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ON THE STEREOCHEMISTRY OF THE ALDOL-ADDITION

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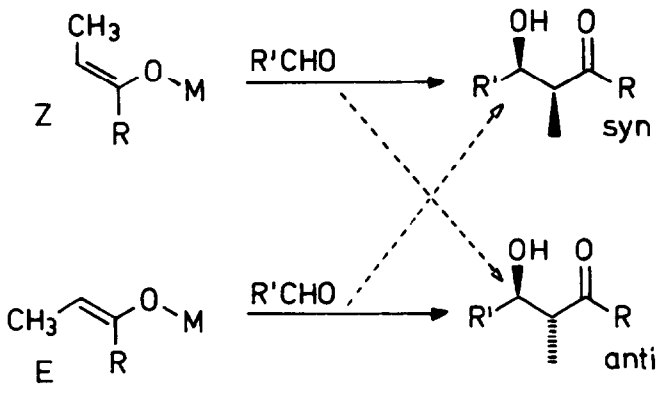
Abstract: NOE-experiments and STO-3G calculations suggest that E-enol borates exist in an U-conformation 7a, whereas the Z-enol borates should prefer the extended conformation 8b. These observations have been linked to the stereoselectivity of the aldol addition. The resulting predictions are in line with the stereoselectivity observed on addition of cyclohexenol borates to benzaldehyde.

The aldol-addition is one of the important diastereogenic reactions in which two new stereocenters are formed.[1] In general the reaction is considered to proceed via chair like transition states 2 such that Z-enolates lead to syn-aldols and that E-enolates lead to anti-aldols.

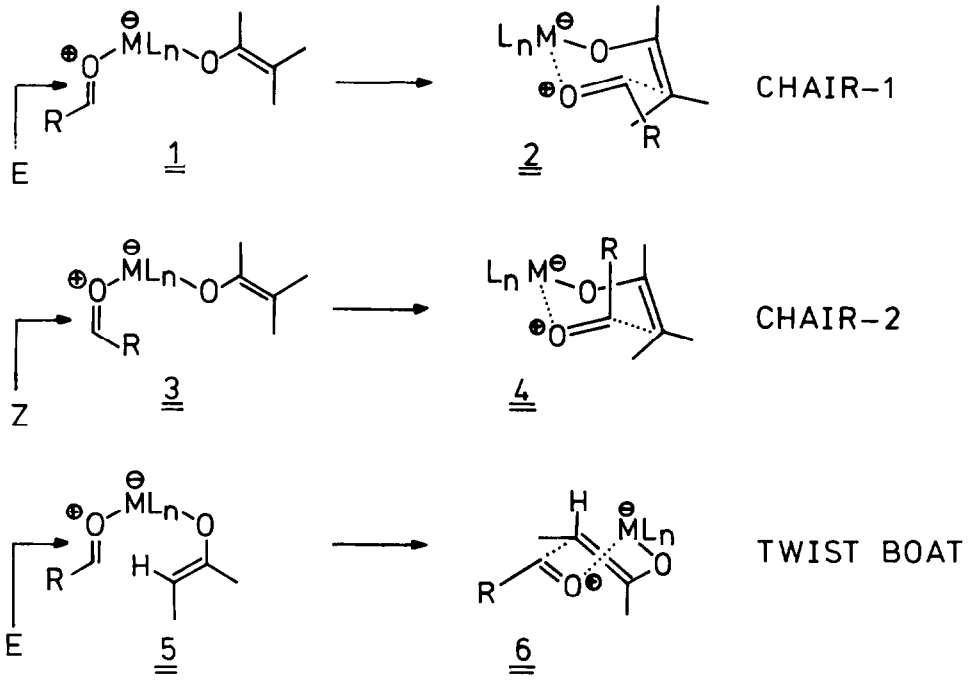


The occasional reports of aberrant behaviour[2,3] have been ascribed to reactions proceeding via boat type transition states[3] cf. 6 or via chair type transition states 4 with an axial arrangement of the aldehyde group. The pertinent reviews[1] give only vague hints as to why such aberrant behaviour is prominent mainly with E-enolates and particularly so for enolates of cyclohexanone[3] and cyclopentanone[4].

We became fully aware of this situation by our recent observation of an unexpected syn-selective aldol addition of E-enol borates.[5] In search of an explanation we suspected that the stereoselectivity of the aldol addition may be

connected to the conformations available to the enol borates. We therefore studied this aspect both computationally and by NOE experiments.

Our reasoning is as follows: The aldol addition should commence with a coordination of the Lewis-acidic metal to the aldehyde. In case that the Lewis acid coordinates by a single vacant orbital (e.g. BF_3 or other boron compounds) the complexes 1 with E-geometry should be formed in preference over those with Z-geometry 3.[6,7] For instance, the benzaldehyde · BF_3 adduct has the E-configuration.[8]



Proceeding further along the reaction coordinate of the aldol addition bonding of the enolate carbon to the aldehyde carbon must occur. It is likely that the entity R-C=O-M remains rigidly coplanar[9] during this process until the incoming enolate carbon has bonded extensively. Because only then sufficient electron density has been transferred into the π^*-orbital of the carbonyl group to facilitate a change in the dihedral angle of the R-C-O-M-unit.

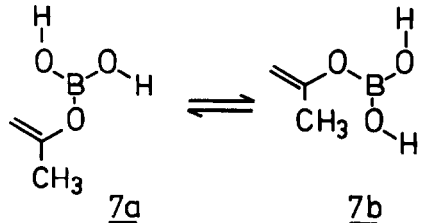
With this notion in mind we see that the complex 1 will adopt with very little nuclear motion the familiar transition state 2 (CHAIR-1) of the aldol addition. Aberrant stereoselectivity would require a reaction either via the transition state 4 (CHAIR-2) or 6 (TWIST BOAT). We believe that the former process is unfavorable because the precursor arrangement 3 for such a transition state 4 is already energetically unfavorable due to the Z-coordination of the aldehyde. More important: The very factors destabilizing the Z-arrangement 3 will be felt in the transition state 4. Thus aldol addition with aberrant stereoselectivity are likely to proceed via a twist boat transition state 6.[3]

The key feature is that these twist boat transition states can be attained most readily if the enolate is able to assume an U-conformation, viz. 5. Again this arrangement can adopt with very little nuclear motion the twist-boat transition state 6, maintaining the R-C=O-Lewis acid unit coplanar. The transformation of 5

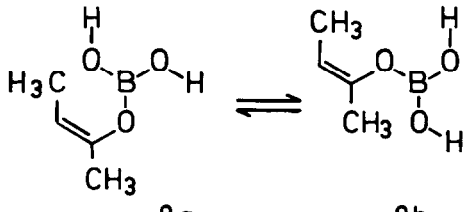
into a chair transition state 7 is not excluded, but involves considerable rotations and pushing of the aldehyde-H into the enolate π-cloud. This is avoided in going from 5 to 6.

According to this analysis the stereoselectivity of the aldol addition depends on the conformations available to the metal enolate: Those enolates, that can only exist in the extended arrangement (M-O-C=C zigzag) should react selectively via the well established chair transition state 2. Metal enolates that can assume or even prefer the U-arrangement, vic. 5, have the option to react also via the twist boat transition state 6 to the aberrant syn-aldol.

It therefore became of interest to determine the preferred conformation of enolates and in particular of enol borates as well as the energy difference between the extended and the U-conformation for these species. Ab initio STO-3G calculations on an MNDO optimized geometry[10] of the model structure 7 suggest that the U-conformation 7a is by 1 - 2 kcal more stable than the extended conformation 7b. This can be rationalized in terms of a through-space interaction involving 6 π-electrons, probably supported by an electrostatic attraction between a negatively charged oxygen atom and a positively charged hydrogen atom, which are separated by 2.6 A.



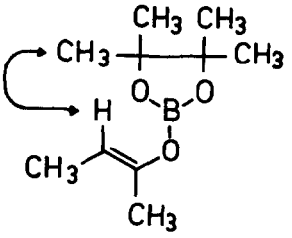
7a 7b



8a 8b

The results of these calculations are in line with NOE-experiments on the E-enol-borates 9 and 10, which revealed clear NOE effects between the positions indicated. These enol borates therefore exist predominantly in the U-conformation showing the same conformational preferences as E-enol ethers[11,12] or E-enols.[13]

Calculations on the model 8 for a Z-enol borate suggest that now the extended conformation 8b is preferred by 3 to 5 kcal relative to 8a, in line with the conformational preferences of Z-enols.[13] This is probably due to increased angle strain in the U-conformation caused by steric repulsion. Attempts to determine the conformation of the Z-enol-borate 11 by NOE-experiments remained inconclusive.



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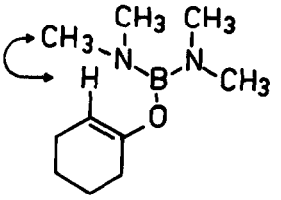

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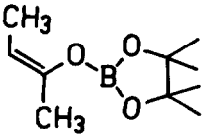
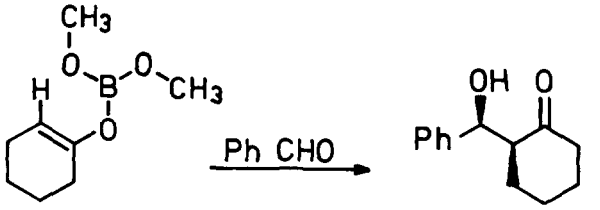


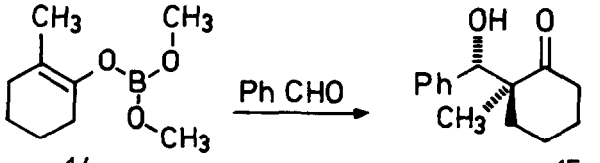
11

Any correlation of these results with the stereochemistry of the aldol addition has to regard the Curtin Hammett principle according to which it would not matter in what conformation the starting enolate exists.[14] Rather it is important which conformations are energetically available to the enolates! Of course, factors that stabilize a certain ground state conformation of an enolate may persist in the transition state of the aldol addition. From the above calculations and experiments it is obvious that only E-enolates have a reasonable chance to adopt both conformations and in consequence aberrant stereoselectivity in the aldol addition should be restricted to those.

For data on these predictions let us inspect again the reactions of the enol borates: The E-enol borates 10 and 12 added to benzaldehyde leading to the aberrant syn-aldol 13[5,15] with a selectivity in excess of 90 %. To test whether this is a particular feature of the cyclohexenyl system or whether the enolate conformation is decisive, we studied the enol borate 14 in which the syn-conformation is precluded: The enol borate 14 generated from the Li-enolate[5] no longer added to benzaldehyde under the normal conditions.[5] The aldol addition could be forced to proceed at room temperature by 4 kbar pressure, yielding the adduct 15[16] with >95 % diastereoselectivity. This is the diastereomer expected from a reaction via the chair transition state 2. Our experiment thus complements the recent observation[3] on the aldol addition of the titanium enolate corresponding to 14, similarly leading to 15.



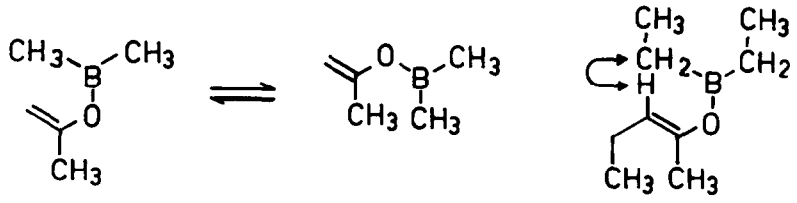
12 13



14 15

While this discussion points out that it is the E-enolates that may react via twist-boat transition states 6 to syn-aldols, it remained to be demonstrated that such a transition state is favored over the chair transition state at least in the case of the enol borate additions. To clarify this aspect the group of Gennari and Scolastico has recently carried out MNDO-calculations of the transition states of this particular reaction.[17] It is gratifying that indeed the twist boat transition state came out to be the lowest energy one of the transition states examined.

In contrast to the aberrant enol borate addition that of enol borinates follows the classical pattern in that E-enol borinates such as 17 lead to anti-aldols.[1] In accord with these results Gennari's calculations show that in these reactions the chair transition state is of lowest energy. Is this connected with a preference of the ground state enol borinates for an extended conformation, viz. 16b? Both computational and NOE studies negate this hypothesis:



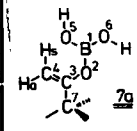
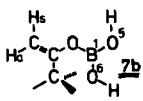
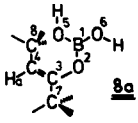
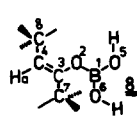
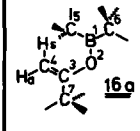
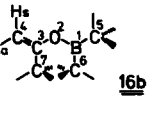
16a 16b 17

STO-3G calculations on the model 16 for an enol borinate showed the U-conformation 16a to be favored by 1 - 2 kcal over the extended conformation 16b. Again, this may be rationalized in terms of stabilizing through space interactions. The methyl group can act as a π-donor via its pseudo π-orbital thus leading to a 6 π ensemble. These calculations are consistent with an experimentally observed NOE-effect between the indicated positions in the enol borinate 17, demonstrating that the U-conformation is the predominating one.

In conclusion, we propose that Z-enolates exist exclusively in an extended conformation, which is maintained in a chair transition state of the aldol addition. The reaction proceeding only via this type of transition state is stereospecific. E-enolates may exist both in an extended and an U-conformation. The latter makes twist-boat transition states in the aldol addition accessible. Therefore, the addition of E-enolates to aldehydes may proceed via two types of transition states of comparable energy, and hence, may no longer be stereoselective.

We are grateful to the Fonds der Chemischen Industrie for support of this study and for granting a fellowship to S.F. We also thank Dr. C. Gennari, Milano and Dr. E. Nakamura, Tokyo for liberal exchange of informations.

Calculated Geometries and Energies of Enol Borates 7, 8 and Enol Borinates 16[a]

Parameter	 7a	 7b	 8a	 8b	 16a	 16b
R(1,2)	1.374	1.373	1.369	1.373	1.352	1.349
R(2,3)	1.366	1.369	1.359	1.365	1.366	1.370
R(3,4)	1.354	1.359	1.359	1.365	1.353	1.359
R(3,7)	1.521	1.512	1.528	1.516	1.521	1.512
R(1,5)	1.366	1.372	1.363	1.372	1.573	1.581
R(1,6)	1.372	1.366	1.374	1.366	1.580	1.574
R(4,8)			1.492	1.494		
α(1,2,3)	134.7	135.0	140.9	135.4	138.5	139.3
α(2,3,4)	127.0	114.9	130.7	117.0	126.9	115.1
α(2,3,7)	109.9	121.9	108.3	121.2	110.3	122.0
α(7,3,4)	123.1	123.2	121.0	121.7	122.8	122.9
α(3,4,Hs)	126.4	124.4	133.9[b]	130.3[b]	126.2	124.3
α(3,4,Ha)	121.1	122.1	115.2	117.5	121.2	122.1
α(5,1,2)	123.5	116.9	124.2	117.1	125.9	113.6
α(5,1,6)	119.4	119.4	119.3	119.4	120.5	120.2
α(H,5,1)	115.9	117.1	116.1	117.1	111.1[c]	114.7[c]
α(1,6,H)	117.3	115.9	117.2	116.1	115.0[c]	111.6[c]
α(6,1,2)	117.1	123.7	116.5	123.5	113.6	126.2
E(STO-3G)	-362.30924		-400.88114		-291.69309	
ΔH_f°	-207.1		-211.5		-78.0	
ΔE	0	1.70	0	-5.5	0	1.9
$\Delta\Delta H_f^\circ$ [d]	0	1.00	0	-3.2	0	1.2

[a] MNDO geometries. Bond length in Å, bond angles in deg. Absolute energies E in hartree, relative energies and heats of formation in kcal/mol.

[b] Angle α(3,4,8) is given.

[c] H is the in-plane hydrogen atom of the methyl group

[d] Relative enthalpies $\Delta\Delta H_f^\circ$ have been corrected for correlation effects according to W. THIEL, J.Am.Chem.Soc. 103, 1413 (1981).

Experimental

NOE-Experiments: 9: Irradiation into the methyl singlet at δ = 1.27 ppm caused a NOE-enhancement of the vinyl-signal at δ = 4.99 ppm. 10: Irradiation into the methyl singlet at δ = 2.56 ppm caused a differential NOE of 7 % at the vinyl signal at δ = 4.66 ppm. 17: (prepared according to[18]). Irradiation into the signals of the boron-ethyl-groups at δ = 0.67 - 0.92 ppm caused among others a NOE-enhancement of the vinyl signal at δ = 4.71 ppm.

Cyclohexenyloxy-bis(dimethylamino)borane (10): The enolate of cyclohexanone (12.0 g, 122 mmol) was generated in 100 ml of THF by the addition of lithium-diisopropylamide and treated at -78 °C with chloro-bis(dimethylamino)borane[19] (17.9 g, 133 mmol). The next day concentration and distillation resulted in 95 % of 10 as colourless oil of b.p. 55 °C/0.2 Torr. ^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.51 - 1.56 (m, 2H), 1.65 - 1.71 (m, 2H), 2.0 - 2.06 (m, 4H), 2.56 (s, 12H), 4.66 (m, 1H). - ^{13}C nmr ($CDCl_3$): δ = 22.3, 23.0, 23.7, 28.5, 37.9, 100.7, 150.6.

$C_{10}H_{21}BN_2O$ (196.1)	Calc.	C 61.24	H 10.79	N 14.29
	Found	C 60.52	H 10.75	N 14.62

Addition of cyclohexenyloxy-dimethoxy-borane 12 to benzaldehyde: The enolate of cyclohexanol generated at 0 °C from 1-trimethylsilyloxy-cyclohexene (0.79 g, 4.6 mmol) and n-butyllithium in 50 ml THF was reacted at -78 °C with chloro-dimethoxy-borane (0.54 g, 5 mmol). After 2 h benzaldehyde (0.49 g, 4.6 mmol) was added at -78 °C. After three more hours at this temperature the reaction was quenched by addition of 100 ml of aqueous $NaHCO_3$-solution. The mixture was extracted 4 times with 40 ml of ether. The dried (Na_2SO_4) extracts gave on concentration 0.78 g (93 %) of 13, syn/anti = 92:8.[15]

Addition of 2-methyl-1-cyclohexenyloxy-dimethoxy-borane 14 to benzaldehyde: The enolate was generated from 2-methyl-1-trimethylsilyloxy-cyclohexene[20] (0.37 g, 2 mmol) in 30 ml of THF by n-butyllithium at 25 °C. After cooling to -90 °C chloro-dimethoxy-borane (0.44 g, 4 mmol) was added and the mixture was warmed to -40 °C over 1 h. The mixture was concentrated to a volume of 8 ml taken up in 10 ml of cyclohexane and concentrated again to 8 ml, all operations at -20 °C. After addition of benzaldehyde (0.24 g, 2.3 mmol) the mixture was pressurized for 3 h at 4 kbar. The mixture was taken up in 10 ml of petroleum ether and was hydrolyzed by a 0.25 m phosphate buffer (pH 7, 50 ml). After extraction 3 times with 30 ml of pentane and 2 times with 20 ml of ether the dried (Na_2SO_4) extracts were concentrated. ^{1}H nmr analysis of the residue showed the presence of S*,S*-15 in a yield of ca. 50 %. The diastereomere ratio was determined from the 400 MHz ^{1}H nmr spectrum to be >97:<3.

From a non-stereoselective enolate addition the diastereomers of 15 were separated by HPLC on LiChrosorb Si 60 with petroleum ether/ethyl acetate = 85 : 15 and showed the following data:[16]

15 (S*,S*): ^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.25 - 1.29 (m, 1H), 1.55 - 1.77 (m, 4H), 1.99 - 2.05 (m, 1H), 2.37 - 2.42 (m, 1H), 2.57 - 2.63(m, 1H), 3.96 (broad s, 1H), 4.97 (s, 1H), 7.27 - 7.33 (m, 5H). - ^{13}C nmr ($CDCl_3$): δ = 15.9, 20.6, 27.2, 36.9, 38.9, 52.7, 77.4, 127.4, 127.5, 128.0, 139.1, 218.7.

$C_{14}H_{18}O_2$ (218.3)	Calc.	C 77.03	H 8.31
	Found	C 76.86	H 8.44

Epi-15 (R*,S*): ^{1}H nmr (400 MHz, $CDCl_3$): δ = 1.07 (s, 3H), 1.35 - 1.42 (m, 1H), 1.59 - 1.77 (m, 3H), 1.98 - 2.03 (m, 1H), 2.11 - 2.18 (m, 1H), 2.34 - 2.39 (m, 1H), 2.54 - 2.62 (m, 1H), 3.07 (broad s, 1H), 5.08 (s, 1H), 7.27 - 7.33 (m, 5H). - ^{13}C nmr ($CDCl_3$): δ = 20.5, 21.5, 26.5, 31.3, 39.4, 53.6, 77.3, 127.4, 127.6, 128.1, 139.5, 217.8.

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