Similarly, there seems to be no simple way to explain the parabolic dependence using the hypothesis of the ground-state distortions of the C_{2v} symmetry of the carbonyl charge density.⁴³ This hypothesis is a legacy of discussing chemical reactivity of molecular systems in terms of wavefunctions of the reactants in their isolated states. It appears now that nucleophilic addition to carbonyls cannot be adequately described in such a way.

Acknowledgment. The author thanks Prof. K. B. Wiberg for granting access to the computer facilities at Yale and for numerous invaluable comments and suggestions. This investigation was supported in part by the NIH grant to Prof. Wiberg.

Supporting Information Available: Gaussian-92 and -93 archive entries are listed for the representative structures (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9713722

(33) Eliel, E. L.; Frye, S. V.; Hortelano, E. R.; Chen, X.; Bai, X. *Pure Appl. Chem.* **1991**, *63*, 1591. Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(34) Di Maio, G.; Li, W.; Migneco, L.; Vecchi, E. *Tetrahedron* **1986**, *42*, 4837.

(35) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302.

(36) Senda, Y.; Sakurai, H.; Nakano, S.; Itoh, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3297. Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1009.

(37) Calvet, A.; Levisalles, J. *Tetrahedron Lett.* **1972**, 2157. Agami, C.; Kazakos, A.; Levisalles, J.; Sevin, A. *Tetrahedron* **1980**, *36*, 2977.

(38) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411.

(39) Geneste, P.; Lamaty, G. *Bull. Soc. Chim. Fr.* **1968**, 669. Geneste, P.; Lamaty, G.; Roque, J.-P. *Tetrahedron* **1971**, *27*, 5539 and 5561. Geneste, P.; Lamaty, G.; Moreau, C.; Roque, J.-P. *Tetrahedron Lett.* **1970**, 5011.

(40) Geneste, P.; Lamaty, G.; Roque, J.-P. *Tetrahedron Lett.* **1970**, 5007.

(41) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

(42) Huet, J.; Maroni-Barnaud, Y.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159.

(43) Klein, J. *Tetrahedron Lett.* **1973**, 4307. Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146. Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017. Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614. Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057.