101 (10), 75 (16), 74 (10), 73 (9), 58 (12), 57 (21), 56 (9). The ether filtrate was shaken with 2 M sulfuric acid, dried, and distilled after removal of the ether. The product, boiling at 70–100 °C, contained less pure **8** and weighed 0.74 g.

Preparation of 2-Oxobutanoic Acid Ethyl Ester (6). The ester, **6**, was prepared by the method of Vogel and Schinz.[10] 3-Methyl-2-oxobutanedioic acid diethyl ester, **1a**, 0.60 g (3.0 mmol), was refluxed with 6 M hydrochloric acid for 2 h. The flask was attached to a continuous extractor, and extraction was carried out with ether. After evaporation of the ether, the residue was taken up in absolute alcohol to which 3 drops of concentrated hydrochloric acid was added. After 5 h of refluxing the solution was treated with decolorizing carbon and sodium hydrogen carbonate. The solvent was removed on the rotary evaporator, and the residue was subjected to a Kugelrohr distillation at reduced pressure. At an oven temperature of 67–70 °C, 0.01 g of **6** was obtained, 2.6%. Spectral data: MS *m/z* 130 (7), 75 (1), 58 (3), 57 (100), 56 (4), 45 (2).

Preparation of 2-Methyl-3-oxopropanoic Acid Ethyl Ester (7). The ester, **7**, was prepared by a method analogous to that of Holmes and Trevoy[11] using ethyl formate and ethyl propionate. To 1.00 g of sodium hydride (2.5 mmol) suspended in ether were added 2.55 mL of ethanol in 5 mL of ether, 2.95 g (40 mmol) of ethyl formate in 10 mL of ether, and, in portions, 2.04 g (20 mmol) of ethyl propionate in 5 mL of ether. After 2 days the reaction mixture was transferred to a separatory funnel and 20 mL of water was added followed by enough sulfuric acid to bring the pH to 1. Four extractions with 20, 10, 10, and 10 mL of ether were performed. The extracts were concentrated, and a molecular distillation was carried out on the residue. Fraction 4, bath temperature 120–140 °C, was about 80% pure by GC–MS analysis. A portion of this fraction was subjected to preparative GLC to obtain the sample for spectroscopic analysis which showed the presence of keto and enol forms. Analysis by GC/MS yielded two components in the chromatogram. It is believed that the first component is the keto form and the second the enol form; MS *m/z* (keto) 130 (23), 102 (25), 85 (44), 83 (14), 56 (100); (enol) 130 (4), 102 (62), 85 (85), 74 (88), 73 (37), 57 (50), 56 (100).

Reaction of 3-Oxo-3-phenylpropanoic Acid Ethyl Ester with Water. The reactor was charged with (0.40 g, 2 mmol) of ethyl benzoylacetate (Aldrich tech grade), 1.60 g of diglyme, recently distilled, and 0.36 g (20 mmol) of water. The mixture was heated for 16 h at 105 °C. The products consisted mainly of carbon dioxide and acetophenone, which was identified by its mass spectrum and comparison with the mass spectrum of an authentic sample. On a preparative scale, a mixture of 0.96 g (5.0 mmol) of ethyl benzoylacetate and 3 g of water was refluxed for 16 h and then extracted with methylene chloride. The extract was dried by shaking with anhydrous sodium sulfate, concentrated on a rotary evaporator, and subjected to Kugelrohr distillation. Acetophenone boiling at an oven temperature of 95–108 °C (14 Torr) was collected. Yield 0.42 g, 70%.

Reaction of Ethyl Pyruvate with Methanol. Ethyl pyruvate, 0.12 g (1.0 mmol) and 0.64 g of methanol (20 mmol) were heated to 110 °C in the reactor for 16 h and then subjected to GC–MS analysis. The relative peak areas for the methyl to ethyl esters were 19:50.

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Registry No. 1a, 759-65-9; **1b**, 63921-06-2; **2a**, 99380-59-3; **2b**, 99380-58-2; **6**, 15933-07-0; **7**, 27772-62-9; **8**, 126615-15-4; $H_3CCH_2CO_2Et$, 105-37-3; EtO_2CCO_2Et, 95-92-1; $H_3CO_2CCO_2CH_3$, 553-90-2; $H_3CCH_2CO_2CH_3$, 554-12-1; $PhCOCH_2CO_2Et$, 94-02-0; HCO_2Et, 109-94-4; $PhCOCH_3$, 98-86-2; H_3CCOCO_2Et, 617-35-6; propanoic-1-^{13}C acid sodium salt, 62601-06-3; propanoic-1-^{13}C acid ethyl ester, 78217-95-5.

Transition-State Modeling of the Aldol Reaction of Boron Enolates: A Force Field Approach

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A force field model for the aldol reactions of ketone-derived enol borinates with aldehydes has been developed, based on MM2 and ab initio calculations, which can reproduce the geometries and energies of the ab initio transition structures **1**–**14** (±0.2 kcal mol^{-1}). It reproduces the experimental syn:anti stereoselectivity for the aldol additions of simple *Z* and *E* substituted enol borinates derived from ethyl ketones, and it shows that unsubstituted enol borinates (methyl ketone derived) have a greater degree of flexibility with a larger number of accessible chair and boat transition structures found. The force field also reproduces the aldehyde *si*/*re* face selectivity in the aldol reactions of a range of chiral *Z* enol borinates for which experimental data is available, and it may be a useful predictive tool for assessing stereoselection in new reactions. New ab initio calculations (RHF/3-21G) are described, which indicate the existence, not only of the chair and the twist-boat (boat A) reported by Houk, but also of an additional boat transition structure (boat B) found by the force field. In the aldol reactions of unsubstituted and *E* substituted enol borinates, boat B is likely to be involved as well as the chair and boat A; its omission from the development of the force field may explain the poor treatment of methyl ketone reactions.

Aldol reactions of metal enolates with aldehydes are among the most useful methods for stereocontrolled carbon–carbon bond formation in organic synthesis.[1,2] For example, the aldol reaction of an ethyl ketone with an aldehyde introduces two new chiral centers producing four possible stereoisomers (see Scheme I). For synthetic purposes, controlled formation of each individual stereo-

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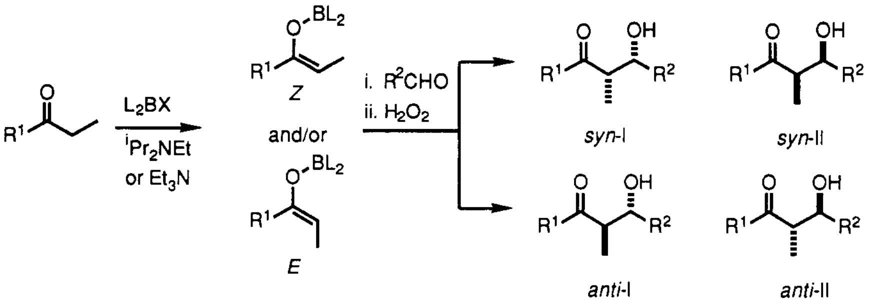
0022-3263/90/1955-3576$02.50/0

Scheme I. The Aldol Reactions of Enol Borinates



isomer is highly desirable, leading to the intensive study of a wide range of different metal enolates over the last 2 decades. A large body of data has subsequently accrued in this area, and many useful aldol processes have been developed which feature high levels of diastereoselectivity (syn:anti) and/or enantioselectivity (syn-I:syn-II, anti-I: anti-II). In this respect, the aldol reactions of enol borinates are of particular value.[3]

After the first pericyclic chair model proposed by Zimmerman and Traxler,[4] a great variety of empirical transition structures and a large number of effects have been suggested to rationalize aldol stereoselectivity.[2-6] Recently, several theoretical studies,[7-11] including both semiempirical[8] and ab initio[9-11] calculations, have tried to make the experimental complexity of aldol reactions more understandable. However, a workable quantitative model which might have application in predicting the sense and degree of stereoselectivity in new situations is still lacking. As part of a project aimed at the rational design and synthesis of new chiral boron enolate reagents for asymmetric aldol reactions, we have undertaken the development of an appropriate transition structure force field which should be able to reproduce the stereoselectivity of known reactions of chiral boron enolate systems.

The force field approach to modeling reaction pathways, as pioneered by Houk,[12] treats transition structures as pseudo-ground states and develops suitable MM2[13] parameters. Menger[14] observes that such an approach does not always model transition states and that ground-state models can give superior results. However, for the aldol reaction there are no ground-state analogues which can be easily adopted. For the enol borinate aldol reaction, there are likely to be at least two intermediates in the reaction before the final cyclic transition state, i.e. the enolate itself and the enolate–aldehyde ate complex. The rate of interconversion of these intermediates and the rate of equilibration of different conformations of each intermediate are unknown. From the rapidity and exothermicity of the boron-mediated aldol reaction, Hoffmann[9] and Paterson[10] assumed an early transition state resembling the enolate (i.e. the degree of bond formation with the aldehyde is small), where the reaction stereoselectivity is primarily controlled by the conformational preferences of the boron enolate (Hammond postulate conditions[15]). This kind of approach gave interesting results and, in some cases, a qualitative agreement with the observed stereoselectivity, but quantitative correlation was poor. Alternatively, if the Curtin–Hammett principle[16] is assumed to be operative and can be applied to all the intermediates before the final transition state, then the experimental aldol stereoselectivity, obtained under conditions of kinetic control, will be determined by the relative energies of all the competing transition structures. We have chosen to investigate this latter possibility and here describe the development and application of an "aldol force field" for enol borinates.

Results and Discussion

Force Field Development. We started by developing a force field for the aldol reactions of enol borinates following the Houk approach,[12] where equilibrium bond lengths and angles from ab initio calculations on the transition structures are incorporated in MM2 for those bonds that are forming or breaking. The positions of all atoms are optimized using a force field consisting of existing MM2 parameters and new parameters developed for

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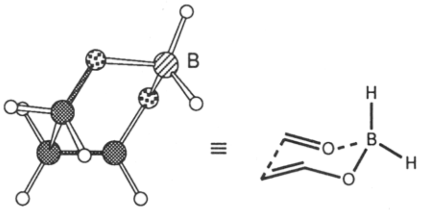
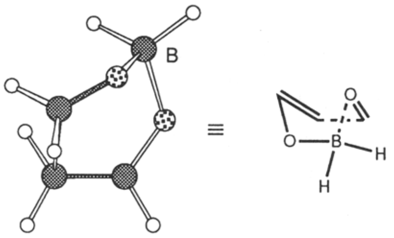
atoms involved in bonding changes.

We started from the chair (**1**) and the twist-boat (= boat A) (**2**) transition structures for the enol dihydroborinate of ethanal adding to formaldehyde, i.e. the all hydrogen case, for which the ab initio geometries were available from the work of Houk.[11] We made use of the existing parameters for boron (van der Waals radius, ϵ)[10] and used bond angles and lengths from the mean ab initio values. The corresponding force constants were taken either from Allinger's MM2 force field[13] or from the ones already calculated for boron enolates,[10] adjusting them as seemed appropriate. The carbon–carbon bond that is formed in the aldol reaction was assigned as a "zero-order" bond and given a small force constant. Assisted by a Löwdin population analysis, intramolecular electrostatic interactions were modeled by assigning a charge to each atom.[17] Torsional parameters were added as were necessary to hold the geometry to the ab initio structure with the size of the torsional terms V_1, V_2, V_3 found by trial and error, following Allinger's recommendations.[18] Stretch–bending terms were set to zero for all the sp^2 carbons. The values were entered as a special substructure in version 2.5 of MacroModel.[19]

chair (**1**)



boat A (**2**)



A force field was found which could duplicate the geometries and the relative energies of the chair and the twist-boat transition structures with all hydrogen substituents. One methyl at a time was then added in six of the seven possible positions of the all hydrogen chair **1** and the twist-boat **2** (the seventh being equatorial methyl on boron) to give structures **3**–**14** shown below, and the force field reoptimized in order to reproduce the relative energies and geometries of the ab initio structures.[11] The methyl group of the aldehyde can go in one of the two possible orientations: for the chair the two geometries correspond to the methyl group being axial or equatorial, i.e. structures **5** and **6**, but this nomenclature cannot easily be extended to the boats. We therefore refer to the structures which have the methyl group cis to the boron as structure (cis), as in **4**, and those for which the group is trans as structure (trans), as in **3**. The force field presented in Table I was obtained, by the process of trial and error, which fitted all the ab initio data to a reasonable degree (± 0.2 kcal mol^{-1}); the relative energies for structures **1**–**14** calculated by the force field compared to the corresponding ab initio values

Table I. Force Field Parameters for Enol Borinate Transition Structures

```
Main Force Field:   Radius        E             Offset
                    (angstrom)    (Kcal mol-1)  (angstrom)
 6  Z0              1.9800        0.0340        0.0000

Substructure:
-3
 C  Borinate Transition State : charges
 9  Z0*O3-C2=C2*C2=O2(*1)
-4
 8   0.1600  -0.1800   0.1000  -0.0800   0.1000  -0.1000

-3
 C  Borinate Transition State
 9  Z0*O3-C2=C2*C2=O2(*1)
-2
 1   1  H1                1.1960     4.6000
 1   1  C3                1.5800     4.0000
 1   1   2                1.5360     6.2000
 1   2   3                1.3140     6.0000
 1   3   4                1.3560     9.6000
 1   4   5                2.2630     3.0000
 1   5   6                1.2720     8.0000
 1   6   1                1.5910     5.5000
 2   2   1   6           97.7000     0.4600
 2   1   6   5          120.5000     0.7700
 2   6   5   4          103.2500     0.4600
 2   5   4   3           90.0000     0.3800
 2   4   3   2          124.0000     0.5000
 2   3   2   1          120.2000     0.3000
 2  H1   4   5          100.0000     0.1000
 2  C3   4   5           87.0000     0.3000
 2   4   5  H1           92.7000     0.1000
 2   6   1  H1          108.0700     0.1000
 2  H1   1  H1          118.2000     0.3000
 2  H1   1   2          111.3250     0.3000
 2   6   1  C3          110.0000     0.1000
 2  C3   1  H1          118.0000     0.3000
 2  C3   1  C3          118.0000     0.3000
 2  C3   1   2          112.0000     0.3000
 2  H1  C3   1          111.0000     0.3000
 2  C3  C3   1          115.0000     0.3000
 2  H1   4   3          119.4500     0.3000
 2  H1   4  H1          117.5500     0.3000
 2  H1   3   4          119.9000     0.3000
 2   2   3  H1          115.6000     0.3000
 2  C3   5   6          119.0000     0.4000
 2  C3   5   4          100.0000     0.1000
 2  C3   3   2          117.9000     0.4000
 2  C3   3   4          119.5000     0.4000
 4  00   1   2  00        0.0000     0.0000     0.0000
 4  00   2   3  00        0.0000     0.0000     0.0000
 4  00   3   4  00        0.0000     0.0000     0.0000
 4  00   4   5  00        0.0000     0.0000     0.0000
 4  00   5   6  00        0.0000     0.0000     0.0000
 4  00   6   1  00        0.0000     0.0000     0.0000
 4   1   2   3   4        0.0000     3.0000     0.0000
 4  H1   1   2   3        0.0000     0.0000     0.8000
 4  H1   1   6   5        0.0000     0.2000     0.0000
 4   2   3   4  H1        0.0000     5.0000     0.0000
 4  H1   3   4  H1        0.0000     5.0000     0.0000
 4   2   3   4  C3        0.0000    10.0000     0.0000
 4  H1   3   4  C3        0.0000     8.0000     0.0000
 4  C3   3   4  H1        0.0000     5.0000     0.0000
 4  H1  C3   4   3        0.0000     0.0000     0.0000
 4  H1  C3   4   5        0.0000     0.0000     0.0000
 4   3   4   5   6        0.0000     1.5000     0.0000
 4  C3   4   5  H1        0.0000     0.0000     0.2300
 4  C3   4   5   6       -0.5500     2.5000     3.0000
 4   2   3   4   5        0.0000     0.0000     1.0000
 4   4   5   6   1        1.4860    -0.9500     0.6700
 4   5   6   1   2        0.0000     0.0000     0.3000
 4  C3   5   6   1        0.8000     1.0000    -1.9000
 4  C3   5   4   3        0.3000    -0.5000     0.0000
 4  H1  C3   5   6        0.0000     0.0000     0.0000
 4  H1  C3   5   4        0.0000     0.0000     0.2000
 4  H1  C3   3   2        0.0000     0.0000     0.0000
 4  H1  C3   3   4        0.0000     0.0000     0.0000
 4  H1   3   2   1        0.0000     0.6000     0.0000
 4  C3   3   2   1        0.0000    -0.3500     0.6500
 4  C3   3   4   5        0.0000     0.0000     0.2500
 4  C3   1   2   3        0.0000     0.0000     1.2000
 4  H1  C3   1   2        0.0000     0.0000     0.0000
 4  H1  C3   1   6        0.0000     0.0000     0.0000
 4  H1  C3   1  H1        0.0000     0.0000     0.2000
 4  H1  C3   1  C3        0.0000     0.0000     0.2000
 4  C3  C3   1   2        0.0000     0.0000     0.0000
 4  C3  C3   1   6        0.0000     0.0000     0.0000
 4  C3  C3   1  C3        0.0000     0.0000     0.0000
 4  H1  C3   1  C3        0.0000     0.0000     0.2000
 4  H1  C3  C3   1        0.0000     0.0000     0.0000
 4  C3  C3  C3   1        0.0000     0.0000     0.0000
 4  C3  C3   3   4        0.0000     0.0000     0.0000
 4  C3  C3   3   2        0.0000     0.0000     0.0000
 4  Si  C3   3   2        0.0000     0.0000     0.0000
 4  Si  C3   3   4        0.0000     0.0000     0.0000
 4  C3  Si  C3   3        0.0000     0.0000     0.0000
 4  H1  C2   5   4        0.0000     0.0000     0.0000
 4  C3  C2   5   4        0.0000     0.0000     0.0000
 4  C2  C2   5   4        0.0000     0.0000     0.0000
 4  C3  C3   5   4        0.0000     0.0000     0.0000
 5   3  00  00  00        0.0000     0.0000
 5   4  00  00  00        0.0000     0.0000
 5   5  00  00  00        0.0000     0.0000
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[17] (a) Löwdin, P. O. *Phys. Rev.* **1955**, *97*, 1474. (b) Macromodel[19] uses the partial charge treatment of electrostatics instead of the MM2 standard dipole–dipole electrostatics.

[18] Allinger, N. L. *Brief guidelines for obtaining parameters for the MM2 system*, April 1988.

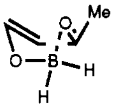
[19] Copyright Columbia University. We thank Professor Still for providing copies of his program.

Table II. Comparison between ab Initio and Force Field Calculations (Relative Energies, kcal mol^{-1})

	ab initio[a]	force field[b]	description
chair 1	1.4	1.40	MeCHO enolate + $H_2C{=}O$
boat A 2	0.0	0.00	
boat A (trans) 3	0.0	0.00	MeCHO enolate + MeCHO
boat A (cis) 4	1.6	1.44	
chair ax (cis) 5	4.2[c]	4.01	
chair eq (trans) 6	2.4	2.51	
boat A 7	0.0	0.00	MeCOMe enolate + $H_2C{=}O$
chair 8	0.4	0.42	
boat A 9	0.0	0.00	MeCHO enolate + $H_2C{=}O$
chair 10	0.1	0.30	(B-Me ax)
boat A 11	4.0	3.85	EtCHO Z enolate + $H_2C{=}O$
chair 12	0.0	0.00	
boat A 13	0.0	0.00	EtCHO E enolate + $H_2C{=}O$
chair 14	0.1	0.20	

[a] Reference 11. [b] This paper. [c] Collapses to boat A (trans) upon optimization.

are given in Table II. By the use of the Multiconformer[20] subroutine of MacroModel, with a 30° resolution, we made sure that there were no other minima on the potential surface. The force field appeared to be reasonably robust, because the random alteration of some of the terms did not make a large change in the resulting geometries or energy differences.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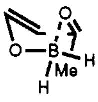
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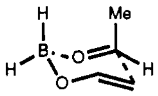
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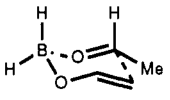
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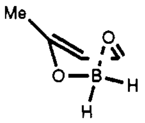
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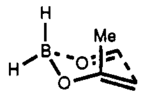
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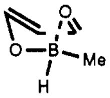
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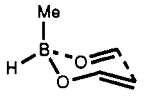
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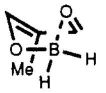
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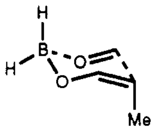
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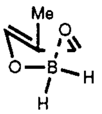
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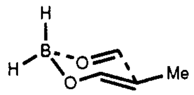

14

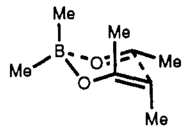
Aldol Reactions of Achiral Enolates: Syn/Anti Selectivities. The field was then extended to cases with more than one methyl group attached, and it was found that the extra methyl groups did not result in serious distortion of the transition structures. The conformational space available to those fully substituted structures was searched using Multiconformer[19,20] at 30° resolution. In the cases where syn and anti isomers could be formed, two separate Multiconformer runs were necessary: one with the aldehyde methyl group cis to the boron, and the other with it trans. The results were then combined to calculate the Boltzmann distribution.

From the results for the *Z* and *E* enol borinates of butanone adding to ethanal, see Table III, the model seems well behaved. A Boltzmann distribution, calculated at −78 °C for the competing transition structures 15–18, predicts essentially complete syn selectivity (syn:anti = 99:1) for the reaction of the *Z* enol dimethyl borinate, i.e. the chair pathway dominates, and a reduced anti selectivity (anti:syn = 86:14) from the corresponding transition structures 19–22 for the *E* enol borinate, i.e. an increased contribution from the boat pathway. These ratios are in close agreement with those found experimentally for butyl ligands on boron.[2,3c,n]

Table III. Force Field Calculations (Relative Energies, kcal mol^{-1})

	force field	description	syn/anti at −78 °C[c]
chair eq (trans) 15[a]	0.00	EtCOMe Z enolate +	99:1
chair ax (cis) 16[b]	1.93	MeCHO (Me-B-Me)	
boat A (trans) 17[b]	2.74		
boat A (cis) 18[a]	5.35		
chair eq (trans) 19[b]	0.00	EtCOMe E enolate +	14:86
boat A (trans) 20[a]	0.79	MeCHO (Me-B-Me)	
chair ax (cis) 21[a]	1.28		
boat A (cis) 22[b]	1.60		

[a] Leads to the syn isomer. [b] Leads to the anti isomer. [c] From a Boltzmann distribution of the competing structures at 195 K.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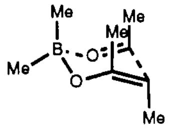
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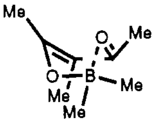
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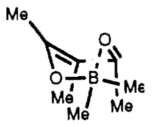
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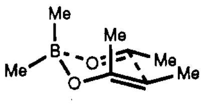
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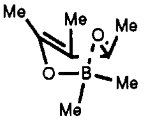
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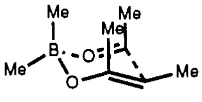
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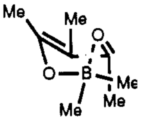
22

We also tested the force field in an unsubstituted enol borinate case, i.e. the acetone enol dimethylborinate addition to ethanal. Multiconformer (30° resolution) found seven minima within 2.5 kcal mol^{-1}, which shows a great deal of flexibility for methyl ketone enolate transition structures, in agreement with the experimental observations.[6]

Aldol Reactions of Chiral Enolates: Aldehyde π-Face Selectivities. We next used this force field to model the transition structures of a number of chiral enolate reactions for which the experimental results are available.[3f,j,l,6] The additional torsional terms needed to model the alkyl ligands were set to zero: because we had no data with which to choose better terms we decided to use the simplest possible numbers. The conformational space was searched with Multiconformer using a 30° resolution for each dihedral angle including all rotatable bonds of the transition structure "core" substituents. Two separate Multiconformer runs were necessary: one with attack at the aldehyde *si* face and the other with the *re* face. The transition structures found by this search were analyzed by a Boltzmann distribution of the various conformers (within 2.5 kcal mol^{-1}) leading to each stereoisomer. The force field calculations predicted 100% syn selectivity for the *Z* enolates (exp.[3f,j,l] syn:anti ratios >95:5) and the correct sense of aldehyde π-facial selectivity.

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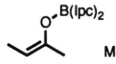
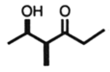
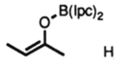
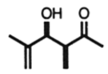
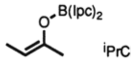
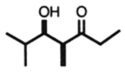
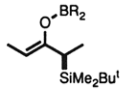
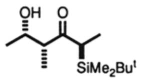
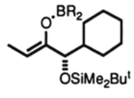
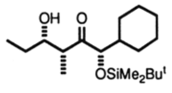
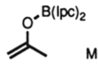
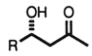
(20) Lipton, M.; Still, W. C. *J. Comp. Chem.* **1988**, *9*, 343.

Table IV. Comparison of Experimental and Calculated Selectivities in Asymmetric Aldol Reactions

entry	enol borinate/ aldehyde in calculation	experimental major aldol isomer (ref)	experimental aldehyde *si*/*re* face selectivity	calculated aldehyde *si*/*re* face selectivity
1	 MeCHO (ligands from (+)-α-pinene)	 (3j)[a]	10:1[a]	19:1
2	 H_2C=C(Me)CHO (ligands from (+)-α-pinene)	 (3j,6)[b]	27:1[b]	24:1
3	 ${}^iPrCHO$ (ligands from (+)-α-pinene)	 (3j)[a]	5:1[a]	5:1
4	 MeCHO (R_2B = 9-BBN)	 (3f)[c]	1:99[c]	1:24
5	 MeCHO (R_2B = 9-BBN)	 (3l)[d]	1:17[d]	1:16
6	 MeCHO (ligands from (+)-α-pinene)	 (6)[e]	1:6[e]	1:1

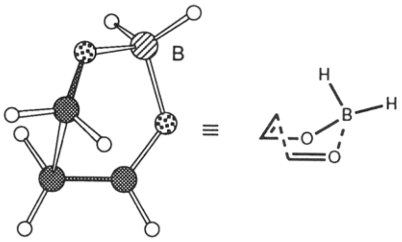
[a] Result obtained with *Z* enol borinate from 3-pentanone. [b] 27:1 ratio with Z enol borinate from butanone (ref 6); 19:1 ratio with *Z* enol borinate from 3-pentanone (ref 3j). [c] Result obtained with enol dibutylborinate. [d] Result obtained with 1-propanal. [e] 1:8 ratio with 1-propanal; 1:3.6 ratio with benzaldehyde; 1:6.4 ratio with methacrolein.

Quantitative agreement between calculated and experimental aldehyde *si*/*re* face ratios ranged from fair to excellent, as shown in Table IV. In the case of the asymmetric aldol additions of *Z* enol borinates of ethyl ketones with chiral Ipc ligands attached to boron, the force field was sensitive to the nature of the aldehyde and predicted reduced enantioselectivity for isobutanal (entry 3) relative to other aldehydes (entries 1–2), as is found experimentally.[3j] For the *Z* enol borinates of the two α-chiral ethyl ketones (modeled as their 9-BBN enol derivatives) in entries 4 and 5, there was also a good match between the calculated and experimental[3f,l] stereoselectivities. One should note that there is inversion of aldehyde face selectivity occurring upon the unsubstituted $(Ipc)_2B$-enolate addition (*si*/*re* = 1:6) relative to *Z* substituted enolates (*si*/*re* = 5-27:1), compare entries 1–3 with entry 6 of Table IV.[6,10] The intervention of a boat transition structure has been invoked to rationalize this result.[6] In the case of the *Z*-substituted enolates, a full Multiconformer search of the transition-state "core" was able to generate only chairs (entries 1–5), while nine transition structures within 1.5 kcal mol^{-1} were found in the unsubstituted case (entry 6). Two of these were chairs, five were boats A, and two were new transition structures which we term boats B (see below). At this stage, we decided to more closely examine boat B by ab initio calculations to assess its significance on the potential surface, since it had not previously been considered.

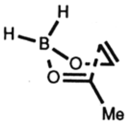
Transition Structures from ab Initio Calculations. We found this new boat B by ab initio calculations (GAUSSIAN 82, 3-21G)[21–23] to correspond to a transition structure **23** for the aldol reaction of the enol dihydroborinate of ethanal with formaldehyde (the all hydrogen case), in addition to the chair **1** and twist-boat **2** (= boat A) reported by Houk.[11] It had one negative eigenvalue, and semiempirical calculations (AM1) confirmed that it was a true transition structure.[24] The C=C···C=O torsional angle of boat B, **23**, was 73° compared with 25° for Houk's twist-boat transition structure **2**.

Semiempirical calculations (AM1) were carried out on structures **1**, **2**, and **23** (details in the supplementary material). Good geometry fit and close duplication of the relative ab initio transition structure energies were obtained, indicating that an allowance for electron correlation should be unnecessary.

boat B (**23**)



We then repeated Houk's ab initio calculations on the aldol reaction of the enol dihydroborinate of ethanal with ethanal, considering the new boat B, as well as the chair and the twist-boat (= boat A) reported by Houk, this time finding *six* structures. These correspond to the transition structures: chairs **5** and **6**, boats A **3** and **4**, and boats B **24** and **25**, i.e. where the extra methyl group is added to formaldehyde in each of the two possible geometries. The chair structure **5** with the methyl group axial is not a real transition state and collapses to a twist-boat, as Houk has also reported.[11] Boat B was found to be an important transition structure in all the cases reported in Table I, cf. the additional structures **26**, **27**, and **28**, except for the addition of the *Z* enolate of propanal to formaldehyde, where only the chair and boat A were found to exist. The C=C—O—B torsional angle in boat B was only 9° and so a *Z* substituent on the double bond would introduce severe steric hindrance for this structure in comparison with the chair and boat A. The complete set of revised ab initio results for these aldol reactions are summarized in Table V.



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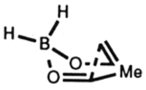

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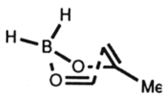

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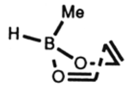

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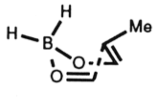

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(21) Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, R. A.; Fluder, E. M.; Pople, J. A. Carnegie-Mellon University, Pittsburgh, PA 15213.

(22) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(23) We used Baker's transition structure searching algorithm, see: Baker, J. *J. Comp. Chem.* **1987**, *7*, 385.

(24) See supplementary material. (a) Dewar, M. J. S.; Zoebish, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Jie, C.; Zoebish, E. G. *Organometallics* **1988**, *7*, 513.

Table V. Ab Initio Calculations (Relative Energies, kcal mol^{-1})

	ab initio[a]	ab initio[b]	description
chair **1**	1.4	1.33	MeCHO enolate + $H_2C{=}O$
boat A **2**	0.0	0.00	
boat B **23**	-	1.74	
boat A (trans) **3**	0.0	0.00	MeCHO enolate + MeCHO
boat A (cis) **4**	1.6	1.64	
boat B (trans) **24**	-	1.79	
chair ax. (cis) **5**	4.2[c]	4.15[c]	
chair eq. (trans) **6**	2.4	2.39	
boat B (cis) **25**	-	3.00	
boat A **7**	0.0	0.00	MeCOMe enolate + $H_2C{=}O$
chair **8**	0.4	0.42	
boat B **26**	-	1.67	
boat A **9**	0.0	0.00	MeCHO enolate + $H_2C{=}O$
chair **10**	0.1	0.10	(B-Me ax)
boat B **27**	-	2.73	
boat A **11**	4.0	4.0	EtCHO Z enolate + $H_2C{=}O$
chair **12**	0.0	0.00	
boat A **13**	0.0	0.00	EtCHO E enolate + $H_2C{=}O$
chair **14**	0.1	0.10	
boat B **28**	-	1.52	

[a] Reference 11. [b] This paper. [c] Collapses to boat A (trans) upon optimization.

The poor treatment of the acetone enolate case (Table IV, entry 6) by our existing aldol force field, therefore, may reflect the importance of a contribution from the boat B transition structure for unsubstituted and *E* enol borinates, since it has been so far neglected in the calibration of the force field.

Conclusions

A force field model for the aldol reactions of ketone-derived enol borinates with aldehydes has been developed, which can reproduce the ab initio geometries and energies of the transition structures **1**–**14** (±0.2 kcal mol^{-1}). It reproduces the experimental syn:anti stereoselectivity for the aldol additions of simple *Z*- and *E*-substituted enol borinates derived from ethyl ketones, and it shows that unsubstituted enol borinates (methyl ketone derived) have a greater degree of flexibility. The force field also reproduces the experimental aldehyde *si*/*re* face selectivity in the aldol reactions of a range of chiral *Z* enol borinates. In the aldol reactions of unsubstituted and *E*-substituted enol borinates, the new transition structure boat B is likely to be important as well as the chair and the twist-boat reported by Houk (= boat A); its omission from the development of the force field may explain the poor treatment of methyl ketone reactions.

In summary, the aldol force field described here is probably well designed for treating the *Z* enol borinates (where boat B is not a transition structure), but is likely to be inadequate for the *E*-substituted and the unsubstituted structures. We are now trying to develop a comprehensive field and to calibrate it with all the existing transition structures, including all the boats B.

All the foregoing results indicate that the relative energies of the competing transition states define the selectivity of the boron-mediated aldol reaction, i.e. the Curtin Hammett principle applies. The force field developed here may be useful as a predictive tool for assessing stereoselection in new aldol reactions and for the rational design of new chiral boron enolate reagents for asymmetric synthesis.

Acknowledgment. We thank Professor Clark Still, Dr. George Chang, Dr. Tom Hendrickson (Columbia University), Professor Scott Kahn (University of Illinois), and Professor Ken Houk (UCLA) for assistance and advice. Financial support from CNR, SERC, Lilly Research Centre (CASE Award to J.M.G.), NATO (0368/88), and the Commission of the European Communities (SCI*.0324.C-[JR]) is gratefully acknowledged. The Cambridge University Computer Service is thanked for providing computer time.

Supplementary Material Available: Details of ab initio calculations, including Z-matrices for structures **1**–**8** and **23**–**28**, and semiempirical calculations (8 pages). Ordering information is given on any current masthead page.