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The remarkable configurational stability of *ortho*,*ortho*′-tetrafluoro substituted biphenyls: 2,2′,4,4′,6,6′-hexafluorobiphenyl-3,3′-dicarboxylic acid as a model

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Abstract—Optically active 2,2′,4,4′,6,6′-hexafluorobiphenyl-3,3′-dicarboxylic acid was obtained through its brucine salt. The half-life time for racemization was determined at various temperatures and the torsional barrier for racemization was calculated to be 25.4 kcal/mol. These results prove, contrary to textbook knowledge, that *ortho*,*ortho*′-tetrafluoro substituted biphenyls are resolvable.

Biaryls are not only the central unit in various natural products and in many chiral ligands,[1] but the biphenyl core belongs also to the six or seven privileged structures of the pharmaceutical industry.[2] Recently we reported on the synthesis and inhibitory activity of various 2,2′,6,6′- and 3,3′,5,5′-tetrafluoro substituted biphenylmethyl imidazoles towards 17α-hydroxylase-C17,20-lyase.[3] It makes a striking difference whether the two pairs of fluorine atoms are introduced at the 2,2′,6,6′- or at the 3,3′,5,5′-positions of the biphenyl unit. We were able to show that the biological activities differ significantly between the two series of inhibitors with respect to the different torsion angles between the two phenyl rings of the biphenyl unit.

The steric requirements of fluorine relative to other atoms or groups have always been and remain a controversial issue. Although most researchers tend to attribute to the lightest halogen a size similar to that of hydrogen,[4] others prefer to relate it to hydroxy or even methyl groups.[5]

Controversial results can be found in the literature dealing with the question, whether *ortho*,*ortho*′-tetrafluoro substituted biphenyls are resolvable or not. 'A nonresolvable, tetra-*ortho* substituted biphenyl is shown in …'. This statement from Adams and Yuan referring to the unsuccessful resolution of 2,2′,6,6′-tetrafluoro-5,5′-dichloro-1,1′-biphenyl-3,3′-dicarboxylic acid[6] can be found in a modern textbook of organic stereochemistry.[7]

In agreement with this description, Csizmadia and co-workers calculated, using the AM1 formalism, the torsional barrier of 2,2′,6,6′-tetrafluorobiphenyl to be 16 kcal/mol.[8] More recently, Grein calculated various torsion angles and rotational barriers of substituted biphenyls using the B3LYP/6-311+G* formalism. He found already a torsional barrier of 12.6 kcal/mol for 2,2′-difluorobiphenyl.[9] Kawano and co-workers reported a torsional barrier of 25.6 kcal/mol for an *ortho*-tetrafluoro substituted biphenyl.[10] In various examples the fluoro compounds fall closer to the unsubstituted than the methyl substituted congeners as far as the barriers of rotation are concerned.[11] In contrast, 6,6′-difluoro-2,2′-bis(diphenylphosphino)biphenyl[12] does not follow this pattern with a barrier to racemization at least twice that of the unsubstituted bis-phosphine.[13]

In the framework of our investigations on atropisomeric biaryls, an important point is the knowledge of their rotational barriers and their torsion angles. Therefore, it seemed appropriate to re-evaluate experimentally the

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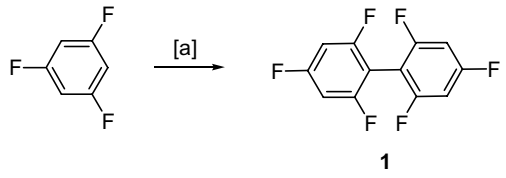
torsional barrier of an *ortho*,*ortho*′-tetrafluoro substituted biphenyl.

2,2′,4,4′,6,6′-Hexafluorobiphenyl (**1**)[14] was obtained in a one-pot three-step procedure from 1,3,5-trifluorobenzene by an optimized copper-catalyzed aryl–aryl coupling (Scheme 1).[15] Metalation of 1,3,5-trifluorobenzene with *sec*-butyllithium, transmetalation with copper(II) bromide and subsequent addition of nitrobenzene gave the desired biphenyl in 79% yield.

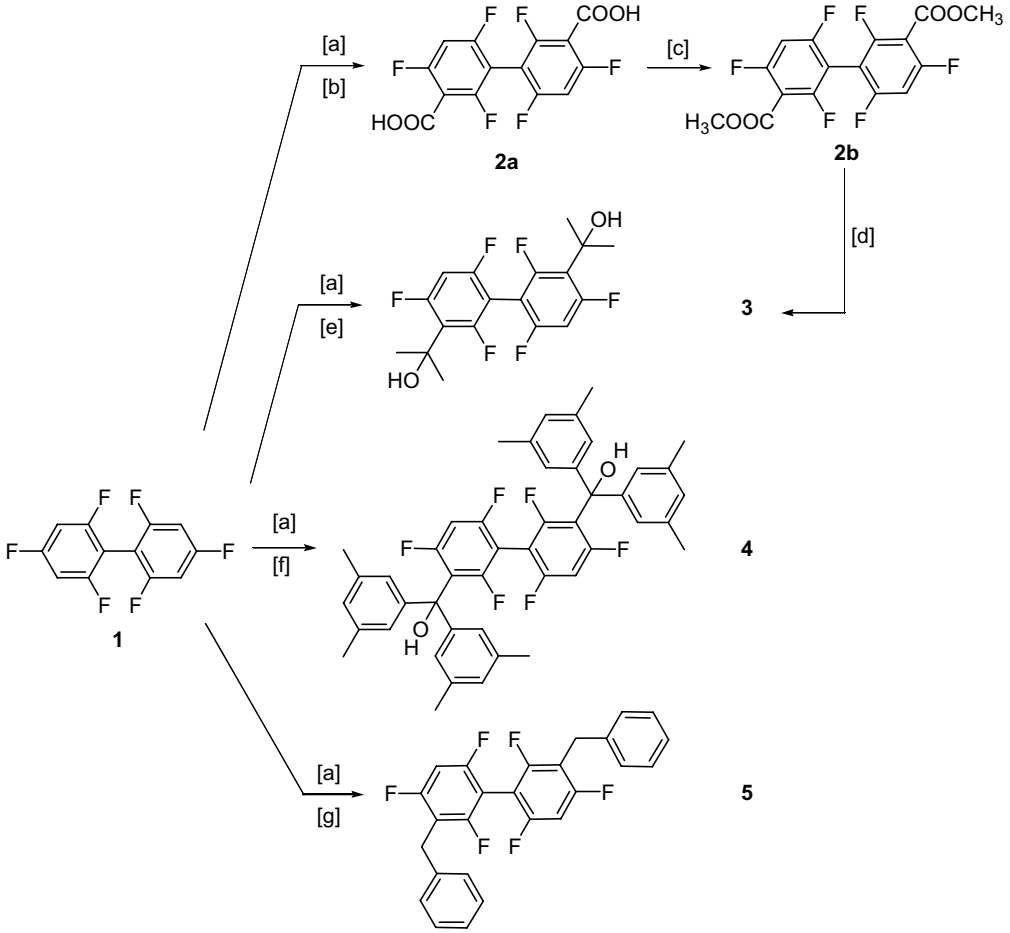
The biphenyl **1** underwent smooth double metalation using *sec*-butyllithium. Carboxylation and neutralization afforded the diacid **2a** (87%)[16] and, after treatment with diazomethane, the ester **2b** (91%)[17] (Scheme 2). In the same way, the alcohols **3** (58%)[18] and **4** (71%),[19] as well as the derivative **5** (24%)[20] were obtained after trapping the organometallic intermediate with acetone, tetramethylbenzophenone,[21] and benzyl bromide, respectively. The alcohol **3** was also obtained in a yield of 63% after treatment of the ester **2b** with methylmagnesium bromide.



Scheme 1. Reagents and conditions: (a) 1. *sec*-butyllithium in THF, 45 min at −75 °C; 2. copper(II) bromide, 45 min at −75 °C; 3. nitrobenzene, −75–25 °C.

First we decided to determine the torsional barrier of the biaryls **3**–**5** by temperature variable NMR studies. Unfortunately, these compounds did not reveal an opportune chemical shift difference between the diastereotopic methyl groups (compounds **3** and **4**) or hydrogens (compound **5**).

Therefore, we decided to determine kinetically the racemization rate constant, following the change of optical activity as a function of time. This approach required the separation of enantiomers, which was performed with the diacid **2a** by converting it to its brucine salt. Although Adams and Yuan reported that in *ortho*-tetrafluoro substituted biphenyls the *ortho* groups do not interfere sufficiently to allow resolution,[6] we obtained the brucine salts in the course of the resolution, which gave, after their decomposition, the two enan-



Scheme 2. Reagents and conditions: (a) *sec*-butyllithium in THF, 45 min at −75 °C; (b) 1. CO_2, 2. $H_3O^{\oplus}$; (c) diazomethane, diethyl ether; (d) H_3CMgBr in THF, 2 h at +75 °C (reflux); (e) acetone; (f) O=(3,5-$(CH_3)_2C_6H_3)_2$;[21] (g) benzyl bromide.

Table 1. Racemization data[a] of the diacid (−)-**2a**

T (°C)	log k	$t_{1/2}$ (min)
50.0 (±0.1)	−3.42	1800
60.0 (±0.1)	−2.92	568
75.0 (±0.1)	−2.26	78
88.9 (±0.1)	−1.55	25

[a] A solution of the diacid (−)-**2a** (100 mg, 0.29 mmol) in dioxane (20 mL) was used. Aliquots were withdrawn on a logarithmic scale of time, cooled to −75 °C and the rotatory power was measured. The rate constant k at the different temperatures was graphically determined.

tiomerically pure diacids (−)-**2a** and (+)-**2a**.[22] Next, racemization experiments were performed in dioxane with the (−)-diacid **2a** (the results are shown in Table 1). The activation energy for racemization of this diacid was determined graphically and calculated by the least squares method at 95% confidence limit, which gave, based on the Arrhenius equation, an activation energy $E_a = 25.4$ (±0.8) kcal/mol.

The influence of substituents in the *meta* and *para* positions of the biphenyl unit on the torsional barrier are smaller than the influence of *ortho* substituents. For 3,3′-dihalide substituted biphenyls all torsional barriers are virtually the same.[9] However, it is known that additional *meta* substituents exert a stabilizing 'buttressing effect' by preventing the outward bending of an *ortho* substituent.[7,23] By comparing 2,2′,4,4′,6,6′-hexafluorobiphenyl-3,3′-dicarboxylic acid (**2a**) with 2,2′,6,6′-tetrafluoro-5,5′-dichloro-1,1′-biphenyl-3,3′-dicarboxylic acid, described by Adams and Yuan,[6] one could expect a higher torsional barrier in the latter case, due to an additional 'buttressing effect' of the two chloro-substitutents in positions 5 and 5′.

The influence of substituents in the *para* position depends mainly on electronic effects. Resonance effects, which stabilize the planar transition state by increasing conjugation are expected when electron-donating groups on one phenyl ring are combined with electron-accepting groups in the other. Electron-donating substituents increase the electron density at the carbon atoms in the pivot bond and facilitate in this way the out-of-plain bending in the transition state. Both effects decrease the rotational barrier.[24] Fluoro substituents are significant resonance donors but their field effect is opposite and even higher. Thus, they reduce the overall electron density and lower the rate constant of racemization as König and co-workers demonstrated by dynamic gas chromatography.[24] Therefore, 2,2′,4,4′,6,6′-hexafluorobiphenyl-3,3′-dicarboxylic acid (**2a**) should have a higher torsional barrier, due to the *para*-fluorine atoms than 2,2′,6,6′-tetrafluorobiphenyl-3,3′-dicarboxylic acid. However, comparing our results (25.4 kcal/mol for (−)-**2a**) with those obtained by Kawano and co-workers[10] for 2,2′,6,6′-tetrafluorobiphenyl-3,3′-dicarboxylic acid (25.6 kcal/mol), the additional *para*-fluorine atoms do not increase the torsional barrier.

The molecular structure[25] of 2,2′,4,4′,6,6′-hexafluorobiphenyl (**1**) is shown in Figure 1. The unsubstituted

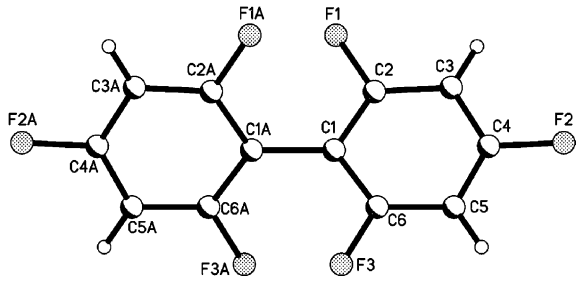


Figure 1. X-ray structure of 2,2′,4,4′,6,6′-hexafluorobiphenyl (**1**).

biphenyl is twisted in the gas phase with a torsion angle of 45°.[26] In the solid state, the two phenyl rings are absolutely coplanar.[9,27] In contrast, in biphenyl **1** the two aryl rings of the biphenyl unit occupy distinctly separate planes with torsion angles C2–C1–C1A–C2A of 55.6(3)° and C6–C1–C1A–C6A of 59.5(3)°. This was anticipated by the torsion angle of 59.7°[28] for perfluorobiphenyl and even 57.6°[29] for 2,2′-difluorobiphenyl. Thus, fluorination at the *ortho*-position has a significant influence on the torsion angles.

In conclusion, the results of this work indicate that *ortho*,*ortho*′-tetrafluoro substituted biphenyls are very well resolvable having a torsional barrier of 25.4 kcal/mol as determined for 2,2′,4,4′,6,6′-hexafluorobiphenyl-3,3′-dicarboxylic acid (−)-(**2a**). Since the fluorine atom is only 0.27 Å larger than the hydrogen atom[30] one could anticipate a small increase in the torsional barrier upon *ortho*,*ortho*′-tetrafluoro substitution. Nevertheless, the small steric influence of fluorine substitution leads, probably due to the lone pair–lone pair repulsion of the fluorine atoms, to a significant increase in the torsional barrier and torsion angles.

Acknowledgements

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16. Compound **2a**: colorless needles (from hexanes/ethyl acetate); mp 228–229 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 7.67$ (t, $J = 9.3$ Hz, 2H); elemental analysis (%) calcd for $C_{14}H_4F_6O_4$ (350.18): C, 48.02; H, 1.15. Found: C, 48.13; H 1.37.
17. Compound **2b**: colorless platelets (from ethanol); mp 121–124 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.89$ (t, $J = 8.7$ Hz, 2H), 3.96 (s, 6H).
18. Compound **3**: colorless needles (from pentanes at −30 °C); mp 15–20 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.80$ (dd, $J = 12.5$, 6.9 Hz, 2H), 2.86 (s, 2H), 1.74 (s, 12H); elemental analysis (%) calcd for $C_{18}H_{16}F_6O_2$ (378.31): C, 57.15; H, 4.26. Found: C, 57.55; H, 4.29.
19. Compound **4**: colorless needles (from ethanol); mp 146–148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.93$ (s, 4H), 6.85 (s, 8H), 6.71 (dd, $J = 11.5$, 8.5 Hz, 2H), 3.53 (br. s, 2H), 2.37 (s, 12H), 2.34 (s, 12H); elemental analysis (%) calcd for $C_{46}H_{40}F_6O_2$ (738.80): C, 74.78; H, 5.46. Found: C, 74.66; H, 5.25.
20. Compound **5**: colorless needles (from pentanes at −30 °C); mp 0–5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.3$ (m, 10H), 6.9 (m, 2H), 4.06 (s, 4H); elemental analysis (%) calcd for $C_{26}H_{16}F_6$ (442.40): C, 70.59; H, 3.65. Found: C, 70.61; H, 3.72.
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