# Solution Structure of a Chiral Dialkylboron Enolate by NMR Spectroscopy and Simulated Annealing: Unusual Stabilization of This Intermediate by a Boron−Nitrogen Interaction

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The understanding of stereo- and enantioselective reactions is indispensable for todays challenges in medicinal chemistry, as most enzymes and receptors strictly discriminate between stereoisomers. Spatial complementarity between ligands and target enzymes can be achieved by designing all relative and absolute stereogenic centers of new ligands. The combination of multidimensional NMR spectroscopy with computational approaches such as simulated annealing and distance geometry yields information about the conformation and relative configuration of key intermediates in those stereospecific syntheses of relevant compounds.

The aldol reaction is still one of the most popular carbon−carbon bond forming transformation, while using preformed enol derivatives provides an effective way to control stereoselectivity.[1] In particular, the introduction of architecturally refined enolate metal centers improves its stereochemical attributes remarkably. Especially boron enolates[2] and tetrachlorotitanium enolates leads to well-defined transition states and high stereoselective yields.[3]

Chiral oxazolidinones have been utilized as chiral auxiliaries in different types of reactions[4] with high enantioselectivity. The asymmetric induction of the boron mediated aldol reaction is accomplished in a noninteractive way; i.e., the reaction is simply blocked at one side of the substrate. For dialkylboryl enolates, the stereochemistry of the kinetic aldol product was shown to be related to enolate geometry.

During our investigations of the enantioselective synthesis of propanolamine based compounds, we observed that the aldol reaction of a chiral oxazolidinone acylated with phenyl acetic acid yielded the desired aldol product with high diastereo- and enantioselectivity. However, the corresponding reaction using the 2-pyridyl acetic acid derivative for acylation led exclusively to the dialkylboryl enolate intermediate **1** (Scheme 1). This situation was further complicated because chiral 3-pyridyl acetic acid derivatives behaved as expected during an aldol reaction. To understand this remarkable stability of 2-pyridyl dialkylboron enolates, we studied the conformation of the dibutylboryl enolate in $CDCl_3$ solution using 2D-NMR spectroscopy and restrained simulated annealing, as suitable crystals for X-ray crystallography were not obtained.

All NMR spectra were recorded on a Bruker DRX 600 spectrometer at 300 K using 20 mg of the dibutylboryl enolate **1** in 0.5 mL of $CDCl_3$.[5] The $^1$H and $^{13}$C assignments are given in the Supporting Information (Table S1), diastereotopic protons at C9 and C11 could be assigned using NOE derived distances, $^3J$(C,H) and $^3J$(H,H) coupling constants. Furthermore, the known absolute configuration at C10 and the constrained five membered ring system permitted the unambiguous assignment of protons at C9. Here the experimental coupling constant of 7.8 Hz between H10 and H9$^{proR}$ is in agreement with a dihedral angle of 9.6° in the five membered ring system after simulated annealing. This translates to a theoretical coupling constant of 8.4 Hz. On the other hand the experimental coupling constant $J_{H10-H9}{}^{proS}$ is 2.7 Hz, which corresponds to the calculated dihedral angle of −117.4° (theoretical coupling constant 2.8 Hz). The population of three rotameric states around the oxazolidine side chain torsion N7−C10−C11−C12 was calculated based on coupling constants $J_{H10-H11}{}^{proS}$ and $J_{H10-H11}{}^{proR}$.[6] This side chain torsion predominantly adopts the 180° orientation (65%), while +60° and −60° are less populated (5%, 30%), respectively, due to steric hindrance. Only one distinct set of signals was found in the $^1$H and $^{13}$C NMR spectra, no conformational change slow on the NMR time scale could be determined by line-broadening effects. All other criteria for conformational homogeneity were fulfilled,[7] all experimental data are

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(5) Homonuclear 2D-NMR experiments (DQF−COSY (Derome, A.; Williamson, M. *J. Magn. Reson*. **1990**, *88*, 177−185.), TOCSY (Bax A.; Davis, D. G. *J. Magn. Reson*. **1985**, *65*, 355−360.), and NOESY (Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys*. **1979**, *71*, 4546−4553.)) were performed with a spectral width of 8 ppm. These spectra were recorded with 1024 increments in $t_1$ and 4096 complex data points in $t_2$. For the NOESY 16 transients were averaged for each $t_1$ value, for COSY and TOCSY 8 transients. Mixing times of 70 or 150 ms were used for TOCSY and ROESY spectra, respectively. Data processing was done using the XWIN NMR software from Bruker. For HMQC (Bax, A.; Subramanian, S. *J. Magn. Reson*. **1986**, *67*, 565−569.) spectra 1024 increments (16 scans) with 4096 complex data points in $t_2$ were collected using a sweep width of 8 ppm in the proton and 165 ppm in the carbon dimension. The HMBC (Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093−2094.) spectra were acquired with a sweep width of 8 ppm in the proton and 200 ppm in the carbon dimension. A total of 48 transients were averaged for each of 1024 increments in $t_1$, and 4096 complex points in $t_2$ were recorded. A delay of 70 ms was taken for the development of long-range correlations.

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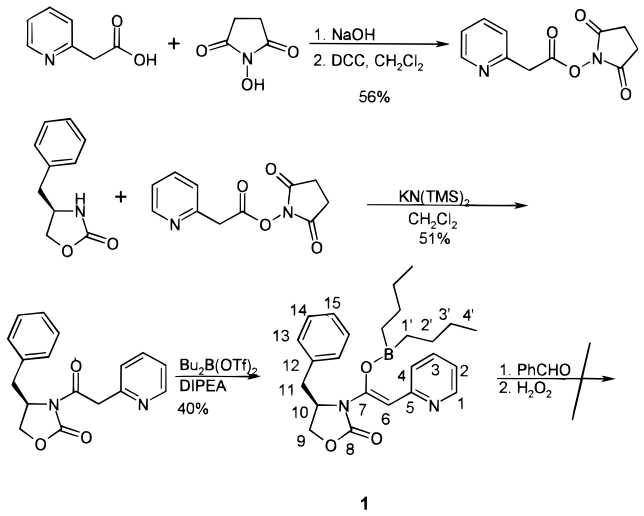
**Scheme 1. Synthesis and Atom Numbering of the Dibutylboryl Enolate 1**




**1**

consistent with the assumption of a predominant single conformation, except for the butyl side chains.

Quantitative information on interproton distances for the structure determination was obtained from analyzing a 600 MHz 2D NOESY spectrum in $CDCl_3$ with 500 ms mixing time. Volume integrals of the individually assigned cross-peaks were converted into distance constraints using the isolated spin pair approximation. The NOE restrained simulated annealing calculations[8] were performed utilizing 23 nontrivial interproton distances (Table S2).[9] Partial charges were calculated using MOPAC 6.0[10] with the AM1 Hamiltonian.[11]

As an interaction between boron and nitrogen will not be modeled correctly using force field methods (e.g., the used TRIPOS 6.0 force field,[12] two different 600 ps simulations (100 cycles at 6 ps) were carried out. The first run did not utilize any additional B−N bond in the molecular topology, while the postulated B − N interaction was incorporated as additional bond for the starting geometry during a second simulation. Acceptable structures were selected based on the maximum pairwise rmsd method,[13] for each structure the pairwise rmsd to all structures with lower target function values was computed and the maximum rmsd as a function of the constraint violation value was plotted. Structures corresponding to the first plateau were selected, leading to an ensemble of 15 acceptable conformers for the first run with an average restraint violation of 0.041 Å and 19 conformers for the second run (average restraint violation 0.037 Å) with the B−N bond. Only the constraint $H9^{proS}$ to $H11^{proS}$ is violated more than 0.1 Å, demonstrating a good agreement between experiment and simulation, when taking only one conformation into account. There is no evidence like conflicting NOE data to account for a conformational equilibrium.

Both simulations result in a short distance between N1 and B1 with a bonding interaction forming a six-membered heterocyclus and a similar shape of all conformers. The short distance between protons H4 and H6 (exptl 2.5 Å, calcd 2.43 Å) is only possible when the 2-pyridyl side chain allows a close proximity between boron and its aromatic nitrogen. Additional support of a single conformer is given by remarkable chemical shift differences for both diastereotopic boron-complexing butyl groups, indicating a rigid, conformationally different environment, which is confirmed by NOEs involving both butyl groups to protons H1, H10, H11, and H13.

While the planarity of pyridine and phenyl rings is without question, the six-membered heterocyclus B1−O1−C7−C6−C5−N1 significantly deviates from planarity. The characteristic dihedral angle B1−O1−C7−C6 adopts an average value of −16.2 ° (std: 10.6°) for 15 conformers from the first run and −13.1° (std: 10.2°) for the 19 conformers from the second run. To check, whether this is an artifact from force field optimizations, those 15 conformers were fully geometry optimized using MOPAC 6.0 with the AM1 Hamiltonian.[14] Twelve out of 15 conformers from simulated annealing led to a completely planar six-membered ring (dihedral angle B1−O1−C7−C6: −2.2° SD: 5.8). Their average heat of formation ($\Delta H_f$) is −111.62 kcal/mol (SD 0.49 kcal/mol), while for the alternative conformers with a six-membered ring deviating from planarity, higher heats of formation between −93.18 and −98.89 kcal/mol are computed (dihedral angle B1−O1−C7−C6: between −72.6° and −86.1°). The acceptable 12 superimposed conformers after MOPAC geometry optimization are superimposed in Figure 1.

To address the questions, whether a close boron − nitrogen distance lead to a very stable structure, relaxed conformational maps were computed for the stable dibutylboryl enolate **1** with an ortho-substituted pyridine fragment and the corresponding reactive dibutylboryl enolate **2** containing a meta-substituted pyridine nucleus. Those relaxed conformational maps were computed by incrementing the dihedral angles C7−C6−C5−N1 in **1** or C7−C6−C5−C1 in **2** in steps of 10°. The resulting conformers were minimized using the TRIPOS 6.0 force field using a quasi Newton−Raphson procedure and then subjected to a full geometry optimization using MOPAC AM1. In Figure 2 the computed heats of formation (in kcal/mol) are plotted on the *y*-axis versus the dihedral

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(9) All modelling work was performed using SYBYL (Versions 6.4 and 6.5, Tripos, St. Louis, MO, 1998.) on Silicon Graphics workstations. A time step of 0.5 fs was used for the integration of Newton's equation of motion. Kinetic energy was included by coupling the system to a thermal bath (Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Di Nola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684−3690). The dielectricity function was set to 1. The NOE derived distance constraints were applied as a biharmonic constraining function with a force constant of 10 kcal/mol*Å$^2$. Upper and lower distance limits were set to plus and minus 10% of the experimental distances, for nondiastereotopically assigned methylene and methyl protons, 0.9 and 1.0 Å were added to the upper bound. The atomic velocities were applied following a Boltzmann distribution about the center of mass to obtain a starting temperature of 1000 K. After simulating for 1.0 ps at this high temperature, the system temperature was stepwise reduced using an exponential function over a 5.0 ps period to reach a final temperature of 100 K. This results in 100 cycles of a 6.0 ps simulated annealing protocol for each simulation.

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(14) Full geometry optimization level using all bonds and angles, the convergence option precise and the additional MOPAC keywords NOMM, and XYZ were used.

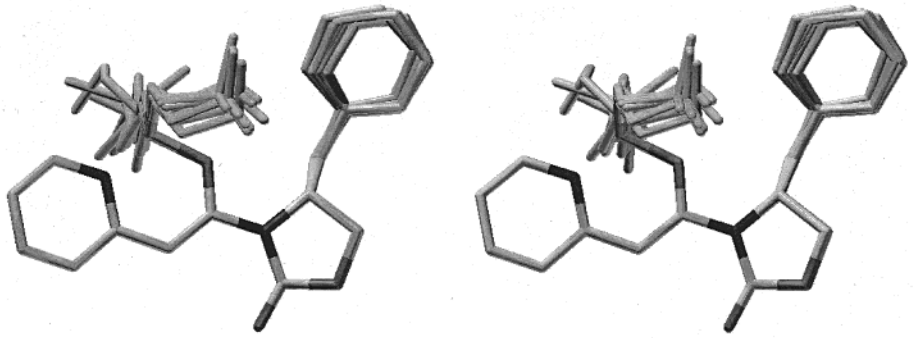

**Figure 1.** Stereoview of the superimposed ensemble of 12 acceptable conformers for the dibutylboryl enolate **1** after restrained simulated annealing and MOPAC AM1 full geometry optimization. Protons are omitted for clarity.

angle C7−C6−C5−N1 (deg) for the stable dibutylboryl enolate **1** and the corresponding angle C7−C6−C5−C1 in the reactive dibutylboryl enolate **2**. Only for **1** a minimum value is observed, when this torsion angle adopts values between −30 and +20°, corresponding to a close B−N distance (1.58 Å). Such a close distance is not possible in the meta-substituted pyridine derivative **2**, there is no orientation leading to a stabilization of this regioisomer. Due to internal structural constraints in **2**, formation of a seven-membered ring for stabilization by adding another intramolecular coordination pattern to the central boron is impossible. Although two X-ray structures of boron enolates[15] with boron−nitrogen bonds (distance: 1.60, 1.64 Å) are present in the Cambridge crystallographic database,[16] those nitrogens have no aromatic character, causing the formed six-membered heterocycles to deviate significantly from planarity. In contrast, the herein reported conformation suggests a nearly planar, stable 6-membered cyclus.

The remarkable stability of the dialkylboron enolate 1 from this study is caused by the coordination of the 2-pyridyl nitrogen with boron, as could be demonstrated using the combined application of NMR spectroscopy and quantum chemical calculations. Only **1** is internally stabilized by formation of a six-membered heterocyclus with a boron−nitrogen bond (1.58 Å), while this is not possible for **2**. As this coordination causes a reduced Lewis acidity of the boron, an activation of the benzaldehyde carbonyl-oxygen atom is no longer possible. Hence, the cyclic six-membered Zimmermann/Traxler transition state could not be formed and no subsequent

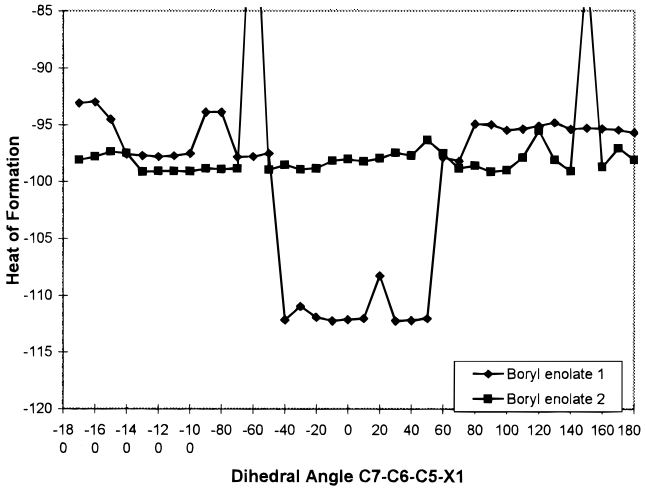


**Figure 2.** Heats of formation (in kcal/mol) versus dihedral angle C7−C6−C5−N1 (deg) for the stable dibutylboryl enolate **1** and the corresponding angle C7−C6−C5−C1 in the reactive dibutylboryl enolate **2** obtained using full MOPAC AM1 geometry optimization using grid searching.

reaction to the desired aldol product occurs. The present work demonstrates that the combined application of modern techniques for conformational analysis led to an improved understanding of very different reactivities in chemically slightly different derivatives for a well-documented reaction in many syntheses of biologically relevant molecules.

**Supporting Information Available:** Additional tables with $^{1}H$, $^{13}C$ chemical shifts, experimentally derived distance constraints, computed averaged distances for the diarylboryl enolate **1** and experimental procedures for the preparation of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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