ENANTIOENRICHED AXIALLY CHIRAL β-DIKETIMINES: DETERMINATION OF THE IAN-AMINE BARRIER TO ATROPISOMERIZATION†

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Abstract – Enantioenriched (>98% ee) β-diketimines derived from isoquinoline and 2-Amino Naphthalene ('IAN-amines') were prepared. Thermal racemization of a series of R-IAN amines (R = NH₂, NHMe, NMe₂) revealed a high barrier to atropisomerization (~30 kcal/mol) and its relative insensitivity to substitution at the aminonaphthalene nitrogen. Molecular mechanics calculations accurately predicted the observed relative substituent effects.

INTRODUCTION

Chiral non-racemic amines are versatile tools for the development of chiral auxiliaries¹ and enantioselective reactions.² Yet β-diketimines are nearly undeveloped in asymmetric synthesis³ despite their otherwise thoroughly developed coordination chemistry as a class of N,N-chelating ligand.⁴ We recently introduced the IAN-amines (1) as the first axially chiral β-diketimines.⁵ Embedding the

† This paper is dedicated to Professor Leo A. Paquette - a uniquely gifted scientist, statesman, and mentor - for his many contributions, including those to physical organic chemistry and asymmetric synthesis.
The diketimine framework into a binaphthyl backbone sterically and electronically distorts the usual resonance delocalization of the chelating ligand, thereby creating an interesting ligand for metal-based catalysis of organic reactions. This desymmetrization would be compromised, however, if the barrier to atropisomerization is low under operating conditions desired for most organic reactions (room temperature or below). Hence, determination of the barrier to atropisomerization is critical to the future development of IAN-amines. The need for an inherently high barrier is also important since the perception that 'buttressing' by substituents at the 3-position of binaphthyls can be used in a general way to raise the atropisomerization barrier is not supported by the literature. We report here the determination of the atropisomerization barrier within a series of sterically diverse enantioenriched IAN-amines. In all cases, racemization is undetectable at room temperature and relatively insensitive to the size of the substituents at the naphthyl amine nitrogen.

RESULTS AND DISCUSSION

Racemic IAN-amines (1a-c) were prepared using the method described previously. As is typical of nearly all R-IAN amines we have prepared, the enantiomers resolve well on several chiral, non-racemic stationary phases. For example, the parent IAN-amine (1a) exhibited retention times of 19.0/39.7 min, 15.6/17.9 min, and 34.1/80.0 min on analytical Daicel Chiralpak OD, AD, and OJ columns respectively (10% 1PrOH/hexanes at 1.0 mL/min). Preparatory HPLC on an AD column readily provided sufficient enantiopure (>98% ee) IAN-amine with which to determine the barrier to atropisomerization for the series (1a-c).

![Figure 1. Experimental Determination of R-IAN Amine Free Energy (\(\Delta G^\ddagger_{\text{rac}}\)) of Atropisomerization (Racemization)](image)

<table>
<thead>
<tr>
<th>IAN (1a)</th>
<th>Me-IAN (1b)</th>
<th>Me2-IAN (1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta G^\ddagger_{\text{rac}}) (kcal/mol)</td>
<td>30.0</td>
<td>31.3</td>
</tr>
<tr>
<td>(t_{1/2}) (69.5 °C)</td>
<td>&gt;6 days</td>
<td></td>
</tr>
</tbody>
</table>

Solutions (50 mM) of enantioenriched IANs (1a-c) in anhydrous toluene were warmed in a constant temperature bath (± 0.1 °C). Aliquots were removed at various intervals and enantiomeric ratios were
measured by analytical HPLC using a Chiralpak AD column. A plot of the enantiomeric ratios as a function of time according to the equation described by Hirao7 resulted in the linear plots depicted in Figure 1. Using the slope of these lines, values of $[\Delta G^\circ]_{\text{rac}} = 30.0, 31.3,$ and 29.8 kcal/mol were determined for 1a, 1b, and 1c, respectively. Qualitatively, these values translate to a half-life of 6 days or greater at 69.5 °C.

Molecular mechanics calculations were used to determine the relative free enthalpy of minimized biaryl conformers throughout a complete (360°) rotation of the biaryl $\|$ bond. The resulting calculated $[\Delta H^\circ]_{\text{rac}}$ for 1a-c are provided in Table 1. The calculated barriers to racemization (35.3, 36.2, 33.7 kcal/mol for 1a, 1b, 1c, respectively) approximate almost perfectly (deviation < 4%) the relative energy differences from experiment (30.0, 31.3, 29.8 kcal/mol for 1a, 1b, 1c, respectively, Figure 1). We therefore suggest that relative entropic contributions to racemization as a function of amine substituent are negligible. Moreover, a clear energetic difference is observed between anti-1 and syn-1, the two possible conformers leading to racemization.9 Not surprisingly, anti-1 is substantially lower in energy than the syn-1 conformer due to the lower energetic cost to bring the nitrogen lone electron pair in plane with the C-8′ hydrogen. The excellent correlation between experiment and calculation suggests that the latter may be used as a

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>biaryl angle $^b$</th>
<th>$[\Delta H^\circ]$ (kcal/mol)</th>
<th>$[\Delta H^\circ]$ (kcal/mol)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>95</td>
<td>50.9</td>
<td>35.3</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>94</td>
<td>54.9</td>
<td>36.2</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>93</td>
<td>51.1</td>
<td>33.9</td>
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<tr>
<td>4</td>
<td>iPr</td>
<td>H</td>
<td>98</td>
<td>51.8</td>
<td>38.2</td>
</tr>
<tr>
<td>5</td>
<td>tBu</td>
<td>H</td>
<td>72</td>
<td>61.4</td>
<td>41.5</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Me</td>
<td>107</td>
<td>49.8</td>
<td>33.7</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Me</td>
<td>93</td>
<td>49.7</td>
<td>32.6</td>
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<tr>
<td>8</td>
<td>tBu</td>
<td>tBu</td>
<td>72</td>
<td>61.4</td>
<td>41.5</td>
</tr>
</tbody>
</table>

$^a$Calculated using PCMODEL. The dihedral driver (1° increments, with minimization at each) was then used to measure $[\Delta H^\circ]$. Values in bold can be compared to $[\Delta G^\circ]$ measured experimentally: 30.0, 31.3, and 29.8 kcal/mol respectively. $^b$Angle between naphthalene ring planes (measured by $[\Delta N\mathcal{C}C\mathcal{C}]$) in the calculated lowest energy conformation.
predictive tool.

Calculations of racemization barriers for IAN-amines not yet synthesized predict that substantial variation in the size of the naphthyl amine substituents is possible without compromising their configurational integrity (entries 3-5, 7-8, Table 1). Although phenyl substitution of the parent IAN to form Ph-IAN (1d) lowers the racemization barrier relative to all other secondary IAN derivatives examined, the expected half-life remains greater than Me₂-IAN (1c) (Table 1, cf. entries 3, 6). Among alkyl substituents, a substantial increase in configurational integrity accompanies increasing substitution (Table 1, entries 1,2,4,5). Bu-IAN is an interesting case since the calculations suggest ground state destabilization is not significant - both planar conformers of the binaphthyl system are >44 kcal/mol above the ground state, whereas the other secondary amines are less than 39 kcal/mol above the ground state. The tertiary amine derivatives (1c, 1g, and 1h) behave similarly. Me,Ph-IAN Exhibits the lowest calculated racemization barrier (32.6 kcal/mol), but remains only 1.1 kcal/mol lower than Me₂-IAN. Comparison of the tertiary IAN-amines to their secondary amine counterparts reveals the trend in which increased naphthylamine substitution lowers the racemization barrier, but not dramatically. A direct comparison between atropisomerization barriers of isoquinoline-derived R-IAN amines, Brown's Quinap¹⁰ and 2-naphthol⁸ derivatives, and Chelucci's thioether¹¹ is not possible due to the lack of quantitative measurements resulting from the latter studies. However, a trend of decreasing atropisomerization barriers as a function of the 2'-substituent is evident from these studies: PPh₂ (Quinap) ~ SMe > NR¹R² (IAN-amines) >> OH.

In summary, kinetic measurements were used to determine the free energy for racemization in a series of IAN-amines. Relative to the parent IAN-amine, the secondary and tertiary amine derivatives exhibited atropisomerization barriers within 1 kcal/mol. These barriers translate to half-lives of about 6 days at 69.5 °C. Molecular mechanics (MMX) calculations accurately chart the substituent effects and were used to predict the barrier to racemization for presently unknown enantioenriched IAN-amines. This companion study of experiment and calculation provides a first look at the atropisomerization process for IAN-amines at the molecular level, and establishes their viability as reagents for enantioselective synthesis.

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REFERENCES AND NOTES