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Atropisomerization in Confined Space; Cucurbiturils as Tools to Determine the Torsional Barrier of Substituted Biphenyls

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The torsional barrier of biphenyls bearing a prochiral dimethylsulfonium group at their 3-position could be determined by variable-temperature ^{1}H NMR spectroscopy only after encapsulation into cucurbit[7]- or -[8]uril, which triggered the splitting of the two methyl signals. Confinement of the biphenyl units into the macrocycles amplifies the dissymmetry caused by the various *ortho*- and *ortho′*-substituents and represents a new tool that can be used to access atropisomerization barriers of bi(hetero)aryl derivatives.

Introduction

Barriers to torsional isomerization along the C_{aryl}–C_{aryl} axis of bi(hetero)aryl derivatives can be determined by using a limited number of analytical methods, each covering a rather specific range of activation energies (see Figure 1).[1] For example, dynamic nuclear magnetic resonance spectroscopy (DNMR) may allow the determination of barriers ranging from 5 to 20 kcal mol^{-1};[2] measuring the optical activity of enantiomerically enriched or pure atropisomers as a function of time at a given temperature affords activation energies ranging from 23 to 33 kcal mol^{-1}; finally, dynamic separation techniques such as dynamic high-performance liquid chromatography (DHPLC), gas chromatography (DGC), stopped-flow DGC and capillary zone electrophoresis (CZE, see Figure 1) cover a wide range of activation barriers, from approximately 15 to 45 kcal mol^{-1}. We note, however, that DNMR is only successful when prochiral groups connected to the biaryl scaffolds resonate at different frequencies at low temperatures, and appear equivalent at higher temperatures, which is by no means guaranteed.[3]

We have recently shown[1] that torsional barriers of substituted biphenyls ranging from 6 to 30 kcal mol^{-1} could be calculated with very high precision and accuracy by density functional theory (DFT) by using the dispersion-corrected B3LYP–D hybrid,[4,5] and triple-ζ doubly-polarized def2-TZVPP basis sets, with enthalpic and entropic corrections at nonzero temperatures; only four barriers out of 39 deviated by more than 1.0 kcal mol^{-1} from experimental data, with negligible mean deviation and a mean absolute deviation as low as 0.47 kcal mol^{-1}; the tolerance of this method is 1.8 kcal mol^{-1}, i.e., 95% of calculated barriers for any new series of biphenyl scaffolds are 99% likely to be within 1.8 kcal mol^{-1} of experimental data. Barriers up to 45 kcal mol^{-1} could also be calculated by using B3LYP–D,[4,5] B97–D[5,6] or TPSS–D3[7] functionals with slightly lower accuracy (see Figure 1).[1]

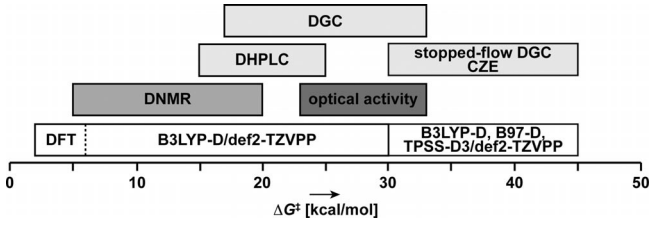

Figure 1. Analytical methods allowing the determination of torsional barriers of bi(hetero)aryl derivatives.

Of course, calculations suffer from the inescapable weakness that predictions may yet fall outside the margin of tolerance. New experimental tools to determine these activation barriers are thus always desirable.

In this study, we show that encapsulation of selected biphenyl derivatives bearing prochiral groups into cucurbit[7]- and cucurbit[8]uril (CB[7] and CB[8])[8] allows the straightforward determination of their torsional barriers by ^{1}H DNMR; such determination would have been impossible in the absence of the macrocycle, due to the indistinguishable resonance of the prochiral groups, regardless of temperature.[9]

Results and Discussion

Guests **1**–**3** were chosen as model structures to illustrate this new method (see Scheme 1), because their biphenyl scaffold was expected to sit inside the cavity of CB[7] and CB[8], and because the positively charged sulfonium substituent should enhance binding affinities by interacting

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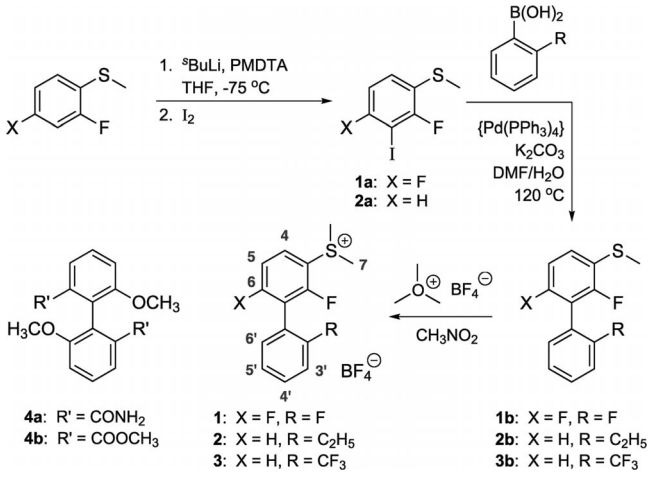
with the carbonylated portal of the macrocycles. In a recent study, we showed that the affinity of CB[7] for a series of biphenyl derivatives bearing a sulfonium unit at the 3-position could reach 10^6 M^{-1}.[10] The two methyl groups of the sulfonium unit are intended to be used as diastereotopic probes during DNMR experiments, but merge into one singlet in ^{1}H NMR spectra carried out in deuterium oxide, [D_4]MeOH and [D_3]acetonitrile (with the exception of biphenyl **3** in the latter solvent), or overlap with the signal of residual water in [D_6]DMSO.



Scheme 1. Preparation of biphenyls **1**–**3** and structure of biphenyls **4**.

Iodoarene **1a** was obtained after metalation of 2,4-difluorothioanisole with *sec*-butyllithium and interception of the aryllithium intermediate with iodine, and was subsequently coupled to (2-fluorophenyl)boronic acid to afford biphenyl **1b**. Methylation of the latter with trimethyloxonium tetrafluoroborate afforded guest **1**. A similar procedure was used to obtain guests **2** and **3** (Scheme 1).

In all three cases, CB[8] encapsulated the phenyl ring bearing substituent R, in deuterium oxide, as indicated by significant upfield shifts of hydrogen nuclei located at the 3′- and 5′-positions (0.42 and 0.39 ppm on average) and especially the 6′-position (δ = 0.66 ppm on average). Furthermore, the ethyl sidechain of guest **2** is situated deep inside the cavity of CB[8], with upfield shifts of 0.72 and 0.93 ppm, for the CH_2 and CH_3 signals, respectively (numbered 8 and 9 in Figure 2, spectra d and e). Exchanges are fast on the NMR time-scale in all cases. Whereas guests **1** and **3** are encapsulated by CB[7] with fast and intermediate exchange rates, respectively, the 2′-ethyl substituent of guest **2** prevents the formation of any complex with CB[7] (see the Supporting Information for titrations of guests **1**–**3** with CB[7] and CB[8]). Binding affinities were measured by isothermal titration calorimetry (ITC), and range from 1.3×10^5 to 8.3×10^6 M^{-1} (Table 1).

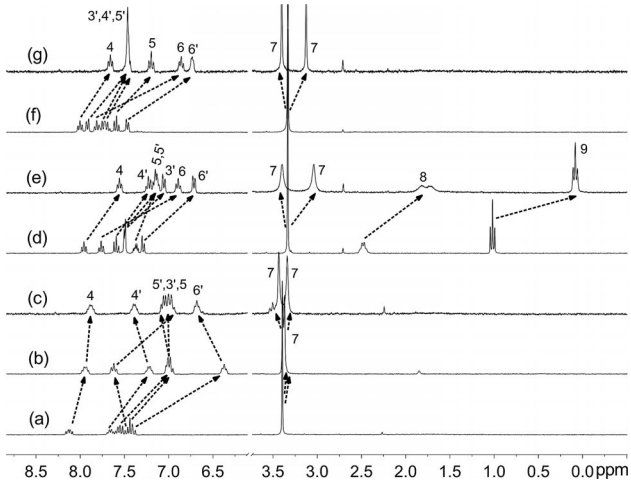


Figure 2. ^{1}H NMR spectra of (a) biphenyl **1**, (b) assembly **1**·CB[7], (c) assembly **1**·CB[8], (d) biphenyl **2**, (e) assembly **2**·CB[8], (f) biphenyl **3**, and (g) assembly **3**·CB[8]. Measurements carried out in D_2O. See Scheme 1 for numbering; signals 8 and 9 refer to the 2′-ethyl substituent of biphenyl **2**.

Biphenyls **1**–**3** are likely very mobile inside the macrocycles, and a series of plausible complexes with similar stabilities (differences in electronic contributions lower than 0.8 kcal mol^{-1}) could be obtained from DFT calculations at the TPSS-D3(BJ)/def2-TZVP level[7,11] (this functional has been successfully tested in supramolecular systems,[12] see experimental section for details). Figure 3 shows the optimized structure of assembly **2**·CB[8], with the ethyl substituent R located deep inside the cavity of the macrocycle, in accordance with ^{1}H NMR experiments.

Table 1. Binding affinities of guests **1**–**3** towards CB[*n*] compounds; activation parameters for the torsional isomerization of biphenyls **1**–**3** in CB[*n*] compounds, and comparison to computational data.

	K_a[a] [M^{-1}]	T_c[b] [°C]	$\Delta H^{\ddagger}$[c] [kcal mol^{-1}]	$T\Delta S^{\ddagger}$[d] [kcal mol^{-1}]	$\Delta G^{\ddagger}_{exp}$[e] [kcal mol^{-1}]	$\Delta G^{\ddagger}_{calc}$[f] [kcal mol^{-1}]	$\Delta\Delta G^{\ddagger}$[g] [kcal mol^{-1}]	$\Delta G^{\ddagger\prime}$[h] [kcal mol^{-1}]
1·CB[7]	4.4 (±0.2) × 10^6	51	18.2 (± 0.5)	1.0 (± 0.5)	17.2	15.8 (16.3)	1.4 (0.9)	13.9
1·CB[8]	1.3 (±0.1) × 10^5	54	15.1 (± 0.3)	–1.2 (± 0.3)	16.3	15.8 (16.3)	0.5 (0.0)	13.9
2·CB[8]	8.3 (±0.4) × 10^6	54	14.7 (± 0.3)	–0.8 (± 0.3)	15.5	14.4 (15.4)	1.1 (0.1)	14.8
3·CB[8]	6.5 (±0.4) × 10^6	114	14.2 (± 0.4)	–4.5 (± 0.5)	18.7	18.5 (17.4)	0.2 (1.3)	16.0
3·CB[8][i]		56			17.0	18.1 (17.0)	–1.1 (0.0)	15.4

[a] Binding affinity. [b] Coalescence temperature. [c] Activation enthalpy. [d] Entropic contribution at coalescence temperature. [e] Free energy of activation as determined by DNMR experiments. [f] Free energy of activation calculated for the free guest at the B3LYP-D/def2-TZVPP level, and, in parentheses, after correction for solvation using the IEFPCM model. [g] Deviation of the experimental torsional barrier inside CB[*n*] from the calculated barrier of the free guest in the gas phase, and, in parentheses, in aqueous solution. [h] Calculated torsional barrier of the free guest in the gas phase, after replacement of the dimethylsulfonium unit with a hydrogen atom. [i] In the presence of CB[8] (0.18 equiv.). All standard errors on experimental free energies of isomerization are 0.1 kcal mol^{-1}.

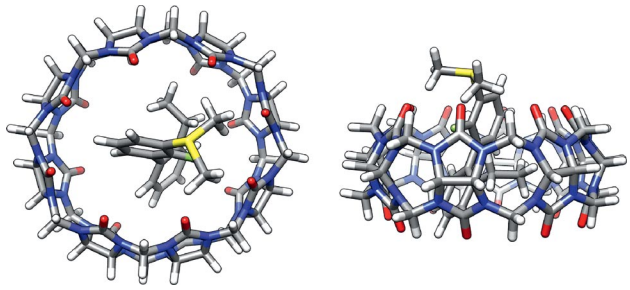


Figure 3. Optimized structure of complex **2**·CB[8].

The key feature of the spectra of complexes **1**·CB[7] and **1**·CB[8] to **3**·CB[8] is the splitting of the dimethylsulfonium signals into two well-defined singlets, with remarkably wide differences in resonance frequencies in some cases (0.02, 0.10, 0.36 and 0.28 ppm, respectively, see Figure 2; no split is observed in assembly **3**·CB[7]). We attribute the splitting to the loose confinement of the guest inside the macrocycles, which still creates a different chemical environment in the immediate surroundings of the two methyl groups, and "amplifies" the dissymmetry caused by *ortho*-substituents R (see Figure 2).

DNMR experiments were then carried out, and rates of torsional isomerization for guests **1**–**3** in CB[8] and biphenyl **1** in CB[7] were determined by line-shape analysis by using a two-site exchange model (see Figure 4, a and b). This model is valid because the exchange rate between various

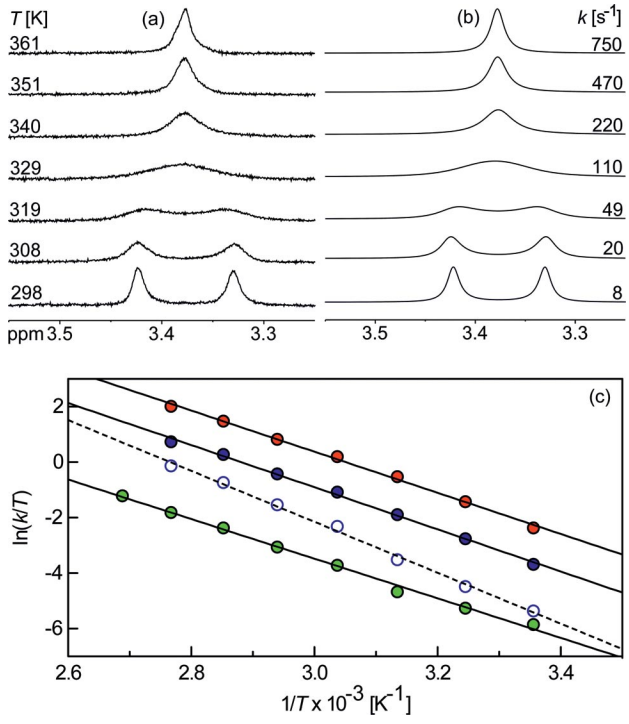


Figure 4. (a) Variable-temperature ^{1}H NMR experiments; resonance of the dimethylsulfonium groups in assembly **1**·CB[8]. (b) NMR simulation. (c) Eyring plot depicting the rates of torsional isomerizations of guest **1** inside CB[7] (empty blue circles), guest **1** in CB[8] (filled blue circles), guest **2** in CB[8] (red circles) and guest **3** in CB[8] (green circles) at various temperatures.

conformations of these CB[*n*]/guest assemblies is very fast on the NMR time-scale, and much faster than rotation along the C_{aryl}–C_{aryl} axis (sharp aromatic signals are observed in all four complexes).[13]

Free energies of activation were determined by using the Eyring equation and by plotting $\ln(k/T)$ vs. $1/T$, where k is the rate of isomerization at temperature T. Enthalpies of activation $\Delta H^{\ddagger}$ could be obtained from the slope of the best straight line, and $\Delta S^{\ddagger}$ from its intersection with the y-axis (see Table 1 and Figure 4, c). Coalescence temperatures were 51, 54, and 54 °C in the case of assemblies **1**·CB[7], **1**·CB[8] and **2**·CB[8], respectively, and extrapolation afforded a coalescence temperature of 114 °C for guest **3** in CB[8].

With the exception of assembly **1**·CB[7], activation enthalpies for the three guests were similar (14.2–15.1 kcal mol^{-1}), and activation entropies ($T\Delta S^{\ddagger}$ ranging from –4.5 to –0.8 kcal mol^{-1}) were responsible for the differences in free energies of activation. The latter in CB[8] were 16.3, 15.5 and 18.7 kcal mol^{-1}, respectively. The barrier of torsional isomerization of guest **1** in CB[7] was slightly higher than in CB[8] (17.2 vs. 16.3 kcal mol^{-1} at 51 °C). It is tempting to attribute the difference to the tighter confinement of guest **1** inside CB[7] compared with CB[8]; however, the difference merely means that the affinity of the transition state of guest **1** towards CB[7] is only 9.1 times greater than towards CB[8], compared to 35 times for the ground state.

The inconveniently high coalescence temperature of complex **3**·CB[8] is caused (1) by the higher activation barrier of the torsional pathway, and (2) by a significant difference in resonance frequencies between the two diastereotopic methylsulfonium groups (δ = 0.28 ppm, see Figure 5). To narrow the latter, we carried out DNMR experiments by using a substoichiometric amount of CB[8] (0.18 equiv., which translates into a 0.05 ppm difference between the two methylsulfonium groups, see Figure 5, b). Coalescence was then observed at 56 °C.

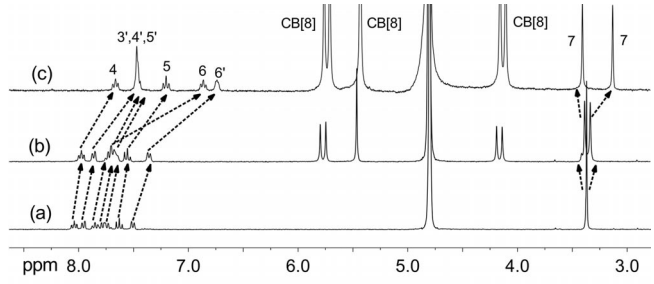


Figure 5. ^{1}H NMR spectra of biphenyl **3**, (a) in the absence of CB[8], and in the presence of (b) CB[8] (0.18 equiv.) and (c) CB[8] (1.0 equiv.).

Although the exchange between free guest **3**, free CB[8] and the corresponding assembly is fast on the NMR timescale at 25 °C (i.e., its activation barrier is lower than ap-

proximately 14 kcal mol^{-1}), it must be greater than the gain in free energy upon CB[8] binding (an affinity of 6.5×10^6 M^{-1} corresponds to a 8.9 kcal mol^{-1} stabilization). This barrier is thus not negligible, and the DNMR simulations had to be carried out with a four-site exchange model. Activation energies of 17.0 and 11.7 ($\pm$0.2) kcal mol^{-1} were obtained for the torsional and guest egression pathways, respectively, at coalescence temperature. The torsional barrier of free guest **3** at 56 °C was then readily extrapolated to 16.9 kcal mol^{-1} (see the Supporting Information for details). A similar method could be applied to guests **1** and **2** with fractions of bound guests greater than approximately 75%, should coalescence temperatures between 25 and 50 °C be desired (see the Supporting Information for titrations of guests **1**–**3** with CB[*n*] macrocycles).

A question that needs to be addressed is whether activation barriers inside CB[*n*] compounds are similar to those in the gas phase and in organic solvents. The slight differences measured between assemblies **1**·CB[7] and **1**·CB[8] (0.9 kcal mol^{-1}), as well as between free guest **3** and its CB[8] complex (1.0 kcal mol^{-1} at 56 °C)[14] suggest so. Whereas solvent effects on torsional barriers have only been assessed systematically on two occasions by using derivatives **4a** and **4b** (see Scheme 1), they were found to barely affect Gibbs energies of activation (by less than 1.2 kcal mol^{-1} among 33 solvents). Because activation energies are determined by DNMR with various solvents to cover adequate temperature ranges[15] (and therefore, an error in the order of 1.2 kcal/mol is tacitly accepted by neglecting solvent effects), torsional barriers measured inside CB[*n*] macrocycles should be no less valid than those measured with various solvents. Furthermore, our previously published DFT calculations were very accurate, even when neglecting solvation effects unless charged substituents were connected to the *ortho* and *ortho′* positions of the biphenyl scaffolds.[1] The cavity of CB[*n*] compounds, as a chemical environment, is thus expected to follow the same trend, and not to cause any major alteration of the free activation energies, compared to gas or solution phase measurements. To support this argument, we calculated the barriers of biphenyl compounds **1**–**3** at the B3LYP–D/def2-TZVPP level by using our previously benchmarked method.[1] Deviations from experimental data inside CB[7] or CB[8] (less than 1.4 kcal mol^{-1}, see Table 1) are all within the tolerance limit of the method (1.8 kcal mol^{-1}). Because a fraction of the guest surface is exposed to the aqueous environment even when surrounded by CB[*n*], we also compared the torsional barriers measured inside CB[7] or CB[8] with calculated barriers obtained after correction with solvation energies (determined with the polarizable continuum solvation model, IEFPCM).[16] In all three cases, again, deviations were all within the tolerance interval (less than 1.3 kcal mol^{-1}, see Table 1). One can thus conclude that CB[*n*] encapsulation of biphenyl derivatives is a valid tool with which to determine their torsional barriers as free species. If necessary, DNMR experiments can be carried out by using various concentrations of CB[*n*], and the activation barrier in neat solvent can even be extrapolated.

As far as biphenyls **1**–**3** are concerned, *syn* conformations (with the two methylsulfonium groups pointing towards the fluorine atom at the 2-position, see Figure 3) are preferred in both ground and transition states by 2.5 and 2.0 kcal mol^{-1} on average, respectively, compared to *anti* conformations [electronic energies obtained with the PW6B95-D3(BJ)[11,17] functional after optimization and vibrational analysis at the B3LYP–D level]. As we have reported in a previous study,[10] solvation smoothens the *syn* preference, which reaches only 0.6 and 0.5 kcal mol^{-1} at the ground and transition states, respectively. In all three biphenyl compounds, the buttressing effect of the dimethylsulfonium unit at the 3-position on the neighboring fluorine substituent decreases isomerization rates significantly. Torsional barriers of biphenyls bearing a hydrogen atom at the 3-position instead of the sulfonium group were calculated (Table 1), and found to be 0.4 to 2.5 kcal mol^{-1} lower. Whereas in guests **2** and **3**, the ethyl or trifluoromethyl R groups at the 2′-position pass over the hydrogen atom at the 6-position in the transition state, calculations suggest that the 2′-fluoro substituent of guest **1** passes preferentially over the buttressed 2-fluoro group, a 2.0 kcal mol^{-1} advantage compared to passage over the fluorine atom at the 6-position. Whereas the sulfonium unit exerts steric buttressing on its *ortho*-positioned neighbor, its positive charge slightly alleviates the electronic density around the fluorine atom, thereby making it more favorable to pass over the 2′-fluoro group. When solvation is taken into account, the preference for the 2-F/2′-F torsional pathway is reduced to 0.6 kcal mol^{-1}.

Finally, the scope and limitations of this method was assessed. When deuterium oxide is used without the addition of cosolvents, coalescence or extrapolated coalescence temperatures should range from approximately –10 to 110 °C; the corresponding activation barriers are approximately 12.5 to 20.5 kcal mol^{-1}. The addition of cosolvents, resulting in a decrease in the melting point of the mixture, may allow the determination of barriers ranging from 11 to 12.5 kcal mol^{-1}, although concerns about the solubility of the CB[*n*] assemblies under these conditions should be raised. We expect that this method will be extended to various bi(hetero)aryl derivatives, and that the latter will not be limited to positively charged scaffolds because CB[*n*] also interact with selected neutral[18] and even negatively charged guests.[10] As shown in this study and in others,[10] binding affinities towards CB[*n*] are not sensitive to minor conformational changes of the guest, therefore the macrocycles are not expected to impact on the torsional barriers more than changes in solvent composition.

Conclusions

We have shown that encapsulation of selected biphenyl derivatives into CB[7] and CB[8] "amplifies" the dissymmetry caused by the 2-, 2′-, 6-, and 6′-substituents, and causes remarkable differences in resonance frequencies of a prochiral dimethylsulfonium group connected to their 3-

position. In the absence of the macrocycle, both methyl groups resonate at the same frequencies, regardless of temperature. We also determined that CB[*n*] encapsulation has a very limited impact on the torsional barriers, and we compared the latter with calculated values obtained by using a highly accurate benchmarked density functional method. To the best of our knowledge, this study is the first case of CB[*n*] use as an analytical accessory to access coveted kinetic parameters, and is anticipated to be applicable to a wide range of bi(hetero)aryl derivatives.

Experimental Section

2,4-Difluoro-3-iodothioanisole (1a): A solution of *sec*-butyllithium (1.4 M in hexane, 4.5 mL, 6.2 mmol) was added to a solution of 2,4-difluorothioanisole (1.0 g, 6.2 mmol) in anhydrous THF (60 mL), and the reaction mixture was kept at –75 °C for 2 h before the addition of iodine (1.6 g, 6.2 mmol). The reaction mixture was then warmed to 25 °C, aq. $Na_2S_2O_3$ (2.0 mL, 50 mg, 0.32 mmol) was added, and the mixture was diluted with water (40 mL) and extracted with diethyl ether (2× 50 mL); the organic layers were dried with Na_2SO_4 and the solvents evaporated. The product was purified by chromatography (silica gel; hexane/ethyl acetate, 19:1) to afford **1a** (1.3 g, 73%) as a white solid; m.p. 42–43 °C. ^{1}H NMR (CD_3CN): δ = 7.40 (m, 1 H, Ar-*H*), 7.03 (t, *J* = 8.8 Hz, 1 H, Ar-*H*), 2.48 (s, 3 H, S-CH_3) ppm. ^{13}C NMR: δ = 161.8 (dd, *J* = 243.3, 5.3 Hz, Ar*C*F), 160.3 (dd, *J* = 240.8, 6.0 Hz, Ar*C*F), 130.8 (dd, *J* = 8.3, 3.8 Hz, Ar*C*), 122.7 (dd, *J* = 20.3, 3.8 Hz, Ar*C*), 112.6 (dd, *J* = 24.0, 3.8 Hz, Ar*C*), 72.2 (t, *J* = 30.0 Hz, Ar*C*), 16.1 (d, *J* = 2.3 Hz, *C*H_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_7H_5F_2IS$ $[M]^+$ 285.911922; found 285.912114.

Methyl(2,2′,6-trifluorobiphenyl-3-yl)sulfane (1b): A solution of potassium carbonate (0.34 g, 2.5 mmol) in H_2O (5.0 mL) was added to a solution of sulfide **1a** (0.35 g, 1.2 mmol), (2-fluorophenyl)boronic acid (0.26 g, 1.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.12 mmol) in *N*,*N*-dimethylformamide (20 mL) under an inert atmosphere. The resulting mixture was heated to 120 °C for 12 h. After cooling to 25 °C, the reaction mixture was filtered through a pad of Celite and the filtrate was then poured into ice-cold water (70 mL), acidified with 1.0 M HCl (5.0 mL), and extracted with dichloromethane (3× 25 mL). The organic fractions were washed with water (60 mL) and brine (60 mL), dried with Na_2SO_4, then concentrated in vacuo. The product was purified by column chromatography (silica gel; hexane/ethyl acetate, 9:1) to afford **1b** (0.28 g, 90%) as a colorless oil. ^{1}H NMR (CD_3CN): δ = 7.57–7.42 (m, 3 H, Ar-*H*), 7.36–7.27 (m, 2 H, Ar-*H*), 7.15 (t, *J* = 8.9 Hz, 1 H, Ar-*H*), 2.51 (s, 3 H, S-CH_3) ppm. ^{13}C NMR: δ = 161.0 (d, *J* = 246.0 Hz, Ar*C*F), 159.5 (dd, *J* = 245.3, 6 Hz, Ar*C*F), 158.2 (dd, *J* = 243.8, 6.8 Hz, Ar*C*F), 133.4 (Ar*C*), 131.8 (d, *J* = 8.3 Hz, Ar*C*), 130.4 (dd, *J* = 9.8, 4.5 Hz, Ar*C*), 125.5 (d, *J* = 3.9 Hz, Ar*C*), 122.7 (dd, *J* = 18.8, 3.8 Hz, Ar*C*), 117.6 (d, *J* = 15.6 Hz, Ar*C*), 116.7 (d, *J* = 21.8 Hz, Ar*C*), 113.5 (t, *J* = 21.0 Hz, Ar*C*), 112.9 (dd, *J* = 23.2, 3.8 Hz, Ar*C*), 16.1 (d, *J* = 2.3 Hz, *C*H_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_9F_3S$ $[M]^+$ 254.037157; found 254.036825.

Dimethyl(2,2′,6-trifluorobiphenyl-3-yl)sulfonium Tetrafluoroborate (1): Trimethyloxonium tetrafluoroborate (36 mg, 0.25 mmol) was added to a solution of biphenyl **1b** (50 mg, 0.19 mmol) in nitromethane (2.0 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 12 h. Methanol (5.0 mL) was then added and the solvents were evaporated under vacuum. Addition of diethyl ether (10 mL) resulted in the formation of the title compound (55 mg, 80%) as a light-yellow powder; m.p. 96–97 °C. ^{1}H NMR (D_2O): δ = 8.13 (q, *J* = 8.4 Hz, 1 H, Ar-*H*), 7.66 (q, *J* = 6.9 Hz, 1 H, Ar-*H*), 7.60–7.49 (m, 2 H, Ar-*H*), 7.46–7.38 (m, 2 H, Ar-*H*), 3.40 [s, 6 H, S(CH_3)$_2$] ppm. ^{13}C NMR (CD_3CN): δ = 163.8 (dd, *J* = 258.4, 7.5 Hz, Ar*C*F), 159.4 (dd, *J* = 264.7, 7.5 Hz, Ar*C*F), 159.4 (d, *J* = 248.1 Hz, Ar*C*F), 133.7 (d, *J* = 11.6 Hz, Ar*C*), 133.2 (d, *J* = 8.4 Hz, Ar*C*), 133.2 (Ar*C*), 125.9 (d, *J* = 3.2 Hz, Ar*C*), 117.0 (d, *J* = 21.5 Hz, Ar*C*), 116.1 (t, *J* = 19.9 Hz, Ar*C*), 115.7 (dd, *J* = 24.8, 3.8 Hz, Ar*C*), 115.4 (Ar*C*), 109.9 (dd, *J* = 15.5, 3.8 Hz, Ar*C*S), 28.7 [d, *J* = 23.7 Hz, S(CH_3)$_2$] ppm. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{12}F_3S$ $[M]^+$ 269.060632; found 269.059939.

2-Fluoro-3-iodothioanisole (2a): A solution of *sec*-butyllithium (1.4 M in hexane, 5.0 mL, 7.0 mmol) was added to a solution of pentamethyldiethylenetriamine (1.3 g, 7.7 mmol) in anhydrous THF (50 mL) at –75 °C, and the reaction mixture was kept at this temperature for 10 min. A solution of 2-fluorothioanizole (1.0 g, 7.0 mmol) in THF (5.0 mL) was added dropwise and the reaction mixture was kept at –75 °C for 2 h, followed by the addition of iodine (1.8 g, 7.0 mmol) in one portion. The resulting mixture was warmed to 25 °C before the addition of aq. $Na_2S_2O_3$ (2.0 mL, 56 mg, 0.35 mmol). The solution was diluted with water (0.10 L) and extracted with diethyl ether (3× 40 mL); the organic layers were dried with Na_2SO_4 and the solvents evaporated. The product after column chromatography (silica gel; hexane/ethyl acetate, 19:1) was a mixture of starting material and product with similar R_f values, and was used in the next step without further purification. HRMS (ESI): *m*/*z* calcd. for C_7H_6FIS $[M]^+$ 267.921344; found 267.921328.

[(2′-Ethyl-2-fluorobiphenyl-3-yl)][(methyl)]sulfane (2b): Prepared in a similar manner to biphenyl **1b**, with 2-fluoro-3-iodothioanisole (**2a**; 0.50 g, 1.9 mmol) and (2-ethylphenyl)boronic acid (0.42 g, 2.8 mmol) instead of 2,4-difluoro-3-iodothioanisole and (2-fluorophenyl)boronic acid. The product was purified by chromatography (silica gel; hexane/dichloromethane, 19:1) to afford **2b** (0.12 g, 26% over two steps) as a colorless oil. ^{1}H NMR (CD_3CN): δ = 7.38–7.24 (m, 5 H, Ar-*H*), 7.18 (t, *J* = 9.6 Hz, 1 H, Ar-*H*), 4.82 (t, *J* = 7.0 Hz, 1 H, Ar-*H*), 2.51 [s, 3 H, S(CH_3)], 2.46 (q, *J* = 7.6 Hz, 2 H, Ar-CH_2), 1.03 (t, *J* = 7.6 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR: δ = 157.3 (d, *J* = 238.5 Hz, Ar*C*F), 143.6, 135.7, 131.1 (Ar*C*), 129.9 (d, *J* = 17.3 Hz, Ar*C*), 129.5 (Ar*C*), 129.4 (d, *J* = 3.0 Hz, Ar*C*), 127.7 (d, *J* = 2.3 Hz, Ar*C*), 127.2 (d, *J* = 18.0 Hz, Ar*C*), 126.8 (Ar*C*), 125.6 (d, *J* = 4.5 Hz, Ar*C*), 27.1 (Ar*C*H_2), 15.7 (CH_2CH_3), 15.2 (d, *J* = 2.3 Hz, SCH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{15}FS$ $[M]^+$ 246.873010; found 246.087235.

(2′-Ethyl-2-fluorobiphenyl-3-yl)dimethylsulfonium (2): Trimethyloxonium tetrafluoroborate (60 mg, 0.42 mmol) was added to a solution of biphenyl **2b** (80 mg, 0.33 mmol) in nitromethane (4.0 mL) under a nitrogen atmosphere. The reaction mixture was heated to 80 °C for 12 h. After cooling to 25 °C, methanol (10 mL) was added and the solvent was evaporated under vacuum. Addition of diethyl ether (10 mL) resulted in the formation of **2** (70 mg, 83%) as a colorless oil that solidified upon standing; m.p. 62–63 °C. ^{1}H NMR (D_2O): δ = 7.96 (t, *J* = 7.2 Hz, 1 H, Ar-*H*), 7.77 (t, *J* = 7.2 Hz, 1 H, Ar-*H*), 7.59 (t, *J* = 7.8 Hz, 1 H, Ar-*H*), 7.49 (m, 2 H, Ar-*H*), 7.14–7.35 (m, 1 H, Ar-*H*), 7.30 (d, *J* = 7.5 Hz, 1 H, Ar-*H*), 3.33 [s, 6 H, S(CH_3)$_2$], 2.48 (q, *J* = 7.8 Hz, 2 H, Ar-CH_2), 1.02 (t, *J* = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (CD_3CN): δ = 159.3 (d, *J* = 250.5 Hz, Ar*C*F), 143.7 (Ar*C*), 139.7 (d, *J* = 4.5 Hz, Ar*C*), 133.5 (Ar*C*), 132.5 (d, *J* = 16.5 Hz, Ar*C*), 131.2, 131.2, 130.5, 129.9 (Ar*C*), 127.5 (d, *J* = 4.5 Hz, Ar*C*), 127.1 (Ar*C*), 113.8 (d, *J* = 15.8 Hz, ArC), 28.6 (Ar*C*H_2), 26.9 [S(*C*H_3)$_2$], 15.7 (CH_2*C*H_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{18}FS$ $[M]^+$ 261.110776; found 261.110079.

[2-Fluoro-2′-(trifluoromethyl)biphenyl-3-yl](methyl)sulfane (3b): Prepared in a similar manner to biphenyl **2b**, with (2-trifluoromethylphenyl)boronic acid (0.74 g, 3.9 mmol) instead of (2-ethylphenyl)-boronic acid. The product was purified by chromatography (silica gel; hexane/ethyl acetate, 99:1) to afford **3b** (0.10 g, 13%) as a colorless oil. ^{1}H NMR (CD_3CN): δ = 7.85 (d, J = 9.0 Hz, 1 H, Ar-*H*), 7.71 (t, J = 7.5 Hz, 1 H, Ar-*H*), 7.63 (t, J = 7.8 Hz, 1 H, Ar-*H*), 7.43–7.38 (m, 2 H, Ar-*H*), 7.25 (t, J = 7.8 Hz, 1 H, Ar-*H*), 7.12 (t, J = 7.2 Hz, 1 H, Ar-*H*), 2.52 [s, 3 H, S(CH_3)] ppm. ^{13}C NMR: δ = 157.7 (d, J = 160.0 Hz, Ar*C*F), 135.4, 133.6, 133.4, 130.1 (Ar*C*), 129.8 (d, J = 30.0 Hz, Ar*C*), 129.4 (Ar*C*), 128.8 (d, J = 2.6 Hz, Ar*C*), 128.1 (d, J = 17.3 Hz), 127.6–127.3 (m, Ar*C* × 2), 125.4 (d, J = 4.3 Hz, Ar*C*), 123.7 (Ar*C*), 15.4 [S(*C*H_3)] ppm. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}F_4S$ $[M]^+$ 286.043385; found 286.043445.

[2-Fluoro-2′-(trifluoromethyl)biphenyl-3-yl]dimethylsulfonium Tetrafluoroborate (3): Obtained in a similar manner to sulfonium **2**, by using biphenyl **3b** (43 mg, 0.15 mmol) instead of biphenyl **2b**, yield 50 mg (86%); light-yellow powder. ^{1}H NMR (D_2O): δ = 8.00 (t, J = 6.6 Hz, 1 H, Ar-*H*), 7.92 (d, J = 7.2 Hz, 1 H, Ar-*H*), 7.81 (t, J = 8.1 Hz, 1 H, Ar-*H*), 7.75–7.66 (m, 2 H, Ar-*H*), 7.59 (t, J = 7.8 Hz, 1 H, Ar-*H*), 7.47 (d, J = 7.0 Hz, 1 H, Ar-*H*), 3.33 [S(CH_3)$_2$, 6 H] ppm. ^{13}C NMR (CD_3CN): δ = 159.5 (d, J = 251.6 Hz, Ar*C*), 13936, 135.8, 133.4, 132.5, 131.1 (Ar*C*), 130.6 (d, J = 16.7 Hz, Ar*C*), 129.8 (d, J = 30.0 Hz, Ar*C*), 127.8 (q, J = 5.1 Hz, Ar*C*), 127.4 (d, J = 4.2 Hz, Ar*C*), 127.1, 123.5 (Ar*C*), 113.8 (d, J = 15.1 Hz, Ar*C*), 28.8 [d, J = 40.0 Hz, S(*C*H_3)$_2$] ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{13}F_4S$ $[M]^+$ 301.066860; found 301.066219.

Computational Details: Conformations of CB[*n*]/guest assemblies were screened at the semi-empirical level (PM7) by using MOPAC 2012,[19] with built-in parameters. The five most stable conformations were further optimized by using TURBOMOLE 6.3.1 (COSMOlogic GmbH & Co. KG, 51381 Leverkusen) at the TPSS-D3(BJ)/def2-SVP level with corrections for solvation using the COSMO model.[20] Convergence criteria were 10^{-6} Hartree and 10^{-3} atomic units as the maximum norm of the Cartesian gradient. Electronic energies were then refined in a single-point calculation with def2-TZVP basis sets (see the Supporting Information for coordinates of the most stable structure of complex **2**·CB[8]). Kinetic parameters for the torsional isomerization of biphenyls **1**–**3** and their analogues bearing a hydrogen atom at the 3-position were calculated by using a known procedure.[1]

Supporting Information (see footnote on the first page of this article): Titration of biphenyl **1** with CB[7] and biphenyl compounds **1**–**3** with CB[8], and characterization of the assemblies; DNMR experiments; ITC results; model for the extrapolation of activation energies to 0% CB[*n*]; Cartesian coordinates of the optimized structure of complex **2**·CB[8]; optimized geometries and activation parameters for torsional isomerization of all biphenyl compounds presented in this study.

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[1] For references pertaining to each analytical method, see: E. Masson, *Org. Biomol. Chem.* **2013**, *11*, 2859–2871.
[2] For recent examples, see: a) A. Mazzanti, L. Lunazzi, M. Minzoni, J. E. Anderson, *J. Org. Chem.* **2006**, *71*, 5474–5481; b) L. Lunazzi, A. Mazzanti, M. Minzoni, *J. Org. Chem.* **2006**, *71*, 9297–9301; c) R. Ruzziconi, S. Spizzichino, A. Mazzanti, L. Lunazzi, M. Schlosser, *Org. Biomol. Chem.* **2010**, *8*, 4463–4471; d) R. Ruzziconi, S. Spizzichino, L. Lunazzi, A. Mazzanti, M. Schlosser, *Chem. Eur. J.* **2009**, *15*, 2645–2652; e) L. Lunazzi, M. Mancinelli, A. Mazzanti, S. Lepri, R. Ruzziconi, M. Schlosser, *Org. Biomol. Chem.* **2012**, *10*, 1847–1855.
[3] F. Leroux, M. Maurin, N. Nicod, R. Scopelliti, *Tetrahedron Lett.* **2004**, *45*, 1899–1902.
[4] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372–1377; b) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.
[5] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787–1799.
[6] A. D. Becke, *J. Chem. Phys.* **1997**, *107*, 8554–8560.
[7] a) J. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.* **2003**, *91*, 146401–146404; b) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104–154119.
[8] a) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, S. L. Isaacs, *Angew. Chem.* **2005**, *117*, 4922; *Angew. Chem. Int. Ed.* **2005**, *44*, 4844–4870; b) E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah, X. Lu, *RSC Adv.* **2012**, *2*, 1213–1247.
[9] This observation is valid even when using an 800 MHz spectrometer.
[10] R. Joseph, E. Masson, *Org. Biomol. Chem.* **2013**, *11*, 3116–3127.
[11] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456–1465.
[12] S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955–9964.
[13] This is not the case in assembly **2**·CB[7]; broad aromatic signals are observed even when the guest is bound quantitatively.
[14] The torsion barrier of guest **3** inside CB[8] is 17.9 kcal mol^{-1} at 56 °C.
[15] A combination of solvents is sometimes used to determine the torsion barrier of one single biphenyl derivative, see for example: G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.
[16] G. Scalmani, M. J. Frisch, *J. Chem. Phys.* **2010**, *132*, 114110–114124.
[17] Y. Zhao, D. G. Truhlar, *J. Phys. Chem. A* **2005**, *109*, 5656–5667.
[18] a) M. V. Rekharsky, T. Mori, C. Yang, Y. H. Ko, N. Selvapalam, H. Kim, D. Sobransingh, A. E. Kaifer, S. Liu, L. Isaacs, W. Chen, S. Moghaddam, M. K. Gilson, K. Kim, Y. Inoue, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20737–20742; b) S. Moghaddam, C. Yang, M. Rekharsky, Y. H. Ko, K. Kim, Y. Inoue, M. K. Gilson, *J. Am. Chem. Soc.* **2011**, *133*, 3570–3581; c) M. Florea, W. M. Nau, *Angew. Chem.* **2011**, *123*, 9510; *Angew. Chem. Int. Ed.* **2011**, *50*, 9338–9342.
[19] James J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA, http://OpenMOPAC.net.
[20] a) A. Klamt, G. Schüürmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, *5*, 799–805; b) A. Klamt, V. Jonas, *J. Chem. Phys.* **1996**, *105*, 9972–9981.

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