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Racemization barriers of atropisomeric 3,3′-bipyrroles: An experimental study with theoretical verification

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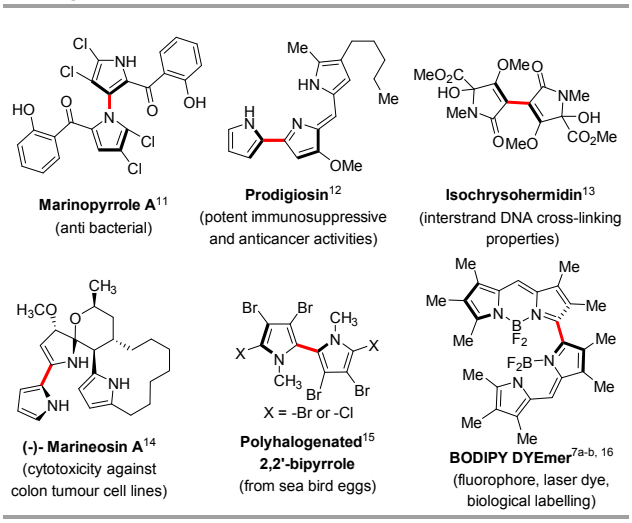
The significant rotational energy barrier about the stereogenic carbon carbon bond of axially chiral 3,3′-bipyrroles have been investigated by the electronic circular dichroism (ECD) spectroscopy, time dependent HPLC analysis, and computational modeling. The results elucidate pathways and transition states involved in configurational inversion, thereby confirming that 3,3′-bipyrrole derivatives can exist in stable and isolable atropisomeric forms.

Introduction

Atropisomers are stereoisomers that principally arise due to the constrained rotation of single bonds flanked by a pair of hindered planar groups; the stereogenicity of these molecules originates from the concept of axial chirality. These optically active molecules allow the stable and specific presentation of functional groups in space and are widely employed in applications such as medicinal chemistry,[1,2] molecular devices,[3] electrochemical polymerization,[4] spectrochemical and photophysical investigations,[5] asymmetric catalysis,[6] and organic dyes.[7] The biological activities, toxicities and pharmacokinetics of an individual atropisomer may fluctuate in biological environment due to significant diastereomeric interactions.[8] Although there is immense interest in biaryl atropisomers, one of the major problems associated with their practical application is that their chiral stability is often poor due to an insufficient atropisomerization energy barrier.[9] Thus, an important area of research is to investigate new kinds of atropisomers having significantly higher atropisomerization energy and deduce the process of determination of their thermodynamic properties.

Owing to the high demand and importance of chiral biaryl scaffolds, numerous reports describe the synthesis, characterization, and calculations of racemization energy barrier for various atropisomers.[8b,10] Although, the field has made substantial progress for important applications including biology[11-15] and materials science[16] (Scheme 1), the advancement has been quite sluggish due to the frequently lower than desired biaryl activation barrier of racemization.[17] For example, to date, only two regiospecific isomeric systems of 1,1′-[17a-c,f] and 2,2′-bipyrroles[17d-g] (Scheme 2a) have been investigated.



Scheme 1. Some important bipyrroles.

We previously developed an unique pathway to construct 3,3′-bipyrroles with highly constrained *ortho*-substitutions and were able to successfully separate two individually pure atropisomers.[18] However, to the best of our knowledge, a systematic study of the activation barrier of racemizations of 3,3′-bipyrrole systems has yet to be reported, which could enable us to identify stable enantiomers that may prove useful in biology and materials science. A critical problem is of course

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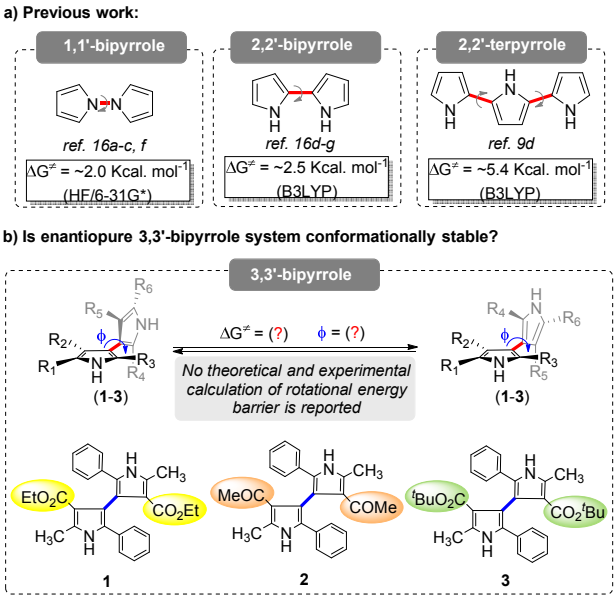
Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectra of 5,5′-dimethyl-2,2′-diphenyl-1*H*,1′*H*-[3,3′]bipyrrolyl-4,4′-dicarboxylic acid diethyl ester (**1**), ECD spectral analysis, HPLC profiles at different time intervals, detailed procedure for determination of physical parameters, computationally evaluated conformers of **1** and additional computational data are provided]. See DOI: 10.1039/x0xx00000x

the overall stability of individual atropisomers for extended periods of time at room temperature.



Scheme 2. Calculation of racemization energy barrier of various atropisomeric bipyrroles.

Thus, given the established biological applications of bipyrrole building blocks, we decided to study the stability of atropisomerically pure 3,3´-bipyrrole derivatives (Scheme 2b). Here, we investigated the rotational energy barrier of 5,5´-dimethyl-2,2´-diphenyl-1*H*,1´*H*-[3,3´]bipyrrolyl-4,4´dicarboxylic acid diethyl ester (**1**), 1,1'-(5,5'-dimethyl-2,2'-diphenyl-1*H*,1'*H*-[3,3'-bipyrrole]-4,4'-diyl)bis(ethan-1-one) (**2**) and di-*tert*-butyl 5,5'-dimethyl-2,2'-diphenyl-1*H*,1'*H*-[3,3'-bipyrrole]-4,4' dicarboxylate (**3**) as a representative examples of 3,3´-bipyrrole system.[18b] Molecule **1** was considered as an exemplar of 3,3'-bipyrrole for this experiment since it is fully substituted (which restricts the free rotation around its chiral axis). Furthermore, the ester groups mounted at 4 and 4'-position allow further functionalization. Notably, bulky substituents, such as phenyl rings at 2 and 2'-position of **1** also provide enough steric bulk to restrict its free rotation.[19] The thermodynamic properties, such as activation barrier of racemization ($\Delta G^{\neq}_{rac}$), activation entropy ($\Delta S^{\neq}_{rac}$) and activation enthalpy ($\Delta H^{\neq}_{rac}$) were determined by Electronic Circular Dichroism (ECD) spectroscopy and time dependent High Performance Liquid Chromatography (HPLC) analysis.[10, 20] Moreover, *ab initio* quantum mechanics theoretical calculations were performed on the same molecule to verify the experimental analysis. Herein, we describe the detailed procedure of analytical and theoretical investigation which reveals the high conformational stability of **1** at ambient temperatures.

Having two pure atropisomers of **1** in hand, the kinetics of racemization was determined by ECD spectroscopy.[19, 10a]

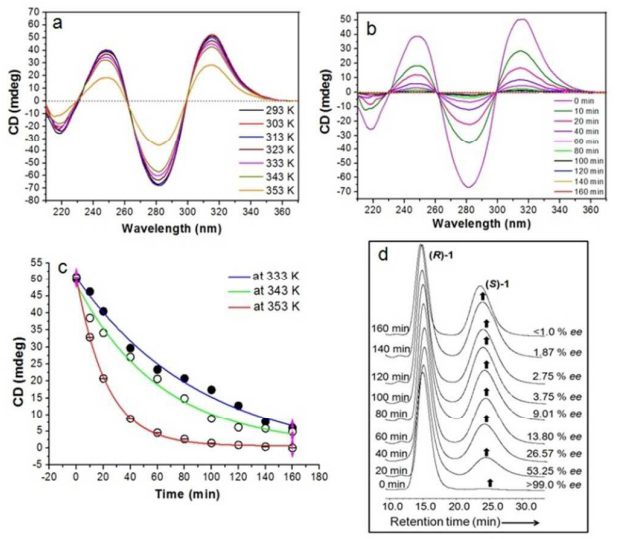


Figure 1. (a) CD spectroscopy of (*R*)-**1** (2.20 mM in EtOH) recorded at 293 to 353 K, (each 10 K raise of temperature required approximately 30 sec.) (b) CD spectroscopy of (*R*)-**1** (2.20 mM in EtOH) recorded at 353 K up to 160 min, (c) Plot of CD (mdeg) of (*R*)-**1** as a function of time (min) for the determination of conformational stability of enantiopure 3,3´-bipyrrole. (d) Chiral HPLC profiles for time dependent racemization of **1** at 353 K.

Molecule	Time (min)	0	10	20	40	60	80	100	120	140	160	170
1	CD (mdeg)	50.56	32.86	20.79	8.75	4.52	2.64	1.47	0.89	0.40	0.03	n.r.[d]
	ee (%)[a]	>99.0	64.34	40.70	17.13	8.85	5.17	2.88	1.74	0.78	0.06	n.r.[d]
	ee (%)[b]	>99.0	[n.d.][c]	53.25	26.57	13.80	9.01	3.75	2.75	1.87	0.75	n.r.[d]
2	*ee* (%)[b]	>99.0	81.09	56.89	20.54	10.33	6.51	2.42	1.48	0.70	n.r.[d]	n.r.[d]
3	*ee* (%)[b]	>99.0	79.98	62.04	32.91	23.49	17.94	15.37	4.37	3.34	1.13	0.49

Table 1. Change of enantiomeric excess (*ee*) of compounds **1**-**3** with variable time interval at 353 K. [a] Decrease of CD intensity in the form of enantiomeric excess with variable time intervals. [b] Decrease of enantiomeric excess determined by HPLC analysis with variable time intervals. [c] n.d. = not determined [d] n.r. = not required (since **1** and **2** were racemized at 140 min and 160 min respectively).

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Molecule	Mode of analysis	Physical Parameters					
		Temp (T, K)	Decay Consant (t_1)	Rate Constant (k_{rac}, sec^{-1})	Eq. Constant ($K^{\neq}_{eq}$)	Half life ($t_{1/2}$)	Activation Barrier of Racemization ($\Delta G^{\neq}_{rac}$, $kcal.mol^{-1}$)
1	**CD**	353	22.590 min	7.377×10^{-4}	10.034×10^{-17}	15.75 min	**25.84**
		343	63.182 min	2.637×10^{-4}	3.692×10^{-17}	43.78 min	**25.78**
		333	94.496 min	1.763×10^{-4}	2.543×10^{-17}	65.48 min	**25.28**
	HPLC	353	30.985 min	5.379×10^{-4}	7.316×10^{-17}	21.47 min	**26.06**
		300	22.279 days	5.195×10^{-7}	8.314×10^{-20}	15.44 days	**26.19**
2	**HPLC**	353	30.653 min	5.437×10^{-4}	7.395×10^{-17}	21.24 min	**26.05**
3	**HPLC**	353	41.051 min	4.060×10^{-4}	5.522×10^{-17}	28.45 min	**26.26**

Table 2. Different kinetic and thermodynamic parameters of **1**-**3** as a function of temperature.

Enantiopure (*R*)-**1** (2.20 mM in EtOH) was subjected to dynamic ECD analysis; CD spectra were recorded at 293 to 353 K at intervals of 10 K. As anticipated, gradual decrease of enantiomeric excess (*ee*; calculated from CD intensity) was observed with increase of temperature (figure 1a). However, complete racemization did not take place even up to 353 K (*ee* of enantiopure (*R*)-**1** was dropped to 54.06 % at 353 K).[19] We envisioned that the pure (*R*)-**1** could be transformed to its racemic mixture, if we prolong the incubation time at 353 K. As anticipated, complete racemization of (*R*)-**1** was achieved after 160 min (figure 1b, table 1a). At lower temperatures (at 343 K and 333 K) the *ee* of (*R*)-**1** was significantly decreased within the same incubation time (160 min) and complete racemization was not attained (figure 1c) (*ee* dropped to 9.41 % at 343 K and 11.74 % at 333 K).[19] We found the optimized condition for complete racemisation of **1** is 160 min incubation at 353 K. Similarly, we also investigated the kinetics of racemization for compounds **2** and **3**; found that they took 140 and 170 min respectively to completely racemized (table 1).[19] The time dependent decrease of *ee* at 353 K was further used to determine kinetic and thermodynamic parameters of **1**-**3** (table 2).[19]

A plot of CD intensity (mdeg) vs time at 353 K confirms a first order exponential decay (figure 1c) giving a first order rate constant (k_{rac}) 7.377×10^{-4} sec^{-1} and equilibrium constant to the transition state ($K^{\neq}_{eq}$) = 10.034×10^{-17}. The activation barrier of racemization ($\Delta G^{\neq}_{rac}$) as calculated from k_{rac} via the Eyring equation (Eqn 1),[19, 10a, 20] is 25.84 $kcal.mol^{-1}$ at 353 K. Activation barrier of racemizations ($\Delta G^{\neq}_{rac}$), similarly obtained at 343 K and 333 K are comparable to the value at 353 K (table 2). A large $\Delta G^{\neq}_{rac}$ supports the stability of enantiopure atropisomers of **1** at room temperature. Finally, in order to understand the mode of racemization, other thermodynamical parameters, such as activation enthalpy ($\Delta H^{\neq}_{rac}$) and activation entropy ($\Delta S^{\neq}_{rac}$) of the isomerization of atropisomer **1** were determined by employing the Eyring equation (Eqn 2)[20] and found to be 27.49 $kcal.mol^{-1}$ and 4.924 $cal.mol^{-1}.K^{-1}$ respectively from the Eyring plot (figure 2).[19]

$$\Delta G^{\neq}_{rac} = -RT\ln\left(\frac{hk_{rac}}{\kappa T k_B}\right) = -RT\ln K^{\neq}_{eq} \qquad (1)$$

$$\ln\frac{k_{rac}}{T} = -\frac{\Delta H^{\neq}}{R}\frac{1}{T} + \ln\frac{k_B}{h} + \frac{\Delta S^{\neq}}{R} \qquad (2)$$

where h = Planck constant, κ (kappa)= transmission coefficient, T = temperature and k_B = Boltzmann constant.

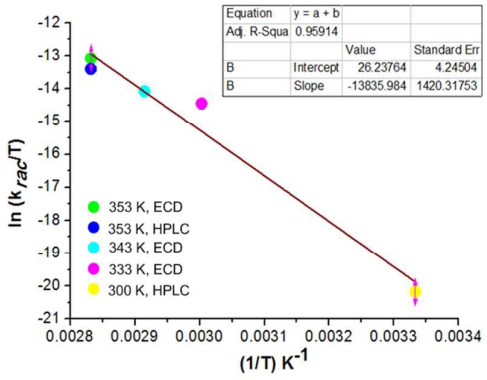

Figure **2**. Eyring plot for the racemization of **1**.

To support ECD spectroscopy results, the racemization kinetics of **1** were followed by chiral HPLC analysis.[10a] Eight samples of enatiomerically pure (*R*)-**1** (2.20 mM in EtOH; identical concentration as in ECD analysis) were incubated at 353 K and each sample was taken out from the incubator at time intervals of 20 min and injected for chiral HPLC analysis (Chiralcel® OJ-H, 5.0 µm × 4.6 mm × 250 mm, solvent 0.3% diethyl amine in hexane: ethanol 90:10, flow rate 1.0 mL/min, 298 K, detection at 254 nm).[19] A gradual decrease of *ee* of (*R*)-**1** was observed with the progress of time. Complete racemization was observed after 160 min (figure 1d, table 1b). The energy required for of (*R*)-**1** was found to be 26.06 kcal.mol^{-1} by HPLC analysis, which was corroborated with ECD analysis.[19] We also curious to determine the room temperature stability of enantiopure (*R*)-**1**. Interestingly, racemization kinetics study shows a momentous exponential decay of enantiomeric excess with time and complete racemization of (*R*)-**1** was observed after 25 days at 300 K (table 2).[19]

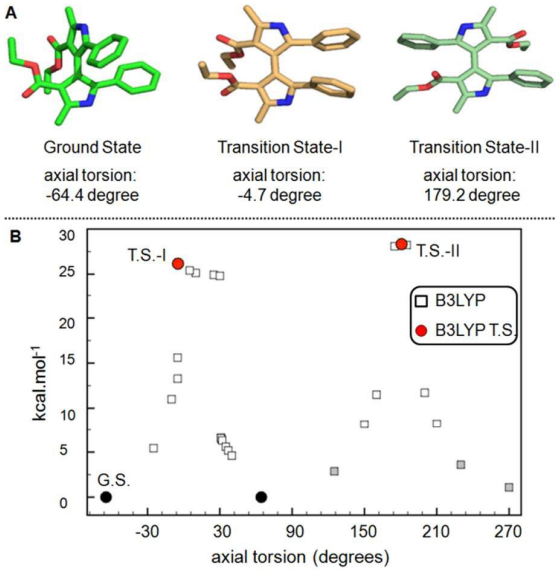

Figure 3. (A) From left: B3LYP/6-311G**//B3LYP/6-311G** optimized ground state, lower energy transition state (TS-I), and higher energy transition state (TS-II) (Hydrogens are omitted for clarity). (B) Energy vs axial torsion plot for internuclear bond rotation in 5,5´-Dimethyl-2,2´-diphenyl-1*H*,1´*H*-[3,3´]bipyrrolyl-4,4´-dicarboxylic acid diethyl ester (**1**). White squares indicate geometries optimized starting from transition states; grey squares were optimized starting from ground states.

To support the results obtained from ECD and HPLC analysis for **1**, the activation barrier of racemization ($\Delta G^{\neq}_{rac}$) for **2** and **3** were also determined by chiral HPLC analysis at incubation temperature of 353 K. The exponential decrease of *ee* for **2** and **3** were found to be similar with that of **1** and gave the comparable results of activation barrier of racemization ($\Delta G^{\neq}_{rac}$) as 26.05 (for **2**) and 26.26 (for **3**) kcal.mol^{-1} (table 2).[19]

To further verify the experimental energy barrier of **1** and to understand the racemization pathway and transition states involved in configurationally inversion, we decided to study the atropisomeric features in more detail with *ab initio* quantum mechanics. Minimum and transition state energies were calculated at the B3LYP/6-311G**//B3LYP/6-311G** level of theory and verified with frequency calculations using Gaussian09.[19, 21]

Molecule **1** is in the lowest energy state when the central torsion angle (as measured from the 2 carbon to the 2´ carbon) is -64.4°. The slightly lower energy transition state for axial rotation is predicted to be 26.2 kcal.mol^{-1} as the phenyl rings cross each other in the *syn* conformation above the minimum. The higher energy transition state, found at 179.2° in the *anti* conformation, predicted to be 28.3 kcal.mol^{-1} (figure 3). The lower energy transition state agrees well with the extrapolated experimental $\Delta G^{\neq}_{rac}$ of around 26 kcal.mol^{-1}. The relative enthalpies of racemisation, as predicted by frequency calculations at the same level of theory, are 25.2 and 27.3 kcal.mol^{-1}, for TS-I and TS-II, respectively-which are also in accord with the high enthalpy barrier extrapolated from the experimental results.

Conclusions

In conclusion, we have characterized, to our knowledge for the first time, the activation barrier of racemization for various 3,3´-bipyrroles. A series of experimental studies confirmed the stability of enantiomerically pure atropisomer of 3,3´-bipyrroles at ambient temperature. The activation barrier of racemization for 3,3´-bipyrrole **1** was experimentally determined to be 26 kcal.mol^{-1} which is in good agreement with the computational results. Similarly, the configurational stability of other 3,3´-bipyrroles (**2** and **3**) have also been determined by the above established protocol. The emerging importance of very slow rate of isomerization of **1**-**3** grants an ease of separation and potential for storage of an individual enantiomer without the erosion of its optical purity, which might be useful for numerous advanced studies.

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Notes and references

The authors declare no competing financial interest.

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The activation barrier of racemization was determined for atropisomeric 3,3′-bipyrroles and they are found to be configurationally stable.