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Analysis of the stereodynamics of 2,2′-disubstituted biphenyls by dynamic chromatography

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Abstract—In contrast to 2,2′-diisopropylbiphenyl, 2-phenyl-2′-isopropylbiphenyl, **1**, and 2-cyclohexyl-2′-phenylbiphenyl, **2**, undergo racemization at room temperature. Chiral HPLC analysis on Chiralcel OD show formation of a temperature-dependent plateau between the well-resolved peaks due to simultaneous enantioseparation and on-column enantioconversion. The rotational energy barrier of these axially chiral compounds has been determined as 91.3 (**1**) and 91.4 kJ/mol (**2**) by computer simulation of experimentally obtained HPLC elution profiles.

The unique chirality and stereodynamics of atropisomeric biaryls has fascinated stereochemists since Christie and Kenner demonstrated in 1922 that 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid and its 4,4′,6,6′-tetranitrobiphenyl derivative can be separated into enantiomers while biphenyl-2,2′-dicarboxylic acid undergoes rapid racemization at room temperature.[1] Today, numerous natural products,[2] pharmaceuticals,[3] catalysts,[4] and sensors[5] possessing a chiral biaryl framework are known. Since the properties and applications of these compounds depend on the energy barrier to rotation about the chiral axis, stereodynamic analysis of axially chiral biaryls has received increasing attention. Mechanistic studies have shown that the rotational energy barrier is mainly determined by steric repulsion between *ortho* substituents whereas *meta* and *para* substituents have a minor effect on the conformational stability of biaryls.[6] The atropisomerization of stereolabile biaryls obeys reversible first-order kinetics and typically involves a highly negative activation entropy due to a sterically crowded transition state exhibiting both aryl planes in a periplanar arrangement.[7]

Stereodynamic analysis of atropisomers often entails chiroptical methods and variable-temperature NMR spectroscopy. However, dynamic chromatography has emerged as an attractive alternative to traditionally used techniques.[8] It is particularly useful when isomerization processes cannot be monitored by NMR spectroscopy due to too high activation energies (>100 kJ/mol) or in cases of unsuccessful resolution of individual NMR signals of the interconverting species. Importantly, only minute sample amounts are required and stereoisomers, for example, enantiomers of axially chiral biphenyls, do not have to be separated prior to analysis. Interconversion of enantiomers during chromatographic separation on a chiral stationary phase generates characteristic elution profiles and peak coalescence. The separation of enantiomers on a chiral stationary phase usually yields a chromatogram with two distinctive peaks. A temperature-dependent plateau between the two peaks is obtained when racemization occurs on the chromatographic time scale. The racemization rate and the height of the plateau increases with the column temperature, and peak coalescence is observed when the enantioconversion is significantly faster than the chromatographic separation process, Figure 1. Following Schurig's seminal work on dynamic chromatography,[9] several groups have successfully used dynamic HPLC, GC, SFC, CE, and MEKC for determination of the racemization kinetics of stereolabile chiral compounds.[10]

To the best of our knowledge, the barrier to atropisomerization of 2-phenyl-2′-isopropylbiphenyl, **1**, and 2-cyclohexyl-2′-phenylbiphenyl, **2**, has not been reported to date. Screening of several cellulose- and amylose-derived HPLC columns revealed that the enantiomers of **1** can be separated on Chiralcel OD at 0 °C, Figure 2.

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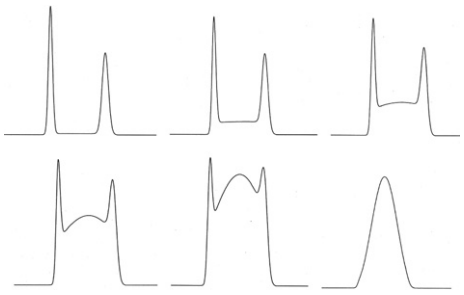


Figure 1. Simulated chromatographic elution profiles showing baseline enantioseparation (top left) and increasing contribution of on-column racemization until peak coalescence is reached (bottom right).

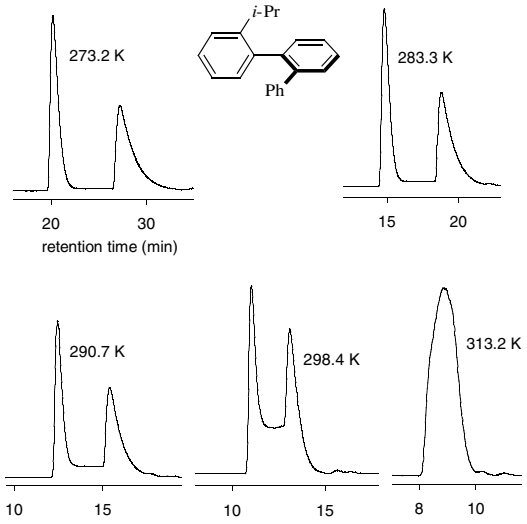


Figure 2. DHPLC of 2-phenyl-2′-isopropylbiphenyl, **1**, on Chiralcel OD using hexanes as mobile phase.

An increase in the column temperature resulted in simultaneous enantioconversion, generating the same peak shapes as shown in Figure 1, and coalescence was observed above room temperature. Computer simulation of these elution profiles was accomplished using readily available chromatographic parameters (number of theoretical plates, void volume time, peak height, and retention times of the enantiomers) in conjunction with reiterative optimization of the enantiomerization rate constant, Figure 3.[11]

We then employed 2-cyclohexyl-2′-phenylbiphenyl in the same HPLC separation process exploring a similar temperature range. Again, dynamic HPLC analysis shows formation of a temperature-dependent plateau between the two peaks due to simultaneous enantioseparation and atropisomerization, Figure 4. Reiterative computer simulation of the experimentally obtained chromatograms gave the corresponding rate constants, Figure 5.

The stability to atropisomerization of several 2,2′-disubstituted biaryls has been studied by polarimetry, variable-temperature NMR spectroscopy, and dynamic chromatography.[12] The rotational energy barriers

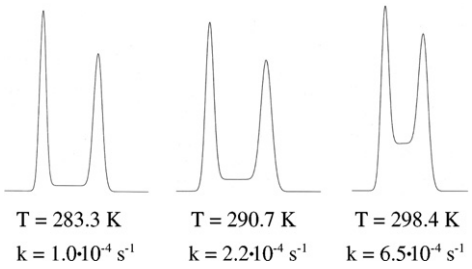


Figure 3. Simulated elution profiles of 2-phenyl-2′-isopropylbiphenyl.

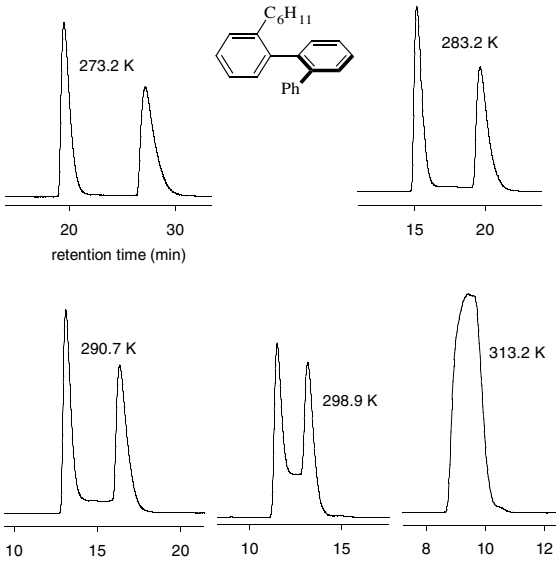


Figure 4. DHPLC of 2-cyclohexyl-2′-phenylbiphenyl, **2**, on Chiralcel OD using hexanes as mobile phase.

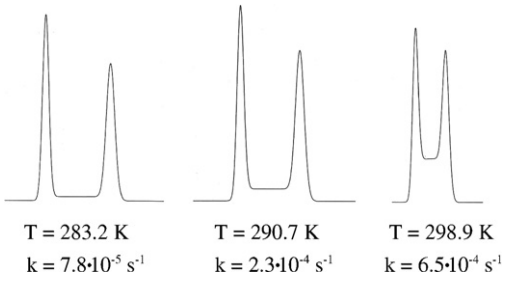


Figure 5. Simulated elution profiles of 2-cyclohexyl-2′-phenylbiphenyl.

obtained provide important information on the conformational stability of these axially chiral biaryls and on the steric bulk of the *ortho* substituents, Figure 6. For example, 2,2′-diiodobiphenyl and 1,1′-binaphthyl have a rotational energy barrier of approximately 100 kJ/mol at 340 and 317 K, respectively. The enantiomers of these atropisomers can be resolved at room temperature, but they readily racemize upon heating.[13] Incorporation of bulky isopropyl groups into the *ortho* positions enhances steric repulsion in the periplanar transition state and thus further increases the Gibbs activation energy, $\Delta G^{\neq}$, to 110.4 kJ/mol. This value increases dramatically to 136.9 kJ/mol (432.9 K) when one isopropyl substituent is replaced by a *tert*-butyl group.

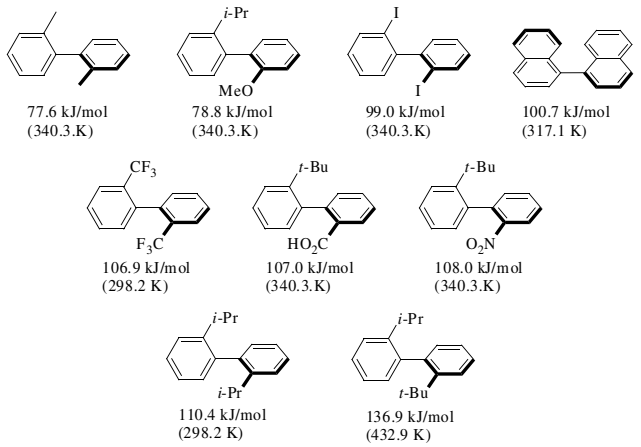
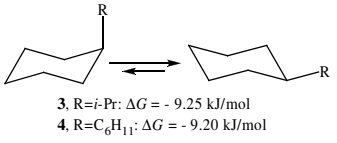


Figure 6. Rotational energy barriers, $\Delta G^{\neq}$, of 2,2′-disubstituted biaryls.

Using the Eyring Eq. 1 the free Gibbs activation energy to atropisomerization of **1** and **2**, $\Delta G^{\neq}$, was calculated as 91.3 and 91.4 kJ/mol (280–298 K), respectively. In contrast to 2,2′-diisopropylbiphenyl, which has a rotational energy barrier of 110.4 kJ/mol, the enantiomers of both **1** and **2** undergo rapid interconversion at room temperature. Apparently, replacement of one isopropyl group by a phenyl ring significantly decreases the steric hindrance to racemization. Our experimental results are in good agreement with semiquantitative calculations conducted by Sternhell and co-workers.[6f] Assuming additivity of steric contributions of *ortho* substituents, which were estimated based on effective van der Waals radii and so-called interference values, they predicted a rotational energy barrier of 85.7(±6.8) kJ/mol for biaryl **1**. The striking similarity in the conformational stability of **1** and **2** can be rationalized based on the comparable size of the isopropyl and cyclohexyl moieties.[14]

$$k = \frac{k_B T}{h} e^{-\Delta G^{\neq}/RT} \quad (1)$$

The similarity of rotational energy barriers of biaryls **1** and **2** corresponds well to previously reported NMR studies showing that isopropyl and cyclohexyl substituents afford the same conformational free energy difference between the axial and the equatorial conformers of monosubstituted cyclohexanes **3** and **4**, Scheme 1.[15] Investigating conformational equilibria and gearing effects in polysubstituted thiazoline 2-thiones, Roussel et al. observed similar effects of isopropyl and cyclohexyl groups on the *syn*/*anti*-ratio of these systems.[16] It is quite remarkable that dynamic HPLC studies, providing kinetic parameters of the atropisomerization of 2,2′-disubstituted biphenyls, and thermodynamic NMR analysis of ring flipping equilibria of cyclohexanes and relative stabilities of *syn*- and *anti*-isomers of sterically crowded thiazoline 2-thiones, respectively, generate compatible information on the steric bulk of isopropyl and cyclohexyl groups.



Scheme 1. Conformational energies of cyclohexanes **3** and **4**.

In summary, the rotational energy barrier of 2-phenyl-2′-isopropylbiphenyl and 2-cyclohexyl-2′-phenylbiphenyl has been determined as 91.3 and 91.4 kJ/mol by computer simulation of experimentally obtained HPLC elution profiles. Comparison with 2,2′-diisopropylbiphenyl reveals that incorporation of isopropyl and cyclohexyl groups into the *ortho* positions of biphenyl provides significantly more steric hindrance to atropisomerization than a phenyl ring. The results underscore the suitability of dynamic chromatography for the determination of the conformational stability of axially chiral compounds and the general significance of the rotational energy barriers of 2,2′-disubstituted biaryls to stereochemical analysis of steric and conformational effects of individual substituents.

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