Theoretical Studies of Stereoselective Aldol Condensations

Cesare Gennari,*† Roberto Todeschini,*‡ Maria G. Beretta,† Giorgio Favini,‡ and Carlo Scolastico†

Dipartimento di Chimica Organica e Industriale, Centro CNR Sostanze Organiche Naturali, and Dipartimento di Chimica Fisica ed Elettrochimica, Universita' di Milano, 20133 Milano, Italy

Received September 23, 1985

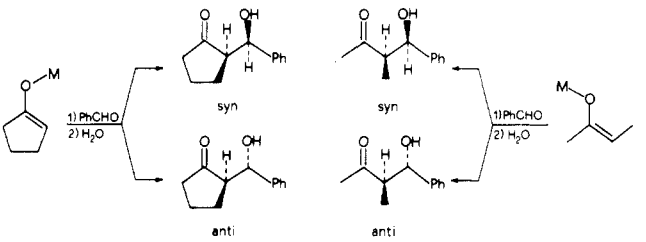
MNDO calculations were performed so as to shed new light on the structure-selectivity data of the aldol condensation process. Three simple cases were chosen for the calculations: the addition to benzaldehyde of the cyclopentanone boron–enolates (both the enol borate and the enol borinate) and of the butanone *Z* boron–enolate (enol borate). The conformations of the starting boron–enolates were found to be s-cis for the (*E*)-enolate and s-trans for the (*Z*)-enolate. Different activation energies during the aldol reaction account for the different reactivity of (*E*)- and (*Z*)-enol borates (*E* compounds are much more reactive than *Z* ones). Transition-state models were designed to account for the kinetic preference shown by the aldol reaction. The calculation data were found to be in good agreement with the experimental results. Starting from (*Z*)-enolates, the half-chair leading to the syn aldol is preferred to both the twist-boat and the half-chair leading to the anti aldol. Starting from (*E*)-enolates, syn aldols are kinetically preferred to anti aldols, in the absence of disturbing steric factors, as in the case of (*E*)-enol borates. The opposite behavior ((*E*)-enolates give anti aldols) is encountered when bulky substituents at the metal disfavor the twist-boat leading to the syn isomer, as in the case of enol borinates.

Several types of transition-state models have been proposed to explain the stereochemical outcome of various aldol addition processes.[1] The most popular has been the pericyclic transition state first proposed by Zimmerman and Traxler,[2] which accounts for much of the structure-selectivity data that are available for lithium–, magnesium–, and zinc–enolates. Chair, idealized transition states correlate the (*Z*)-enolate geometry to syn aldol stereochemistry and the (*E*)-enolate geometry to anti aldol stereochemistry. The idealized chairlike transition states do not explain the observation that (*Z*)-enolates are significantly more stereoselective than (*E*)-enolates,[1] particularly those of cyclopentanone[3] and cyclohexanone.[4,7a] Skewed transition states have been proposed to explain the minor selectivity of the (*E*)-enolates.[1] Both the idealized and the skewed chairlike transition states do not account for the fact that tin–,[5] zirconium–,[6] and titanium–enolates[7] are syn selective, independent of the enolate geometry. The syn selectivity of these enolates has been tentatively explained by using boatlike transition states.[6a,7a] Boron–enolates are even more puzzling: while (alkenyloxy)dialkylboranes (enol borinates) conform strictly to the "Zimmerman rules" (*Z* gives syn, *E* gives anti),[4] (alkenyloxy)dialkoxyboranes (enol borates) are stereoconvergent (*E* and *Z* give syn).[8] The unexpected syn-selective aldol addition of (*E*)-enol borates, reported independently by our own group[8b,c] and by R. W. Hoffmann's group,[8a] stimulated our interest in the aldol condensation transition states. In order to gain a deeper insight into the reaction mechanism we decided to employ theoretical methods (MNDO) to evaluate geometries and energies of the possible transition states.

Procedure

(1) It is well-known that for molecules of too great a complexity ab initio calculations are impossibly expensive. On the other hand, molecular mechanics is designed to work for stable molecules, and while it can be applied to transition states of chemical reactions and to other transient species, such applications tend to be difficult because the necessary empirical data are not readily available. Thus, for many purposes, MNDO calculations (semiempirical) are the best method currently available.[9] All the calculations reported in this paper were performed by the MNDO–SCF method[10] (*QCPE 353*), and the minimum energy geometries were determined by the DFP technique.[11]

Scheme I



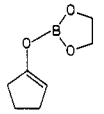
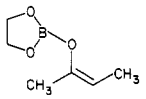
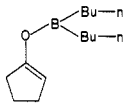
(2) Only a 2-kcal/mol difference in energy is needed between two species before the concentration of one of them becomes vanishingly small at low temperature (−78 °C). Therefore 2 kcal/mol is usually the threshold for an organic reaction to be stereoselective. In our MNDO calculations we were not considering the absolute energy values, but we were comparing the energy differences of a series of conformations of the same system. Therefore even relatively small values of these differences (1–2 kcal/mol) are usually significant: in the comparison of like with like the trend of the error function is expected to be the same, and the results are usually safe.

† Dipartimento di Chimica Organica e Industriale.
‡ Dipartimento di Chimica Fisica ed Elettrochimica.

(1) Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 154–161. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1 and references therein.
(2) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(3) Newton, R. F.; Baxter, A. D.; Roberts, S. M.; Wakefield, B. J.; Wooley, G. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1809.
(4) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
(5) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467. Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353. Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 162.
(6) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, 3975. (b) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, 4607.
(7) (a) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, 3343 and references therein; *Acc. Chem. Res.* **1985**, *18*, 181. (b) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, 4691.
(8) (a) Hoffmann, R. W.; Ditrich, K. *Tetrahedron Lett.* **1984**, 1781. (b) Gennari, C.; Cardani, S.; Colombo, L.; Scolastico, C. *Tetrahedron Lett.* **1984**, 2283. (c) Gennari, C.; Colombo, L.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1984**, *40*, 4051. (d) Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059.
(9) Schröder, S.; Thiel, W. *J. Am. Chem. Soc.* **1985**, *107*, 4422.
(10) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(11) Davidon, W. C. *Comp. J.* **1968**, *11*, 406.

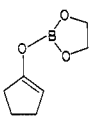
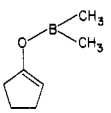
0022-3263/86/1951-0612$01.50/0

Table I. Experimental Data of the Additions to Benzaldehyde of the Boron-Enolates

enolate	syn–anti ratio	yield, %	conditions	$\Delta\Delta G^{\ddagger}$,[c] kcal mol^{-1} ($\Delta G^{\ddagger}$syn − $\Delta G^{\ddagger}$anti)
	24:1[a]	90	−78 °C/CH_2Cl_2	−1.23
	99:1[a]	85	−78 °C/CH_2Cl_2	−1.78
	1:3.5[b]	80	−78 °C/CH_2Cl_2 (−78 → 0 °C)	+0.49

[a] See ref 8b,c. [b] Experiment performed according to ref 4. [c] $\Delta G^{\ddagger}$(syn) − $\Delta G^{\ddagger}$(anti).

Table II. Theoretical Calculations (MNDO) of the Cyclopentanone Additions to Benzaldehyde

		C1–C2, Å		φ, deg		ω, deg		ΔH_f, kcal mol^{-1}		chart		conformation[a]	
enolate	entry	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti
	1	2.00	2.00	180.0	180.0	11.6	9.9	−167.3	−165.2	I	II	TB/HC	HC
	2	2.00	2.00	161.6	94.5	11.9	11.8	−168.6	−165.6			TB	TB/B
	3	1.80	1.80	163.7	98.0	9.2	9.5	−183.2	−181.0				
	4	1.63	1.63	164.5	134.5	7.6	0.0	−192.2	−192.4				
	5	1.59	1.58	166.6	136.3	7.8	1.8	−193.3	−194.0			TB	HC
	6	2.00	2.00	163.2	178.3	11.2	11.2	−59.8	−61.0	III	IV	TB	HB

[a] TB = twist-boat; HB = half-boat; HC = half-chair; B = boat; see ref 17.

(3) Complexes **5** and **6** were not optimized, and should be viewed as hypothetical starting points for the reaction. All the geometrical parameters of the transition-state models were fully optimized, except for those used as "leading parameters" or constraints (C1–C2 distance, φ = 180° constraint, ψ = 0° constraint: see Results and Discussion). All the transition-state models are the best calculated conformations given a fixed C1–C2 bond distance but were not forced to lie on a saddle point of the potential surface (they were not located as real transition states).

Results and Discussion

Three simple cases were chosen for the theoretical calculations: the addition to benzaldehyde of the cyclopentanone enolates (both the enol borate and the enol borinate) and the addition of the butanone (*Z*)-enolate (enol borate) (Scheme I).

The experimental results for these additions are shown in Table I.[8b,c]

The first important point to look at are the starting boron–enolate conformations: ground-state conformations for these enolates had been hypothesized[8c] in analogy with the known conformational preferences of enols and enol ethers.[12]

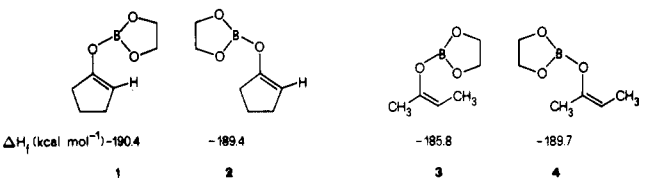


Figure 1.

More recently Professor Hoffmann and co-workers studied the boron–enolate conformations using STO-3G calculations on MNDO-optimized geometries.[13] These calculations, together with ^{1}H NMR–NOE experiments, clearly show that ground-state conformations are s-cis for the (*E*)-enolates [ΔH_f(s-trans) − ΔH_f(s-cis) = 1–2 kcal/mol] and s-trans for the (*Z*)-enolates [ΔH_f(s-cis) − ΔH_f(s-trans) = 3–5 kcal/mol].[13,14]

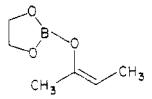
Our MNDO calculations on enol borates **1**–**4** agree with those results: (s-*cis*-**1** is planar and 1.0 kcal/mol more stable than **2**, while s-*trans*-**4** is also planar and 3.9 kcal/mol more stable than **3** (Figure 1). These enolates show the following geometrical features: (a) the torsional angle around the enolate double bond is nearly planar; (b) the dihedral angle χ (Csp^2–O–B–O) is planar for **1**, **2**, and **4**, while almost perpendicular (χ = 101.5°) for **3** because of the steric interaction between the methyl group and the

(12) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451 and references therein. Owen, N. L.; Sheppard, N. *Trans. Faraday Soc.* **1964**, *60*, 634. Owen, N. L.; Seip, H. M. *Phys. Lett.* **1970**, *5*, 162. Samdal, S.; Seip, H. M. *J. Mol. Struct.* **1975**, *28*, 193. Durig, J. R.; Compton, D. A. C. *J. Chem. Phys.* **1978**, *69*, 2028. Capon, B.; Siddhanta, A. K. *J. Org. Chem.* **1984**, *49*, 255. Mersh, J. D.; Sanders, J. K. M. *Tetrahedron Lett.* **1981**, 4029. Bernardi, F.; Epiotis, N. D.; Yates, R. L.; Schlegel, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 2385. Hoffmann, R.; Olofson, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 943.

(13) We are grateful to Professor R. W. Hoffmann (Marburg University, West Germany) for disclosing to us his results prior to publication and for the helpful suggestions and discussions. Hoffmann, R. W.; Ditrick, K.; Froech, S.; Cremer, D. *Tetrahedron* **1985**, *41*, 5517.

(14) Both enol borates and enol borinates were shown to have the same conformational preferences. The examples chosen by Professor Hoffmann and co-workers for their calculations are different from those reported in this paper.

Table III. Theoretical Calculations (MNDO) of the Butanone Additions to Benzaldehyde

enolate	entry	C1–C2, Å		φ, deg		ω, deg		ψ, deg		ΔH_f, kcal mol^{-1}		chart		conformation[a]	
		syn	anti	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti
	1	2.00	2.00	186.5	140.9	31.0	48.3	0.0	0.0	−161.5	−159.4	V	VI	HC	TB
	2	1.59	1.58	179.3	122.0	24.9	37.0	0.0	0.0	−184.7	−182.5			HC	HC
	3	1.59	1.60	172.1	177.5	9.9	8.9	39.6	56.9	−190.5	−192.9			HB	HB

[a] HB = half-boat; TB = twist-boat; HC = half-chair; see ref 17.

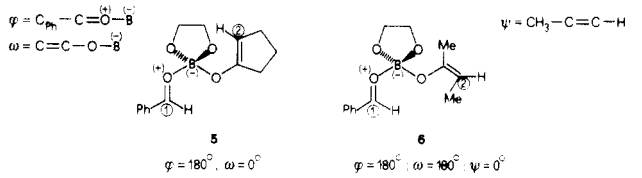


Figure 2.

boron-containing ring; (c) the bond angle ϕ (C=C—O) is remarkably different in **1**–**4** (**1**, ϕ = 132.4°; **2**, ϕ = 120.1°; *3*, ϕ = 128.1°; *4*, ϕ = 116.5°).

The ground-state conformations of the enolates are important for determining the different reactivity of (*Z*)- and (*E*)-enol borates ((*E*)-enol borates are much more reactive than (*Z*)-enol borates).[8a,b,c]

When **1** reacts with benzaldehyde the dihedral angle ω (C=C—O—B) slightly changes from 0° to ca. 12° (vide infra the dihedral angle ω in the transition state, Table II). When **4** reacts with benzaldehyde, ω has to change from 180° to ca. 31° (Table III), that is, close to an energy maximum!

Therefore, in terms of activation energy it is out of the question that **4** has to spend much more energy than **1** to reach the reactive conformation (transition state).

On the assumption that the aldol condensation starts with the coordination of the Lewis acidic boron to the aldehyde carbonyl group, the complexes **5** and **6** (Figure 2) should be formed having the dihedral angle φ (C_{Ph}—C=O$^+$—B$^-$) = 180°.[15] Proceeding along the reaction coordinate, it is conceivable that φ remains close to 180° until the incoming nucleophile (enolate) has bonded extensively so that sufficient electron density has been transferred into the π^*-orbital of the carbonyl group.

We then drew the enolate and the carbonyl carbon together (C1–C2), to a 2-Å distance, maintaining φ = 180°, thus modeling the transition state which should account for the kinetic preference shown by the aldol reaction. Then the φ = 180° constraint was removed, the C1–C2 distance was allowed to shorten by 0.2 Å at a time, and the energy of each generated structure was MNDO minimized. Removing all constraints the fully optimized products were calculated and the minimized C1–C2 distances were found to be between 1.58 and 1.60 Å.

The results for the cyclopentanone additions to benzaldehyde are shown in Table II. First of all it should be noted that the theoretical data are in good (qualitative) agreement with the experimental results (Table I). In the enol borate case, (Table II, entries 1–5) the syn isomer is by 2–3 kcal/mol preferred over the anti isomer (kinetic

Chart I

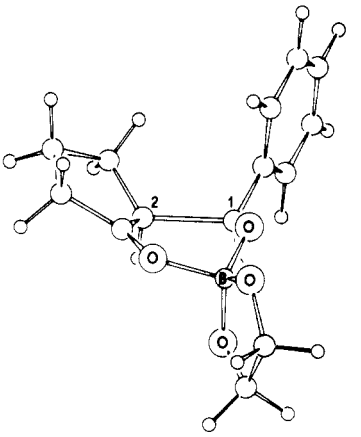


Chart II

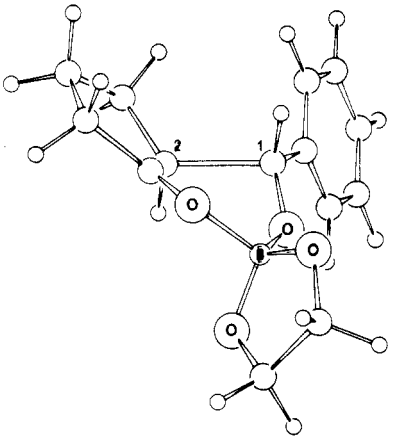
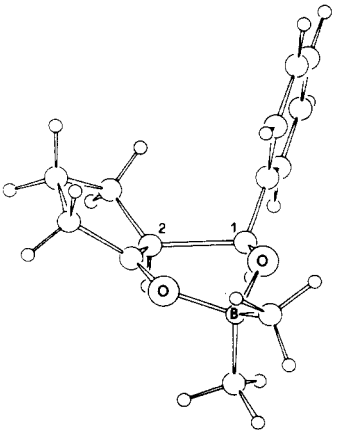


Chart III



(15) The acetaldehyde–BF_3 complex with φ = 180° has been calculated (MNDO) to be at least 2 kcal/mol more stable than with φ = 0° (Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references therein). The crystal structure of the benzaldehyde–BF_3 complex has recently been determined (Reetz, M. T., personal communication). For general references to the Lewis acid–carbonyl complexation, see: Fratiello, A.; Kubo, R.; Chow, S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1205. Lienard, B. H. S.; Thomson, A. J. *J. Chem. Soc., Perkin Trans 2* **1977**, 1400. Olah, G. A.; O'Brien, D. H.; Calin, M. *J. Am. Chem. Soc.* **1967**, *89*, 3582. Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735. Grinvald, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 94. Thil, L.; Rihel, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 591.

Chart IV

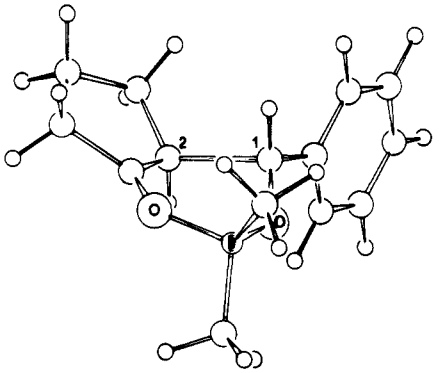


Chart V

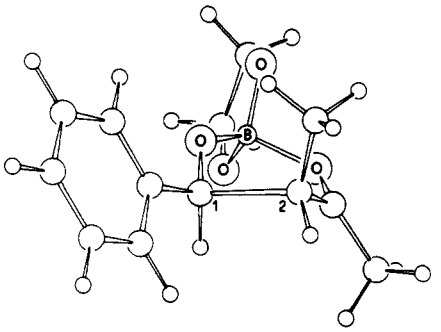
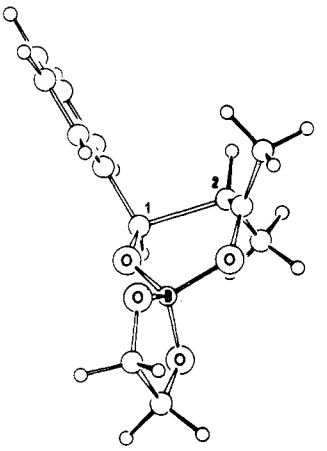


Chart VI



control, long C1–C2 bond distances), while the fully minimized structure (C1–C2 ca. 1.58 Å) shows a 0.7-kcal/mol preference for the anti isomer (thermodynamic control), the over crossing C1–C2 bond distance ($\Delta\Delta H_f$ = ca. 0) being around 1.63 Å. It is well-known that anti aldols are thermodynamically more stable than the syn counterparts.[1]

Another relevant observation regards the transition-state conformations. As it appears evident by the ORTEP views, all the transition-state models show puckered geometries.[16,17]

Simulating the kinetic control, the twist-boat leading to the syn isomer is preferred to both the half-chair and the twist-boat leading to the anti isomer[18] (see Charts I and II).

On the contrary, starting from the (*E*)-enol borinate, the half-boat leading to the anti aldol showed a 1.2-kcal/mol preference over the twist-boat leading to the syn aldol (Table II, entry 6; Charts III and IV). This calculation is in good (qualitative) agreement with the experimental results (Table I), and can be interpreted in terms of the steric hindrance of the axial methyl group at boron, which disfavors the twist-boat leading to the syn isomer because of steric interaction with the hydrogen atoms at C1 and C2. The methyl–hydrogen 1,3-diaxial interaction is eliminated going from the twist-boat (syn) to the half-boat (anti) (compare Charts III and IV).

In the case of the (*Z*)-enol borate, the syn isomer showed a 2.1-kcal/mol kinetic preference over the anti isomer (C1–C2 = 2 Å; entry 1, Table III). In order to keep the enolate in the *Z* configuration, a new constraint was imposed: the methyl and the hydrogen were forced to stay coplanar (CH_3—C=C—H, ψ = 0°, **6** in Figure 2). The minimized structures (C1–C2 = ca. 1.59 Å) having the ψ = 0° constraint still active showed a 2.2-kcal/mol preference for the syn isomer (Table III, entry 2). Only when the ψ = 0° constraint is removed, thus simulating the thermodynamic control, the anti isomer turned out to be more stable (2.4 kcal/mol) (Table III, entry 3). Therefore, in the kinetically controlled process, starting from the (*Z*)-enol borate (Table III, entry 1; Charts V and VI), the half-chair leading to the syn aldol is preferred to the twist-boat leading to the anti aldol, thus following the commonly accepted trend of the (*Z*)-enolates in the aldol condensation.[1]

Summary and Conclusions

MNDO calculations on enol borates show that the ground-state conformations are planar s-cis (ω = 0°) for (*E*)-enol borates and planar s-trans (ω = 180°) for (*Z*)-enol borates. In the transition states of the aldol condensation ω changes from 0° to 12° for (*E*)-enol borates (close to an energy minimum) and from 180° to 31° for (*Z*)-enol borates (close to an energy maximum). Different activation energies thus account for the different reactivity of the (*E*)- and (*Z*)-enol borates (*E* compounds are more reactive than *Z* ones).

The aldol reaction pathway was modeled by using MNDO: at long C1–C2 bond distances and with φ close to 180° the kinetic control was simulated, while the thermodynamic control was simulated by using the fully minimized structures. The calculation data nicely agree with the experimental results, signifying that from our model we can obtain reliable information. Starting from (*Z*)-enolates, the half-chair leading to the syn aldol is preferred to the twist-boat leading to the anti aldol. Starting from (*E*)-enolates, syn aldols are kinetically preferred to anti aldols in the absence of disturbing steric factors, as in the case of (*E*)-enol borates. The opposite behavior (*E* enolates give anti aldols) is encountered when bulky substituents at the metal disfavor the twist-boat leading to the syn isomer because of steric interactions with the axial hydrogens, as in the case of enol borinates.[19,20,21]

(16) The conformations of the transition-state models could be flatter than the real conformations because the MNDO torsional interactions are probably too small.

(17) The conformations were assigned on the basis of the puckering parameters reported by: Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.

(18) For other boatlike transition states containing boron, see: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 4101.

(19) Methyl is known to be much more sterically requiring than OR. The reported conformational *A* values (A = $\Delta G°$ = RT ln K for the axial–equatorial equilibrium in the cyclohexane derivatives) are Me = 1.70 kcal/mol, OCH_3 = 0.60 kcal/mol: Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(20) In the case of the cyclohexanone enol borinate, going from the dibutyl to the more hindered cyclopentyl, thexyl enol borinate the anti–syn ratio is increased from 2:1 to 19:1.[4]

The nonselectivity shown by the *E* lithium enolates[1,3,4,7a] is probably a result of these two opposite trends, but it is more difficult to rationalize because of lithium–enolate aggregation in ethereal solvents.[22]

The "normal" behavior can therefore be defined as follows: *both (E)- and (Z)-enolates prefer syn aldols under kinetic control* (tin–, zirconium–, and titanium–enolates and enol borates).

The "abnormal" behavior ((*E*)-enolates give anti aldols under kinetic control) *is due to the steric hindrance of the cation* and is more pronounced with enol borinates than with lithium–enolates.

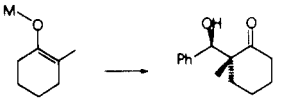
Therefore our calculations shed new light on the enolate selectivity and on the aldol transition-state conformations.

Our transition-state models could possibly also give some aid to rationally design new chiral auxiliaries so that enantiomerically pure aldols can be easily obtained.[23]

Acknowledgment. This work was made possible by the financial support of Ministero Pubblica Istruzione (40% and 60%). We thank P. Pugni for comments and assistance.

Registry No. 1, 100020-83-5; 3, 97231-14-6; (1-cyclopentenyloxy)(dibutyl)boron, 100020-84-6; (1-cyclopentenyloxy)(dimethyl)boron, 100020-85-7; benzaldehyde, 100-52-7; 2-(α-hydroxybenzyl)cyclopentanone (isomer 1), 43108-70-9; 2-(α-hydroxybenzyl)cyclopentanone (isomer 2), 43108-71-0; 3-(α-hydroxybenzyl)-2-butanone (isomer 1), 75600-09-8; 3-(α-hydroxybenzyl)-2-butanone (isomer 2), 81640-13-3.

(21) The experiments performed by Kuwajima and Nakamura[7a] and by Hoffman[13] using cyclohexanone and 2-methylcyclohexanone enolates are nicely interpreted by our model. Cyclohexanone enolates are syn selective (enol borates > 9:1;[8,13] trichlorotitanium–enolate 89:11[7a]), nonselective (lithium–enolate ca. 1:1[7a]), or slightly anti selective (enol borinate 67:33[7a]). In the case of 2-methylcyclohexanone, the substitution of the hydrogen with the methyl disfavors the twist-boat leading to the syn aldol because of the 1,2-methyl–hydrogen interaction (compare Charts III and IV). Therefore all the previously mentioned enolates become anti selective: lithium–enolate, ca. 3:1;[7a] enol borinate, >200:1;[7a] trichlorotitanium enolate, ca. 9:1;[7a] enol borate, >20:1.[13]



(22) THF–solvated lithium–enolates are known to be tetrameric (see: Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617). The O–Li group can then be considered a rather large group. For this kind of discussion, see: Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022.

(23) Part of this work was presented as an invited lecture (C. Gennari) at the IXth International Symposium on "Synthesis in Organic Chemistry", Oxford, July 22–25 1985.

Defined Dimensional Alterations in Enzyme Substrates. General Synthetic Methodology for the Bent Dihydro-*lin*-benzopurines

Thomas M. Stevenson, Franciszek Kaźmierczak,† and Nelson J. Leonard*

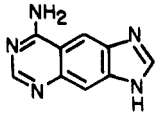
Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received July 19, 1985

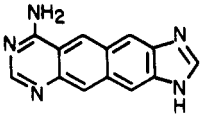
The use of cycloaddition reactions for the synthesis of partially reduced heterocyclic systems has been shown to be an attractive approach to dihydrobenzimidazoles, dihydroquinazolines, and dihydro-*lin*-benzopurines. The first representatives of the bent dihydro-*lin*-benzopurines to be synthesized were 4,9-dihydroimidazo[4,5-*g*]-quinazoline-2,8(1*H*,7*H*)-dione (**20**) and 4,9-dihydro-*lin*-benzouric acid (**21**).

Naturally occurring, modified, and substituted purines have been subjected to close scrutiny by scientists seeking to establish structure–biological activity relationships. The need for more information defining the active sites of enzymes that require purines as substrates or cofactors has led to the synthesis of an ordered series of compounds which we refer to as dimensional probes.[1] These compounds retain both the pyrimidine and imidazole rings present in purines, but they are separated by intervening chemical frameworks. The formal insertion of a benzene ring (actually four additional carbons) into the middle of the adenine ring system leads to a molecule referred to as *lin*-benzoadenine (**1**), and of a naphthalene ring (actually an eight-carbon insertion) to an analogue referred to as *lin*-naphthoadenine (**2**). We have previously described their syntheses, along with the corresponding ribonucleosides, and their biochemical activity.[2]

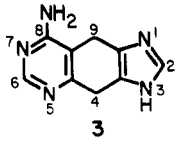
A compound related to **1**, the biochemically active analogue of adenine, is the 4,9-dihydro derivative **3**, which could give a different type of information. Its bent



1



2



3

structure poses the question as to whether the contributing terminal rings of adenine, namely, the pyrimidine and

† Visiting Scientist from Adam Mickiewicz University, Poznań, Poland.

(1) (a) Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128. (b) Leonard, N. J. *Heterocycles* **1979**, *12*, 129. (c) Keyser, G. E.; Leonard, N. J. *J. Org. Chem.* **1976**, *41*, 3529. (d) Scopes, D. I. C.; Barrio, J. R.; Leonard, N. J. *Science (Washington, D.C.)* **1977**, *195*, 296. (e) Leonard, N. J.; Scopes, D. I. C.; VanDerLijn, P.; Barrio, J. R. *Biochemistry* **1978**, *17*, 3677. (f) Kauffman, R. F.; Lardy, H. A.; Barrio, J. R.; Barrio, M. del C., Leonard, N. J. *Biochemistry* **1978**, *17*, 3686. (g) Keyser, G. E.; Leonard, N. J. *J. Org. Chem.* **1979**, *44*, 2989. (h) Leonard, N. J.; Keyser, G. E. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4262. (i) Moder, K. P.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 2613.

0022-3263/86/1951-0616$01.50/0