

**ENANTIOENRICHED AXIALLY CHIRAL \square -DIKETIMINES:
DETERMINATION OF THE IAN-AMINE BARRIER TO
ATROPISOMERIZATION[†]**

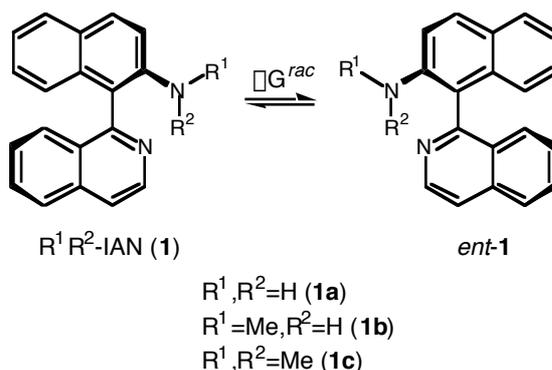
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Abstract – Enantioenriched (>98% ee) \square -diketimines derived from Isoquinoline and 2-Amino Naphthalene ('IAN-amines') were prepared. Thermal racemization of a series of R-IAN amines (R = NH₂, NHMe, NMe₂) revealed a high barrier to atropisomerization (~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 \square -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 \square -diketimines.⁵ Embedding the



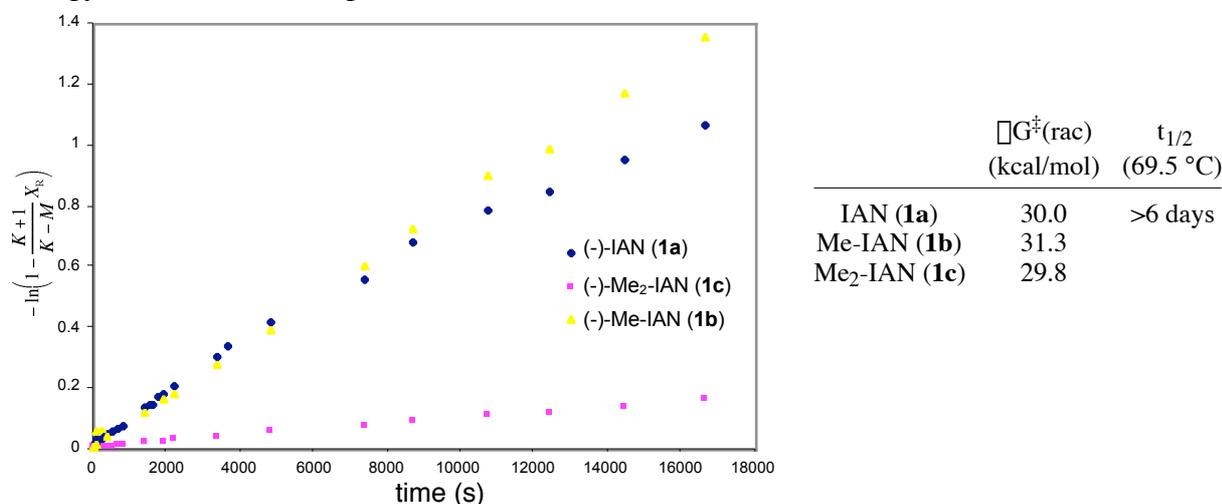
[†] This paper is dedicated to Professor Leo A. Paquette - a uniquely gifted scientist, statesman, and mentor - for his many contributions, including those to physical organic chemistry and asymmetric synthesis.

\square -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).⁶ 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.^{7,8} 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.⁵ 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% *i*PrOH/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)



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 $\Delta G^\ddagger(\text{rac}) = 30.0, 31.3,$ 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 σ bond. The resulting calculated $\Delta H^\ddagger(\text{rac})$ 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 1. Calculated (MMX) Free Energies of Activation for R-IAN Amines^a

$$\text{R}^1\text{R}^2\text{-IAN} \rightleftharpoons \text{ent-R}^1\text{R}^2\text{-IAN}$$

entry	R ¹	R ²	biaryl angle ^b	ΔH^\ddagger (kcal/mol) <i>syn</i>	ΔH^\ddagger (kcal/mol) <i>anti</i>	$\Delta\Delta H$ (kcal/mol)	
1	H	H	1a	95	50.9	35.3	15.6
2	Me	H	1b	94	54.9	36.2	18.7
3	Ph	H	1d	93	51.1	33.9	17.2
4	ⁱ Pr	H	1e	98	51.8	38.2	13.6
5	^t Bu	H	1f	97	50.8	44.3	6.5
<i>3° amines</i>							
6	Me	Me	1c	107	49.8	33.7	16.1
7	Ph	Me	1g	93	49.7	32.6	17.1
8	^t Bu	^t Bu	1h	72	61.4	41.5	19.9

^aCalculated using PCMODEL. The dihedral driver (1° increments, with minimization at each) was then used to measure ΔH^\ddagger . Values in bold can be compared to ΔG^\ddagger measured experimentally: 30.0, 31.3, and 29.8 kcal/mol respectively. ^bAngle between naphthalene ring planes (measured by $\angle \text{N}_2\text{C}_1\text{C}_1'\text{C}_2'$) 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

1. A. Abiko, *Rev. Heteroatom Chem.*, 1997, **17**, 51; H. Waldmann, *Organic Synthesis Highlights II*, 1995, 49.
2. F. Fache, E. Schulz, M. L. Tommasino, and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159; M. Falorni, *Trends in Organic Chemistry*, 1993, **41**, 351.
3. H. Fritischi, U. Leutenegger, and A. Pfaltz, *Angew. Chem.*, 1986, **98**, 1028; H. Fritischi, U. Leutenegger, and A. Pfaltz, *Helv. Chim. Acta*, 1988, **71**, 1553; U. Leutenegger, A. Madin, and A. Pfaltz, *Angew. Chem.*, 1989, **101**, 61. For a similar strategy, see: M. P. Sibi and Y. Asano, *J. Am. Chem. Soc.*, 2001, **123**, 9708.
4. L. Bourget-Merle, M. F. Lappert, and J. R. Severn, *Chem. Rev.*, 2002, **102**, 3031.
5. S. B. Cortright and J. N. Johnston, *Angew. Chem., Int. Ed.*, 2002, **41**, 345.
6. Biaryl ligands with low barriers to atropisomerization may still be used in asymmetric synthesis: M. Tudor, J. Becker, P. White, and M. Gagne, *Organometallics*, 2000, **19**, 4376.
7. H. Tsue, H. Fujinami, T. Itakura, R. Tsuchiya, K. Kobayashi, H. Takahashi, and K. Hirao, *J. Chem. Soc., Perkin Trans. I*, 1999, 3677.
8. S. C. Tucker, J. Brown, J. Oakes, and D. Thornthwaite, *Tetrahedron*, 2001, **57**, 2545.
9. M. Kranz, T. Clark, and P. von R. Schleyer, *J. Org. Chem.*, 1993, **58**, 3317.
10. N. Alcock, J. Brown, and D. Hulmes, *Tetrahedron Asymmetry*, 1993, **4**, 743.
11. G. Chelucci, A. Bacchi, D. Fabbri, A. Saba, and F. Ulgheri, *Tetrahedron Lett.*, 1999, **40**, 553.