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

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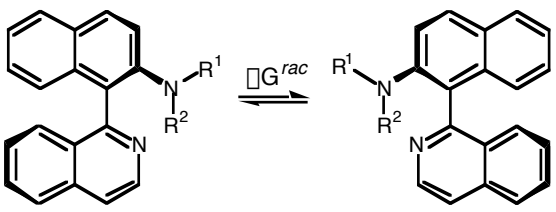
Abstract – Enantioenriched (>98% ee) β-diketimines derived from *I*soquinoline and 2-*A*mino *N*aphthalene ('IAN-amines') were prepared. Thermal racemization of a series of R-IAN amines (R = NH_2, NHMe, NMe_2) revealed a high barrier to atropisomerization (~30 kcal/mol) and its relative insensitivity 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 auxiliaries[1] and enantioselective reactions.[2] Yet β-diketimines are nearly undeveloped in asymmetric synthesis[3] 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



R^1R^2-IAN (**1**) *ent*-**1**

R^1,R^2=H (**1a**)
R^1=Me,R^2=H (**1b**)
R^1,R^2=Me (**1c**)

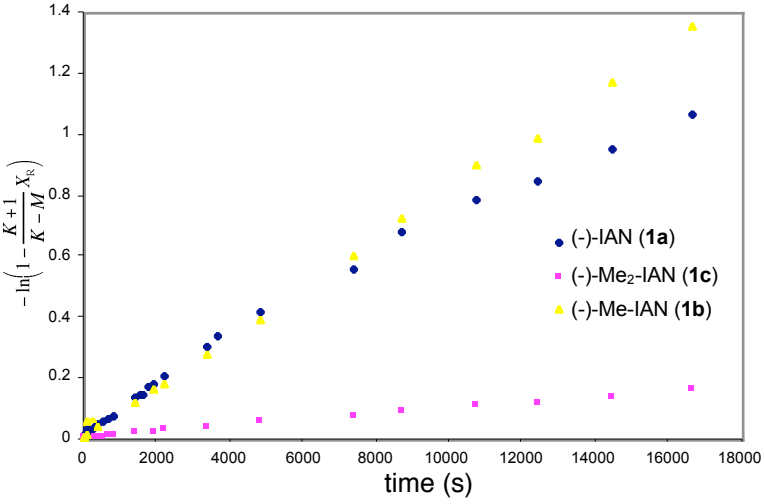
† This paper is dedicated to Professor Leo A. Paquette - a uniquely gifted scientist, statesman, and mentor - for his many contributions, including those to physical organic chemistry and asymmetric synthesis.

□-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 (□G‡(rac)) of Atropisomerization (Racemization)



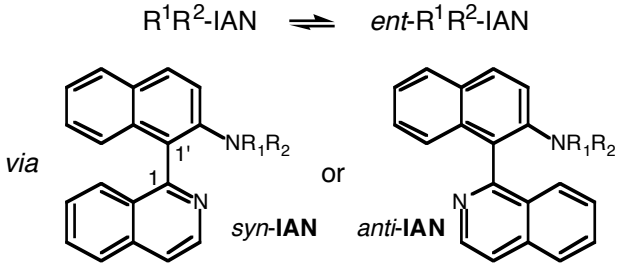
	□G‡(rac) (kcal/mol)	$t_{1/2}$ (69.5 °C)
IAN (**1a**)	30.0	>6 days
Me-IAN (**1b**)	31.3	
Me_2-IAN (**1c**)	29.8	

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 Hirao[7] resulted in the linear plots depicted in Figure 1. Using the slope of these lines, values of $\Delta G^{\ddagger}$(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 C-C bond. The resulting calculated $\Delta H^{\ddagger}$(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 neglible. 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]



entry	R^1	R^2		biaryl angle[b]	$\Delta H^{\ddagger}$ (kcal/mol) *syn*	*anti*	$\Delta\Delta H$ (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
	3° amines						
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

[a]Calculated using PCMODEL. The dihedral driver (1° increments, with minimization at each) was then used to measure $\Delta H^{\ddagger}$. Values in bold can be compared to $\Delta G^{\ddagger}$ measured experimentally: 30.0, 31.3, and 29.8 kcal/mol respectively. [b]Angle between naphthalene ring planes (measured by $\angle N_2C_1C_{1'}C_{2'}$) 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 Me_2-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). ^{t}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 Me_2-IAN. Comparison of the tertiary IAN-amines to their secondary amine counterparts reveals the trend in which increased napthylamine substitution lowers the racemization barrier, but not dramatically. A direct comparison between atropisomerization barriers of isoquinoline-derived R-IAN amines, Brown's Quinap[10] and 2-naphthol[8] derivatives, and Chelucci's thioether[11] 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: PPh_2 (Quinap) ~ SMe > NR^1R^2 (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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