Origins of Stereoselectivity in the α-Alkylation of Chiral Hydrazones

Elizabeth H. Krenske,†‡ K. N. Houk,*‡ Daniel Lim,§ Sarah E. Wengryniuk,§ and Don M. Coltart*§

†Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States. ‡School of Chemistry, The University of Melbourne, VIC 3010, Australia, and Australian Research Council Centre of Excellence for Free Radical Chemistry and Biotechnology, and §Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

houk@chem.ucla.edu; don.coltart@duke.edu

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Density functional theory calculations and experiment reveal the origin of stereoselectivity in the deprotonation—alkylation of chiral N-amino cyclic carbamate (ACC) hydrazones. When the ACC is a rigid, camphor-derived carbamate, the two conformations of the azaenolate intermediate differ in energy due to conformational effects within the oxazolidinone ring and steric interactions between the ACC and the azaenolate. An electrophile adds selectively to the less-hindered π-face of the azaenolate. Although it was earlier reported that use of ACC auxiliaries led to α-alkylated ketones with er values of 82:18 to 98:2, B3LYP calculations predict higher stereoselectivity. Direct measurement of the dr of an α-alkylated hydrazone prior to removal of the auxiliary confirms this prediction; the removal of the auxiliary under the reported conditions can compromise the overall stereoselectivity of the process.

Introduction

The α-alkylation of ketones is a useful synthetic operation, most often achieved via electrophilic addition to a derived azaenolate. Compared with enolates, azaenolates provide improved reactivities, yields, and regioselectivities and can incorporate nitrogen-based chiral auxiliaries.1 Enders’ SAMP/RAMP auxiliaries, the proline-based (R)-1-amino-2-methoxymethylpyrrolidines (Scheme 1), are widely used.1f,g SAMP auxiliaries, the proline-based (enantiomer of the auxiliary can be chosen in advance. There well-defined stereochemical predictability; the appropriate auxiliary under the reported conditions can compromise the overall stereoselectivity of the process.

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-40 °C; R3X, to rt
afford hydrazones and can be recovered quantitatively from the products after alkylation. Deprotonation of an ACC hydrazone is rapid; the stereoselectivity of alkylation is high even without the use of extreme low temperature, and yields are excellent. Among the ACCs that we have investigated to date, camphor-based auxiliary \(4\) (Scheme 2) has proven to give the best yields and enantioselectivities.

A mechanism for the stereoselective alkylation of a SAMP/RAMP hydrazone was proposed by Enders on the basis of crystallographic, spectroscopic, and computational evidence\(^{(4)}\) and is depicted in Scheme 1. Kinetic deprotonation of hydrazone \(1\) gives rise to lithium azaenolate \(2\) which, following equilibration, has the \(E\)-configuration at the CC bond and the \(Z\)-configuration at the CN bond.\(^{(6)}\) The bottom face of \(2\) is blocked by the pyrrolidine ring, and reaction with an electrophile takes place selectively at the top (\(\beta\)) face.\(^{(7)}\)

We proposed\(^{(3)}\) that a similar mechanism is followed in the alkylation of an ACC azaenolate but that the formation of the azaenolate from the hydrazone is controlled by the orientation of the carbonyl group. As shown in Scheme 3, the generalized ACC hydrazone \(9\) would prefer to exist in the conformation depicted as \(9a\), where steric interactions between \(R^2\) and the larger substituent (\(L\)) on the auxiliary are minimized. Coordination of LDA to the carbonyl group would then lead to a “\(\text{syn-directed}\)” deprotonation,\(^{(8)}\) giving the \(E_{\text{CC}}/Z_{\text{CN}}\)-azaenolate \(10a\) as a five-membered chelate. The bottom face of \(10a\) is sterically blocked, and alkylation should take place selectively at the top (\(\beta\)) face.

We present here a computational study of the deprotonation of ACC hydrazones and the alkylation of the lithium azaenolates. Density functional theory calculations provide information about the transition states that lead to the selectivities shown in Scheme 2. However, computations predict even higher stereoselectivities than were originally reported.\(^{(3)}\) This discovery prompted us to measure directly the \(\text{dr}\) of an alkylated hydrazone, prior to its conversion to the ketone. Consistent with theoretical predictions, the \(\text{dr}\) of the hydrazone was higher than the \(\text{er}\) of the final ketone, revealing that the removal of the auxiliary indeed compromised the overall stereoselectivity of the process.

### Results and Discussion

To explore the structural properties of ACC hydrazones, we first examined the parent ACC hydrazone \(11\) (Figure 1). At the B3LYP/6-31G(d) level, two isomers of \(11\) were located, which differ in the conformation about the \(\text{N-N}^1\) bond. The more stable isomer, \(11\text{-syn}\), has a synclinal arrangement of the \(\text{N-N}^1\) bond and the \(\text{N-N}^1\) bond (CNNC\(\text{C-N}^1\) dihedral angle 71°). The other isomer (\(11\text{-anti}\)) has an anti arrangement of these bonds (dihedral angle 150°) and is 4.7 kcal mol\(^{-1}\) less stable (\(\Delta H\text{of}\)). Its lower stability is

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**Figure 1.** Conformers of the ACC hydrazone \(11\) (\(\Delta H\) in kcal mol\(^{-1}\) at 0 K).

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**Scheme 1.** Stereoselective \(\alpha\)-Alkylation of a RAMP Hydrazone\(^{(1)}\)

**Scheme 2.** Asymmetric \(\alpha\)-Alkylation of Ketones Mediated by ACC \(4\)

**Scheme 3.** Model Proposed To Explain Stereoselectivity in the Alkylation of ACC Hydrazones\(^{(3)}\)

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due to repulsive interactions between the C=N and C=O lone pairs. In both isomers of the hydrazone, the ring nitrogen is pyramidal with an average bond angle of 114°.

In this respect, the ACC hydrazone differs from simple carbamates (cf. species 12 and 13, Scheme 4) and instead resembles an N,N-dialkylhydrazone (14). The NR₂ lone pair in 11 and 14 lies roughly in the same plane as the C=N bond, as a result of steric effects.⁹

To study the directed deprotonation of 11, Li(NMe₂)(THF) was used as a model for LDA in THF solution. Both 11-syn and 11-anti can undergo an intramolecular deprotonation reaction, following coordination of Li(NMe₂)(THF) to the carbonyl oxygen. The transition states, TS-11-syn and TS-11-anti, are shown in Figure 2. The reaction involving 11-syn represents the “syn-directed” deprotonation described above (Scheme 3), whereas the reaction of 11-anti leads to the opposite result, formation of a carbanion trans to the ACC group. The “syn-directed” deprotonation pathway is favored: TS-11-syn lies 1.4 kcal mol⁻¹ lower than TS-11-anti. The absolute barriers, relative to the reactant complexes, are very low or negative in the gas phase (ΔH° = 0.3 and −0.6 kcal mol⁻¹, respectively). Because the lowest-energy TS (TS-11-syn) appears to have a vacant coordination site on the lithium, we reoptimized its geometry with a second THF coordinated. The second THF was found to bind in a slightly endergonic fashion (ΔG = +2.4 kcal mol⁻¹ relative to TS-11-syn + THF). For the anti geometry, the lithium is already 4-coordinate in TS-11-anti, and a stable structure containing a second THF could not be located.

For the chiral hydrazone 15, derived from the ACC 4, there are four classes of conformational isomers. These are shown in Figure 3a. Unlike the achiral hydrazone 11, 15 can only adopt a syn conformation. Steric crowding between the rigid bicycloalkane unit and the hydrazone α-methyl group is too severe for anti conformers to be energy minima. The two syn conformers, 15-syn-front and 15-syn-back, correspond to the proposed structures 9a and 9b of Scheme 3, respectively (the terms “front” and “back” refer to the orientation of the carbonyl group). Consistent with the earlier model, 15-syn-front is 3.5 kcal mol⁻¹ more stable than 15-syn-back. The destabilization of 15-syn-back can be traced to the conformation about the N–C₄ bond in the oxazolidinone ring. Although the two conformers of 15-syn are formally related by rotation about the N–N bond, their interconversion also induces a change in configuration at the ring nitrogen. This is depicted in Figure 3b, which shows Newman projections along the N–C₄ bond after the N=CMe₂ group has been replaced by a hydrogen atom (green). The N–C₄ bond in 15-syn-back shows substantial eclipsing, with CNCC and NNCC dihedral angles of 12° and 22°, respectively. By contrast, the smallest dihedral angles about N–C₄ in 15-syn-front are 29° and 56°. The energy difference between the two structures in Figure 3b is 2.2 kcal mol⁻¹ (ΔE).

Transition states for the deprotonation of 15 by coordinated Li(NMe₂)(THF) are shown in Figure 4. The relative energies of the transition states are the same as those of the hydrazones themselves; TS-15-syn-front is 3.5 kcal mol⁻¹ lower in energy than TS-15-syn-back. The barriers relative to reactants (0.5 and 1.1 kcal mol⁻¹, respectively) are similar to those for the achiral TS-11-syn and TS-11-anti. The eclipsing interactions about N–C₄ that were present in 15-syn-back are also present in TS-15-syn-back. There is also a destabilizing steric interaction (shown by the red line) between the hydrazone α-methyl group and the nearby methyl group on the auxiliary. The chiral ACC effectively blocks anti deprotonation and makes the front (β) deprotonation considerably easier than the back (α). The front/back selectivity is calculated to be only marginally affected by solvation. When the transition structures were optimized in THF using the conductorlike polarizable continuum model (CPCM),¹⁰,¹¹ the preference for TS-15-syn-front was ΔΔH° = 3.3 kcal mol⁻¹ (ΔΔG° = 4.2 kcal mol⁻¹ at 298.15 K). A transition state related to TS-15-syn-front but containing a second THF in the coordination sphere of Li⁺ was found to be 1.9 kcal mol⁻¹ less stable (ΔG) in the gas phase.

The overall stereoselectivity of the deprotonation—alkylation sequence is determined by the addition of the azaenolate to the electrophile. The geometry of lithium azaenolate 16 and transition states for its reaction with MeCl are shown in Figure 5. Two THF ligands were included in the coordination sphere of Li⁺. During the alkylation, the ACC can be oriented with its carbonyl group lying in front of or behind the plane of the azaenolate. MeCl can add to either conformer and can approach from either the front or back. Figure 5 shows four transition states, which correspond to these four possible arrangements of the ACC and MeCl with respect to the plane of the azaenolate. The relative enthalpies and free energies are given below each transition state, both for the gas phase and with a THF solvent model in addition to the two explicit THFs.


The lithium azaenolate 16 is subject to the same conformational effects described above for the corresponding hydrazone 15. The ring nitrogen is less pyramidal than in the corresponding hydrazone, with an average bond angle of 117° in 16-front and 118° in 16-back. Pyramidalization at the ring nitrogen has previously been observed in the crystal structure of the SAMP hydrazone 17. The lithium azaenolate 16-back, like its hydrazone precursor, is destabilized by eclipsing interactions about the N—C$_4$ bond. 16-back is also destabilized by steric interactions between the azaenolate and one of the methyl groups on the auxiliary (red line in Figure 5a), similar to those present in the TS for its formation (TS-15-syn-back, Figure 4). These two effects destabilize 16-back by 5 kcal mol$^{-1}$ relative to 16-front. The front-back difference increases to 7 kcal mol$^{-1}$ in their TSs for reaction with MeCl. Additionally, regardless of the conformation of 16, there is a 7 kcal mol$^{-1}$ preference for MeCl to add to the π-face where the carbonyl group (coordinated to Li$^+$) is located (TS-16-A, TS-16-D). Addition to the opposite face (TS-16-B, TS-16-C) is disfavored because of steric repulsion between MeCl and the bicycloalkane group, as indicated by the red lines in Figure 5b. Thus, the alkylation of 16 takes place exclusively through the lower-energy conformer 16-front, and MeCl adds selectively to the front side (TS-16-A). The large stereochemical preference is the result of both steric effects and Li$^+$Cl$^-$ attraction in TS-16-A.

Having established the facial selectivity of alkylation at an unsubstituted azaenolate terminus, we then investigated the alkylation of a substituted azaenolate. Deprotonation at a secondary carbon introduces the additional consideration of $E_{CC}/Z_{CC}$ selectivity. We suggested earlier that $E_{CC}$ azaenolates are formed preferentially, on the basis that the allylation of a 3-pentanone-derived hydrazone and a cyclohexanone-derived hydrazone both led to ketones that had the same configuration at the newly formed stereocenter. Transition states for the deprotonation of an unsymmetrical hydrazone (18) by Li(NMe$_2$)(THF) are shown in Figure 6. The calculated...
barriers confirm the $E_{CC}$ selectivity. The TS leading to azaenolate $19-E_{CC}$ is favored by 2.9 kcal mol$^{-1}$ over the TS leading to $19-Z_{CC}$. Similar selectivity for formation of $E_{CC}$ azaenolates has previously been established for SAMP/RAMP-hydrazones.\(^6\)

Once formed, the azaenolate $19-E_{CC}$ is unlikely to undergo conversion to the $Z_{CC}$ isomer. We calculate a C=C rotational barrier of 43 kcal mol$^{-1}$ for the azaenolate derived from 11, and the barrier for the more-hindered azaenolate $19-E_{CC}$ is likely quite higher. The reaction of $19-E_{CC}$ with MeCl is calculated to have a stereoselectivity similar to that of 16; front-side addition of MeCl to $19-E_{CC}$ is favored by 6.9 kcal mol$^{-1}$ ($\Delta \Delta H^0_{cal}$) over back-side addition (Supporting Information).

Although the B3LYP gas-phase calculations for alkylations of 16 and $19-E_{CC}$ predict the correct major products,\(^3\) they also predict higher stereoselectivity compared with that

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**FIGURE 5.** (a) Conformers of the lithium azaenolate 16 and (b) transition states for alkylation of 16 by MeCl. Both the azaenolate and the TSs for alkylation prefer the carbonyl-front conformation. Addition of MeCl to the $\beta$ face of the azaenolate (TS-16-A) is preferred by 6.5 kcal mol$^{-1}$ over addition to the $\alpha$ face (TS-16-C) in the gas phase. A similar but smaller preference is retained in solution.
reported previously. For example, the allylation of hydrazone 20 with allyl bromide (Scheme 5) was reported to give ketone 22 with an er of 96:4, but the gas-phase activation energies for the reactions of the azaenolates 16 or 19-\(E_{\text{CC}}\) with MeCl predict the product 22-\(\beta\) would be formed exclusively. This high selectivity decreases only slightly with a bulkier electrophile; for example, the alkylation of 16 by EtCl is calculated to have a stereoselectivity of 5.7 kcal mol\(^{-1}\) (cf. 6.5 kcal mol\(^{-1}\) for MeCl).

The very high predicted gas-phase selectivities prompted us to reappraise the experimental selectivities. In our initial study,\(^3\) er values were determined for the ketone products, following hydrolytic cleavage of the auxiliary. We repeated the allylation of 20 (Scheme 5), and this time measured the diastereomer ratio of 21-\(\beta\) to 21-\(\alpha\). HPLC analysis revealed that 21-\(\beta\) and 21-\(\alpha\) were formed in a ratio of >99:1.\(^{12}\) Subsequent hydrolysis of the auxiliary led to 22-\(\beta\) and 22-\(\alpha\) in a ratio of 96:4. Thus, despite the reasonably mild conditions and short reaction time, erosion of stereochemical integrity occurs during the hydrolysis. We are now seeking improved conditions for auxiliary cleavage.

The predicted stereoselectivity in solution, however, is nevertheless not as high as in the gas phase. For example, in the reaction of the azaenolate 16 with MeCl, the TS leading to the minor product (TS-16-\(C\)) has a larger degree of charge transfer to MeCl (0.35 e) than the lowest-energy TS (TS-16-\(A\), 0.29 e).\(^{13}\) This would be expected to lead to enhanced stabilization of the minor TS in solution. We calculated CPCM free energies of solvation for the gas-phase structures in THF. The calculated value of \(\Delta \Delta G^\circ\) in THF at \(-78\) °C is only 1.1 kcal mol\(^{-1}\), corresponding to a dr of 95:5. The same value of \(\Delta \Delta G^\circ\) is obtained if the transition structures are fully optimized in the solvent model. Although this value is not expected to be quantitatively accurate (an accurate treatment of solvent effects would require more sophisticated modeling, including treatment of different coordination states for Li\(^{+}\)) and indeed underestimates the experimental dr, it does indicate that the predicted stereoselectivity is sensitive to solvation.

Conclusion

B3LYP calculations support the model for the stereoselectivity of ketone \(\alpha\)-alkylation shown in Scheme 3. The crucial features are that (i) the conformation of the intermediate azaenolate is controlled by conformational effects in the oxazolidinone ring and by steric repulsion between the chiral auxiliary and the deprotonated group, and (ii) an electrophile reacts preferentially with the lower-energy azaenolate, from the side opposite the bulky bicycloalkane group. These features resemble the mechanism of stereoinduction in the alkylation of SAMP/RAMP hydrazones.\(^4,5\) ACC hydrazones represent a convenient new complement to the SAMP/RAMP methodology.

Theoretical Calculations

B3LYP calculations\(^{14-16}\) were performed with Gaussian 03\(^{17}\) and Gaussian 09.\(^{18}\) The nature of each optimized point was checked by calculation of the vibrational frequencies, and

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(12) No regioisomeric products corresponding to allylation at the \(\alpha\)'-position were formed.

(13) Mulliken charges at the B3LYP/6-31G(d) level.
transition states were further verified by IRC calculations.20

Zero-point energy and thermal corrections were derived from the B3LYP/6-31G(d) frequencies, scaled by Radom’s factors.21

The effects of basis set size were investigated through calculations of the transition states TS-11-3syn and TS-11-anti with the 6-31+G(2d,p) basis (leaving frequencies unscaled); this raised the selectivity in favor of TS-11-3syn from 1.4 to 2.9 kcal mol\(^{-1}\), while the bond lengths involving the transferring proton changed by only 0.1–0.2 Å. The effects of solvation were simulated by means of PCM calculations using UKS radii. Free energies of solvation were calculated for the gas-phase-optimized geometries and were added to the gas-phase free energies to obtain the solution-phase free energies. We also performed geometry optimizations for selected species in THF (Gaussian 09). Solution-phase free energies are quoted at 1 mol L\(^{-1}\).

Molecular graphics were produced with the CYLview program.22 For simplicity, we have only considered monomeric species where the Li\(^+\) is coordinated by one NMe\(_2\) and one or two THF ligands (for the deprotonation step), or by two THF ligands (for the alkylation step). A fuller treatment would involve adducts having alternative coordination numbers and aggregation states, as well as multiple conformational isomers. Collum23 has shown, for example, that at high THF concentrations, the lithium azaenolate derived from cyclohexanone phenylimine exists predominantly as a monomeric species with three THF ligands coordinated to Li\(^+\). The structures, aggregation states, and reactivities of lithium enolates and related species have been studied computationally by Pratt.24 In our simple model complexes, sampling of different THF conformations showed energetic variations amounting to a few tenths of a kcal mol\(^{-1}\).

Experimental Methods

Allylation of 20. n-BuLi (2.5 M in hexanes, 100 μL, 0.250 mmol) was added dropwise over ca. 2 min to a stirred and cooled (−78 °C) solution of diisopropylamine (38.2 μL, 0.272 mmol) in THF (1.0 mL) (Ar atmosphere). The mixture was cooled for 30 min with an ice bath, with additional THF (2 mL). The mixture was stirred for 15 min and then partitioned between Et\(_2\)O and saturated aqueous NaHCO\(_3\). The aqueous phase was extracted with Et\(_2\)O (twice), filtered, and evaporated under reduced pressure to give a colorless, less oil. GC analysis of this material showed a 96:4 mixture of syn- and anti-.

Hydrolysis of 21-β. p-TolSO\(_4\)H\(_2\)O (83 mg; 0.436 mmol) was added to a stirred solution of 21-β (66 mg, 0.218 mmol) in acetone (2 mL). The mixture was stirred for 15 min and then partitioned between Et\(_2\)O and saturated aqueous NaHCO\(_3\). The aqueous phase was extracted with Et\(_2\)O (twice), and the combined organic extracts were washed with brine, dried (MgSO\(_4\)), filtered, and evaporated under reduced pressure to give a colorless oil. GC analysis of this material showed a 96:4 mixture of 22-β:22-α.25 Flash chromatography of the remaining crude material over silica gel using 5:95 Et\(_2\)O/pentane gave 22 (25.8 mg, 94%) as a pure, colorless oil. Spectroscopic data was identical to that reported previously.26

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Supporting Information Available: B3LYP geometries and energies, complete citations for refs 17 and 18, experimental procedures, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Sherbrooke, Canada, 2009; http://www.cylview.org.