Barriers to rotation of the N-alkenyl bond in a series of N-cycloalkenyl-N-benzyl α-haloacetamide derivatives have been measured by variable-temperature NMR experiments. The barriers range from 10 to 18 kcal/mol, depending on ring size and on substituents on the cycloalkene and the amide. The observed trends aid in the design of substituent combinations that provide resolvable enantiomers or diastereomers at ambient temperature. The compounds undergo 4-exo and 5-endo radical cyclizations at rates that may be faster or slower than the estimated rate of N-alkenyl bond rotation in the derived radicals, depending on the substituents.

Introduction

Though still usually classified as disfavored, 5-endo radical cyclizations are increasingly recognized as invaluable synthetic transformations in certain settings. The most widely used class of 5-endo cyclizations is that of radicals derived from α-haloenamides. Such radicals can also provide products of 4-exo cyclization, another disfavored pathway, if substitution patterns dictate. Reactions have been conducted by tin hydride and atom transfer methods (among others) and produce reduced, isomerized, or oxidized products depending on the reaction conditions and the nature of the precursor. Figure 1 shows representative examples of a 5-endo tin hydride cyclization by Ishibashi and co-workers (1a → 3) and 5-endo (4b → 6) and 4-exo (7 → 9) atom transfer cyclizations by Clark and co-workers. Related cyclizations to make larger rings are important in such cyclizations. Fortunately, enamides typically prefer the E-rotamer of the amide N-CO bond and the α-haloenamide cannot reach the alkene. So the amide bond rotation of both the radical precursor and the radical are important in such cyclizations. Fortunately, enamides typically prefer the E-rotamer, so their radicals are formed in a geometry that is predisposed to cyclize.

This page contains a detailed discussion on bond rotation dynamics of enamides, focusing on the analysis of radical precursors and cyclization pathways. It includes sections on rotamers of radical precursors, cyclization of twisted radicals, and results and discussion. The text is interspersed with diagrams and figures illustrating the structures and processes described. The authors explore the rotational dynamics of enamides, emphasizing the importance of understanding the geometry and energetics of these systems to predict and control their behavior in chemical reactions.
This behavior is not consistent with standard amide N–CO bond rotation since such a process should cause all signals to double and should not cause geminal protons to become diastereotropic. Instead, the results are consistent with existence of largely a single E-amide rotamer in solution. The decoalescences are caused by slowing of the N-cyclohexenyl bond rotation, which reveals the diastereotopicity of the pairs of geminal protons.

Using the WINDNMR 7.1 line-shape analysis program(12) to analyze the benzyl peaks of 1a–c, we determined the rotational rate constant \(k_{rot}\) at each temperature \(T\). The standard Eyring plots for chloride 1a, bromide 1b, and iodide 1c are shown in Figure 5. The three lines nearly coincide, showing that the dynamics of the molecules are similar. The activation barriers at 298 K (\(\Delta G^+\)) were also similar: 12.1 kcal/mol for 1a, 11.7 kcal/mol for 1b, and 11.9 kcal/mol for 1c. The activation enthalpies and entropies were calculated in the standard way and are shown in Table 1. To assess solvent effects, the barriers for 1b were also determined in toluene-\(d_6\) (entry 3, 11.1 kcal/mol) and methanol-\(d_4\) (entry 4, 11.6 kcal/mol).

We next extended the studies to the series of eight \(\alpha\)-bromoisobutenamides shown in Figure 6. Most of these precursors undergo 5-endo cyclizations, the exception being 7, which prefers 4-exo cyclization (see Figure 1). The 300 MHz NMR spectra of 1a–c at room temperature were simple, and peak broadening and decoalescence were only observed upon cooling. Only in hindsight did we notice that the benzyl methylene singlets were slightly broadened at rt. In contrast, the rt spectra of the amides in Figure 6 exhibited a range of different behaviors. For example, the benzyl protons of 4a were sharp singlets at room temperature, so only cooling was required, while those of 11 were already a well-resolved pair of doublets, so only heating was needed. The other compounds were in between, with more or less broad (in some cases, extremely broad) resonances, so samples were both cooled and heated. Enamide 12 has an additional stereocenter, so its rotamers are diastereomers, not enantiomers. The equilibrium constant for the two diastereomers 12 is about 2, and we did not attempt to assign the structure of the major rotamer.

To extend the temperature range for data collection in both directions, we used toluene-\(d_6\) as the solvent for this series of variable-temperature experiments. The spectra are gathered in the Supporting Information along with the derived Eyring plots. The benzylic protons were well-resolved from other resonances in every case, so we made these the focal points of the line-shape analyses.

Table 1 lists the rate constants at room temperature and the activation parameters for all the substrates. Among the interesting comparisons, notice that cyclohexenamide 4b with a quaternary carbon on the acyl group has a barrier of 13.3 kcal/mol (entry 7). This is more than 1 kcal/mol higher than the barriers of halides 1a–c with a secondary carbon on the acyl group (entries 1–5). Varying the ring size of the cycloalkenyl group (4b–e, entries 7–10) does not have much effect on the barrier (12.4–13.5 kcal/mol), except when the ring shrinks to five-membered 4a (entry 6, 10.0 kcal/mol). Presumably, as the ring is pinned back by its decreasing size, the barrier goes down. Adding a methyl substituent on the \(N\)-benzyl group to give phenethyl analogue 12 boosts the barrier by about 1 kcal/mol (entry 13).

With an sp\(^3\)-hybridized atom (CH\(_3\)) at the \(\beta\)-position of the enamide, 2-tetralone analogue 7 rather closely resembles cyclohexenamide 4b, though its rotation barrier at 11.7 kcal/mol is reduced by about 1.6 kcal/mol (entry 11). In contrast, with an sp\(^2\)-hybridized atom at the \(\beta\)-position (aromatic C), 1-tetralone enamide 11 is more related to an anilide than a cyclohexenamide. It has the highest rotation barrier observed at 18 kcal/mol (entry 12), though this is surely due primarily to the fact that it is also the only compound in the series to have a non-hydrogen substituent (the phenyl ring of the tetralone) in the \(\beta\)-position. Indeed, only the beginnings of coalescence were observed in the high-temperature spectra for 11, so its barrier measurement may not be as accurate as the others.

Though \(\beta\)-tetralone-derived enamide 7 is closely related to cyclohexenamide 4b, its barrier to rotation is about 1.6 kcal/mol.
Figure 7. The torsion angle of the key exhibited several interesting features that are summarized in rotation barrier.

For example, the sum of the bond angles to nitrogen is not 360°, but 356.9°. In addition, the amide is not completely planar. So the partial rehybridization of N from sp² toward sp³ may also reduce the rotation barrier.

None of the enamides in this study has a barrier to N-alkenyl bond rotation that is high enough to provide for separation of rotamers at room temperature. However, the trends of the past and present results with enamides show parallels to the more well studied anilides. By analogy, it should be generally possible to design resolvable enamides simply by changing the hydrogen substituents on the β- and β'-carbons to non-hydrogen ones. Indeed, Ahlbrecht and co-workers partially resolved compound 13 (Figure 8) about 30 years ago and measured its cyclization barrier (because the β'-substituent is not freely rotating) and be in the range (≥26–27 kcal/mol) that allows for convenient handling at room temperature.

Finally, it is also interesting to compare the rate constants for rotation of radical precursors with the rate constants for cyclization of the derived radicals to deduce which process is faster, cyclization or rotation. This is already possible for one class of radical 2, shown in Figure 9. In round numbers, the rate constant for cyclization of radical 2 at 298 K is about 10⁴ M⁻¹ s⁻¹. Remarkably, this is essentially the same as the rate

Table 1. N-Alkenyl Bond Rotation Rates and Activation Parameters from Variable-Temperature NMR Experiments

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>temp range</th>
<th>sola</th>
<th>kcat 298 K (s⁻¹)</th>
<th>ΔHq (kcal/mol)</th>
<th>ΔSq (cal/mol K)</th>
<th>ΔGq298 (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>297–215 K</td>
<td>C</td>
<td>8.49 × 10³</td>
<td>8.9</td>
<td>-10.6</td>
<td>12.1</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>323–213 K</td>
<td>C</td>
<td>1.58 × 10⁴</td>
<td>8.5</td>
<td>-10.6</td>
<td>11.7</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>323–193 K</td>
<td>T</td>
<td>4.54 × 10⁴</td>
<td>8.1</td>
<td>-10.0</td>
<td>11.1</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>208–213 K</td>
<td>M</td>
<td>1.96 × 10⁴</td>
<td>8.2</td>
<td>-11.3</td>
<td>11.6</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>270–216 K</td>
<td>C</td>
<td>1.12 × 10⁴</td>
<td>9.2</td>
<td>-9.0</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>4a</td>
<td>290–186 K</td>
<td>T</td>
<td>3.11 × 10³</td>
<td>8.0</td>
<td>-6.6</td>
<td>10.0</td>
</tr>
<tr>
<td>7</td>
<td>4b</td>
<td>311–233 K</td>
<td>T</td>
<td>1.06 × 10³</td>
<td>11.3</td>
<td>-6.6</td>
<td>13.3</td>
</tr>
<tr>
<td>8</td>
<td>4c</td>
<td>350–250 K</td>
<td>T</td>
<td>7.35 × 10²</td>
<td>11.8</td>
<td>-5.7</td>
<td>13.5</td>
</tr>
<tr>
<td>9</td>
<td>4d</td>
<td>341–230 K</td>
<td>T</td>
<td>3.09 × 10³</td>
<td>11.4</td>
<td>-4.3</td>
<td>12.7</td>
</tr>
<tr>
<td>10</td>
<td>4e</td>
<td>341–230 K</td>
<td>T</td>
<td>4.88 × 10³</td>
<td>11.4</td>
<td>-3.5</td>
<td>12.4</td>
</tr>
<tr>
<td>11</td>
<td>7b</td>
<td>313–203 K</td>
<td>T</td>
<td>1.77 × 10⁴</td>
<td>9.8</td>
<td>-6.3</td>
<td>11.7</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>379–341 K</td>
<td>T</td>
<td>4.08 × 10⁻¹</td>
<td>11.9</td>
<td>-20.4</td>
<td>18.0</td>
</tr>
<tr>
<td>13</td>
<td>12c</td>
<td>350–271 K</td>
<td>T</td>
<td>1.83 × 10²</td>
<td>12.7</td>
<td>-5.4</td>
<td>14.4</td>
</tr>
</tbody>
</table>

The torsion angle of the key N-alkenyl bond is only 56°. This is smaller than usually observed for related anilides and for enamide 1a. Perhaps the additional overlap of the nitrogen lone pair through the alkene to the fused phenyl ring reduces both the twist angle and the rotation barrier compared to 1b and 4b. In addition, the amide is not completely planar. For example, the sum of the bond angles to nitrogen is not 360° but 356.9°, and the torsion angle of the amide C–N bond to the cycloalkene is not 180° but is only 152°. So the partial rehybridization of N from sp² toward sp³ may also reduce the rotation barrier.

The trend of the past and present results with enamides shows parallels to the more well studied anilides. By analogy, it should be generally possible to design resolvable enamides simply by changing the hydrogen substituents on the β- and β'-carbons to non-hydrogen ones. Indeed, Ahlbrecht and co-workers partially resolved compound 13 (Figure 8) about 30 years ago and measured its cyclization barrier (because the β'-substituent is not freely rotating) and be in the range (≥26–27 kcal/mol) that allows for convenient handling at room temperature.

Finally, it is also interesting to compare the rate constants for rotation of radical precursors with the rate constants for cyclization of the derived radicals to deduce which process is faster, cyclization or rotation. This is already possible for one class of radical 2, shown in Figure 9. In round numbers, the rate constant for cyclization of radical 2 at 298 K is about 10⁴ M⁻¹ s⁻¹. Remarkably, this is essentially the same as the rate

FIGURE 6. Structures of α-haloenamides studied by VT NMR.

FIGURE 7. X-ray crystal structure of 7.

FIGURE 8. Designing resolvable N-cycloalkenyl amides.


constant for rotation of the radical precursors 1a–c. Assuming that the radical 2 has a similar rotation barrier to the precursor 1, radical 2 partitions between direct cyclization and rotation prior to cyclization. Rate constants for cyclization are not known for the other radicals derived from the halides in this study. However, the lowest possible rate constants for successful radical cyclizations under these conditions are in the range of $10^3$ s$^{-1}$. So the radicals derived from 11 and probably also 12 cyclize faster than they rotate.

**Conclusions**

Barriers to rotation of the $N$-alkenyl bond in a series of $N$-cycloalkenyl-$N$-benzyl $\alpha$-haloacetamide derivatives have been measured by variable-temperature NMR experiments. The barriers are all significant and range from 10 to 18 kcal/mol, depending on ring size and on substituents on the cycloalkene and the amide. The trends are qualitatively similar to those observed for anilide derivatives, so it is now possible to design substituent combinations that will provide resolvable enantiomers or diastereomers at ambient temperature. The compounds undergo 4-exo and 5-endo radical cyclizations at rates that may be faster or slower than the estimated rate of $N$-alkenyl bond rotation in the derived radicals, depending on the nature of the substituents that are present.

**Experimental Section**

Representative Procedure for Synthesis of Enamides 4a–e, 7, 11, and 12. Benzyl-2-bromo-$N$-(cyclopent-1-enyl)-2-methyl-propionamide (4a): Benzylamine (30 mmol) was added to the cyclopentanone (30 mmol) in toluene (20 mL), and the mixture was stirred under reflux in a Dean–Stark apparatus for 6 h. The solvent was removed in vacuo to give the crude imine that was used in the next step without further purification. The crude imine (9 mmol) was dissolved in dry toluene (50 mL) and cooled to 0 °C. 2-Bromoisobutyryl bromide (9 mmol) was added dropwise, followed by the slow addition of $N,N$-diethylaniline (9 mmol). The reaction was then stirred for 4 h at room temperature then added to water (50 mL). The layers were separated, and the organic layer was washed with 10% HCl (10 mL). After drying over MgSO$_4$, the solvent was removed in vacuo to give a crude residue that was purified by column chromatography: yield (60%); clear oil; $R_f$ (3:1 petroleum ether/EtOAc) 0.83; IR (film)/cm$^{-1}$ $\nu_{max}$ 2932, 2850, 1633, 1496, 1464, 1453, 1392, 1365, 1108, 729, 697; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21 (5H, m), 5.53 (1H, m), 4.62 (2H, s), 2.39 (2H, m), 2.22 (2H, m), 1.94 (6H, s), 1.85 (2H, q; $J = 7.5$ Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 170.9, 142.6, 137.9, 130.3, 128.7, 128.3, 127.5, 58.3, 52.4, 33.6, 32.3, 30.5, 22.4; ESI $m/z$ 344 ([M]+ Na) 322, 242, 91; found (MNa)$^+$, 344.0620, C$_{16}$H$_{20}$BrNO requires (MNa)$^+$, 344.0626; found C, 56.8; H, 6.0; N, 4.1.

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**Supporting Information Available:** Procedures of synthesis and characterization data of 4a–e, 7, 11, and 12, general methods for VT NMR experiments, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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