Atropisomerism, Biphenyls, and Fluorine: A Comparison of Rotational Barriers and Twist Angles

Frédéric Leroux*[a]

1. Introduction

Axially chiral biaryl compounds are attracting more and more attention. One reason is the growing number of known biologically active natural products that contain the biaryl motif[1] (for example, vancomycin, steganone, and michellamine[1,2]). Furthermore, the stereogenic axes provide rigid molecular frameworks for highly efficient tools in asymmetric synthesis,[3] such as chiral ligands like BINAP[4] and Meo-BIPHEP,[5] just to mention two of the most prominent ones. The biaryl core is also commonly encountered in the liquid-crystal field, where its derivatives have found commercial application.[6] Moreover, the biphenyl unit belongs to the group of six or seven privileged structures,[7] reputated to be "safe bets" in pharmaceutical research because they guarantee versatility and high hit rates. The stretched and slim shape of this aromatic unit enables it to intercalate in the empty space between transmembrane-receptor helices and to be recognized as an unnatural ligand. For example, the biaryl unit is a key feature in the sartan family of drugs for high blood pressure: losartan (Merck, Sharpe and Dohme trademarks: Cozaar, Lorzaar), valsartan (Novartis trademark: Diovan), irbesartan (Bristol–Myers Squibb trademark: Aprovel), or candesartan (Astra trademark: Atacand).[8]

Similarly, the biaryl unit can dive into deep pockets or long clefts of enzymes. In this way, 3′- and 4′-substituted biphenyl derivatives were recognized as extremely potent 17α-hydroxylase-C17,20-lyase (P-450$_{17}$) inhibitors.[9] They could become promising substances for the treatment of steroidal-hormone-dependent cancers, in particular prostate cancer.[10]

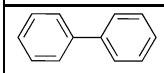
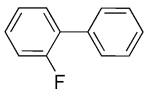
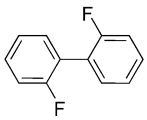
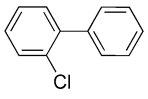
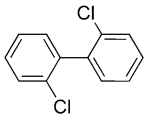
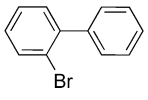
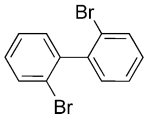
In view of the increasing importance of axially chiral biaryls, attention has to be paid to the stereoisomerism, called atropisomerism, that arises from the hindered rotation about the sp^2–sp^2 carbon–carbon single bond. In this article, the influence of fluorine, the only element capable of mimicking hydrogen by virtue of comparable size ("isosterism"),[11] will mainly be considered, in particlular how it alters the electronic and geometric properties of the biaryl unit.

2. Rotational Barriers of Fluorinated and Non-fluorinated Biphenyls

Christie and Kenner were the first to separate axially chiral biphenyls in 1922.[12] The separation of stereoisomers at room temperature requires energy barriers of at least 22 kcal mol^{-1}. The rotational barrier of biaryl derivatives depends on the nature, position, and number of the substituents. The unsubstituted biphenyl has a rotational barrier of approximately 2 kcal mol^{-1}. Increasing bulkiness of substituents in the *ortho* positions causes increasing conformational stability as a result of steric interactions in the coplanar transition state. The majority of tetra-*ortho*-substituted biaryls have a rotational barrier sufficiently high to prevent racemization of the atropisomers at room temperature. Atropisomeric tri-*ortho*-substituted biaryls frequently racemize above room temperature and di-*ortho*-substituted biphenyl can only be resolved when both substituents are large.[13]

Grein calculated the rotational barrier of substituted biphenyls using the B3LYP6-311+G* formalism.[14] In Table 1, the influence of halide substitution on the rotational barrier is illustrated for mono- and di-*ortho*-substituted biphenyls. As expected, the rotational barrier increases from the smallest halogen to the heaviest halogens. Since the van der Waals radius of the fluorine atom is only 0.27 Å larger than that of the hydrogen atom[15] (see Table 2), one anticipates only a small increase in

Table 1. *Calculated (B3LYP6-311+G*) rotational barriers (ΔE^{tors}) for biphenyl, 2-mono-, and 2,2′-disubstituted biphenyls.*[14]

Compound	ΔE_0^{tors} [kcal mol^{-1}]	Compound	ΔE_{180}^{tors} [kcal mol^{-1}]
	2.2		
	3.0		4.8
	7.6		17.6
	8.6		20.0

[a] *Dr. F. Leroux*
Laboratoire de Stéréochimie associé au CNRS (UMR 7008)
Université Louis Pasteur (ECPM)
25 rue Becquerel, 67087 Strasbourg Cedex 2 (France)
Fax: (+33) 3-90-24-27-42
E-mail: lerouxf@ecpm.u-strasbg.fr

  DOI: 10.1002/cbic.200300906

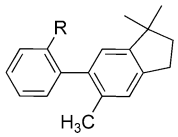
Table 2. *van der Waals radii (r) of hydrogen and first-period elements.*[15]

X	r_{vdW} [Å]
H	1.20
F	1.47
O	1.52
N	1.55
C	1.70

the rotational barrier upon substitution with a fluorine atom. This is true in the case of mono- and difluoro-substituted biphenyls. The increase in rotational barrier is more pronounced for the heavier halogens.

Sternhell and co-workers determined the rotational barriers of numerous *ortho*-substituted 6-aryl-1,1,5-trimethylindanes by dynamic NMR spectroscopy.[16] The results are summarized in Table 3. The study by Sternhell's group offers the possibility to

Table 3. *Rotational barriers (ΔG^{tors}) of* ortho*-substituted 6-aryl-1,1,5-trimethylindanes.*[16]



R	ΔG^{tors}_{340} [kcal mol^{-1}]
H	10.6
F	14.2
Cl	18.8
Br	19.8
I	20.6
OCH_3	16.0
CH_3	19.3
CF_3	21.9
$CH(CH_3)_2$	22.2
C_6H_5	17.6

estimate the rotational barriers of 2,2′-disubstituted biphenyls as the sum of additive contributions, designed as *interference values* (see Table 4). These interference values have, in fact, a high predictive capacity, as Sternhell and co-workers showed by comparing the predicted rotational barriers with experimentally accessible values.

Table 4. *Interference values (I^{X-H}_{340}) of Sternhell and co-workers for the rotational barriers of biphenyls.*[16]

Interacting group X	I^{X-H}_{340} [kcal mol^{-1}]	Interacting group X	I^{X-H}_{340} [kcal mol^{-1}]
H	1.0	CH_3	9.7
F	4.6	SCH_3	9.9
CN	6.1	Br	10.2
OCH_3	6.4	$NHCH_3$	10.6
NO_2	7.7	I	10.9
$N(CH_3)_2$	7.8	$Si(CH_3)_3$	11.3
C_6H_5	7.9	CF_3	12.1
$COOCH_3$	8.2	$CH(CH_3)_2$	12.6
Cl	9.1	$C(CH_3)_3$	18.3

The apparent sizes of substituents roughly parallel the van der Waals radii.[15] It can be seen, whenever comparison can be made with either the van der Waals radii derived from crystallographic data or with effective sizes obtained by Charton,[17] that fluorine (Table 3, 14.2 kcal mol^{-1}), although halfway between a hydrogen atom and a methyl group in size, falls closer to the unsubstituted congener (Table 3, 10.6 kcal mol^{-1}) than the methyl-substituted one (Table 3, 19.3 kcal mol^{-1}) in its rotational barrier. The influence of a trifluoromethyl group on the rotational barrier also becomes obvious from the values in Table 3. Actually, the rotational barrier of the trifluoromethyl-substituted derivative (21.9 kcal mol^{-1}) is slightly less than the rotational barrier of the isopropyl-substituted congener (22.2 kcal mol^{-1}). The trifluoromethyl group is often claimed to be "at least as large as isopropyl".[18] However, one must consider, that a trifluoromethyl group is rotationally symmetrical about its C–C bond axis, a fact that does not hold for an isopropyl group. In the planar biphenyl transition state, the isopropyl group may be oriented in a more favorable conformation, with the bulky methyl groups facing away from the *ortho*′ position. This means, in terms of "effective bulk", that the anisotropic isopropyl group appears to be only slightly larger than the isotropic trifluoromethyl group, although the latter occupies a smaller volume. The calculated van der Waals volume[19] of the trifluoromethyl group (V_{vdW} = 39.8 Å^3 per substituent) is substantially smaller than that of the isopropyl group (V_{vdW} = 56.2 Å^3 per substituent) and lies almost exactly halfway between an isopropyl and a methyl group (V_{vdW} = 21.6 Å^3 per substituent). Thus, a trifluoromethyl group would be comparable by volume, but not by shape, to an ethyl group (V_{vdW} = 38.9 Å^3 per substituent).

According to Table 4, the interference values for a methyl group (9.7 kcal mol^{-1}) and a *tert*-butyl group (18.3 kcal mol^{-1}) allow, with assumption of a linear response of the rotational barrier with the "isotropic substituent volume", the interpolation of the rotational barriers for an ethyl group (12.6 kcal mol^{-1}) and an isopropyl group (15.4 kcal mol^{-1}). However, due to the rotational anisotropy, the "effective bulk" of the ethyl and isopropyl groups should be smaller, a fact that is reflected by the reduced rotational barrier for the isopropyl group (Table 4, 12.6 kcal mol^{-1} instead of 15.4 kcal mol^{-1}). It is interesting to see that the reported value for the trifluoromethyl group (Table 4, 12.1 kcal mol^{-1}) compares well with the interpolated value for an "isotropic" ethyl group (12.6 kcal mol^{-1}). Of course, the real anisotropic ethyl group would have a smaller rotational barrier than the interpolated value.[20]

Nevertheless, electronic contributions of the *ortho* substituents are not negligible. This becomes apparent in the case of fluoro-substituted biphenyls. As mentioned above, in most cases, fluorine appears to be a small substituent with rotational barriers that fall closer to the unsubstituted derivative.[21] The same was observed for the rotational barriers of *ortho*,*ortho*′-disubstituted cumenes[22] and 4,5-disubstituted 9,10-dihydrophenanthrenes.[23] However, controversial results can be found

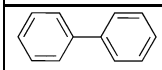
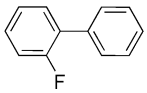
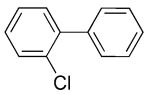
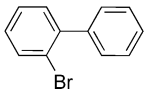
in the literature dealing with the question of whether *ortho*,*ortho*′-tetrafluoro-substituted biphenyls are resolvable or not. "A nonresolvable, tetra-*ortho*-substituted biphenyl is shown in…" This statement from Adams and Yuan referring to the impossible resolution of 2,2′,6,6′-tetrafluoro-5,5′-dichloro-1,1′-biphenyl-3,3′-dicarboxylic acid[24] can be found in a modern textbook of organic stereochemistry.[13] In agreement with this, Csizmadia and co-workers calculated (using the AM1 formalism) the rotational barrier of 2,2′,6,6′-tetrafluorobiphenyl to be 16 kcal mol^{-1}.[25] A more recent study from Grein indicates a rotational barrier for perfluorobiphenyl of 24.5 kcal mol^{-1}.[14] This value is in good agreement with the experimentally determined rotational barrier of 26 kcal mol^{-1}.[26] Similarly, 6,6′-difluoro-2,2′-bis(diphenylphosphino)biphenyl has a surprisingly high rotational barrier ($>$35 kcal mol^{-1})[27] in comparison to its unsubstituted congener 2,2′-bis(diphenylphosphino)biphenyl (22 kcal mol^{-1}).[28] Unfavorable electrostatic interactions between the polar subunits significantly increase the rotational barrier of these compounds.

The influence of substituents in the *meta* and *para* positions of the biphenyl unit on the rotational barriers is smaller than the influence of *ortho* substituents. For 3,3′-dihalide-substituted biphenyls, all rotational barriers are virtually the same.[14] Apparently the two halogen atoms interact little with each other. However, it is known that additional *meta* substituents exert a stabilizing "buttressing effect" by preventing the outward bending of an *ortho* substituent.[13] The influence of substituents in the *para* position depends mainly on electronic effects. Resonance effects that stabilize the planar transition state by increasing conjugation are expected when electron-donating groups on one phenyl ring are combined with electron-accepting groups on the other. Electron-donating substituents increase the electron density at the carbon atoms in the pivot bond and in this way facilitate out-of-plain bending in the transition state. Both effects decrease the rotational barrier.[29]

3. Twist Angles of Fluorinated and Nonfluorinated Biphenyls

The unsubstituted biphenyl is twisted in the gas phase with a twist angle of 45°. In the crystalline state, biphenyl appears to be planar. (A search in the Cambridge Structural Database revealed an average twist angle for the unsubstituted biphenyl of 1°.) However, this is a statistically centered arrangement. When the temperature is lowered, the two phenyl rings become slightly twisted (10° at 40 K).[14] The twist angles of biphenyl and of mono-halide-substituted biphenyls are shown in Table 5. As expected, the twist angle increases when replacing an *ortho* hydrogen atom with a halogen atom, from the calculated angle of 42.5° for biphenyl to 45.1° for 2-fluorobiphenyl, 59.5° for 2-chlorobiphenyl, and 63.6° for 2-bromobiphenyl. Unfortunately, X-ray crystal structure analyses can only be found in the literature for 2-fluorobiphenyl; none were found for the higher homologues. Therefore, the average twist angles for molecules with a 2-halobiphenyl substructure that were available in the Cambridge Structural Database are shown in Table 5.

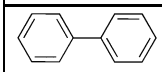
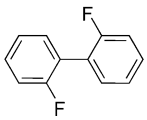
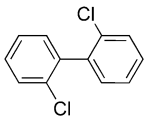
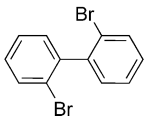
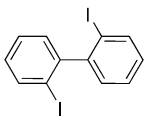
Table 5. *Twist angles (Φ) of biphenyl and 2-halide-substituted biphenyls.*

Compound	Φ^{calcd} [a]	$\Phi^{X\text{-}ray}$
	42.5° [14]	10° [30]
		1° [b]
	45.1° [14]	54.1° [31]
		47° [c]
	59.9° [14]	53° [c]
	63.6° [14]	61° [c]

[a] Calculated by using the B3LYP6-311+G* formalism. [b] Average twist angle of biphenyl from X-ray crystal structures available in the Cambridge Structural Database. [c] Average twist angles of molecules with a 2-halobiphenyl unit as a substructure (from X-ray crystal structures available in the Cambridge Structural Database).

Table 6 reveals the calculated (B3LYP6-311+G*) and measured twist angles of 2,2′-dihalide-substituted biphenyls as well

Table 6. *Twist angles (Φ) of biphenyl and 2,2′-dihalide-substituted biphenyls.*

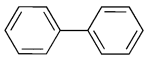
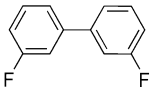
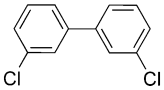
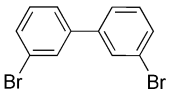
Compound	Φ^{calcd} [a]	$\Phi^{X\text{-}ray}$
	42.5° [14]	10° [30]
		1° [b]
	57.9° [14]	57.6° [32]
		56° [c]
	84.9° [14]	66.5° [33]
		64° [c]
	91.5° [14]	85.4° [34]
		82° [c]
	94.8° [14]	85.3° [35]

[a] Calculated by using the B3LYP6-311+G* formalism. [b] Average twist angle of biphenyl from X-ray crystal structures available in the Cambridge Structural Database. [c] Average twist angles of molecules with a 2,2′-dihalobiphenyl unit as a substructure (from X-ray crystal structures available in the Cambridge Structural Database).

as the average twist angles for molecules with a 2,2′-dihalobiphenyl substructure. Compared with the twist angle of 42.5° for biphenyl, the increased repulsion between the fluorine atoms in 2,2′-difluorobiphenyl causes a shift of 15.4° towards a perpendicular orientation of the two phenyl rings. The calculated values for the heavier halogens are close to 90°. The calculated twist angle for 2,2′-difluorobiphenyl is very close to the value obtained by X-ray diffraction studies. However, the twist angles obtained by this method for the heavier halogens are quite a bit below the calculated ones.

The introduction of fluorine atoms into the *meta* position of the phenyl ring should change neither the form nor the shape of the molecules relative to the nonfluorinated analogues. This prediction was supported by single-crystal X-ray diffraction studies. The biphenyl core in *meta*-difluoro-substituted biphenyls (Table 7) is only slightly twisted around the central C–C axis.[9d]

Table 7. *Twist angles (Φ) of biphenyl and* meta*-substituted biphenyls.*

Compound	Φ^{calcd} [a]	$\Phi^{measured}$
	42.5° [14]	10° [30] [b] 1° [c]
	42.0° [14]	22° [9d] [b]
	42.9° [14]	26° [d]
	43.2° [14]	43.8° [36][e]

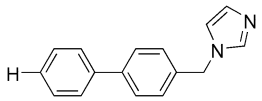
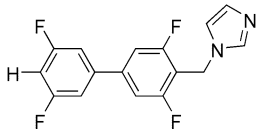
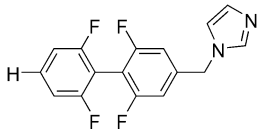
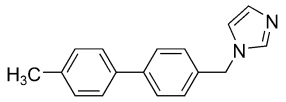
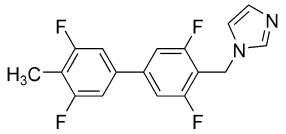
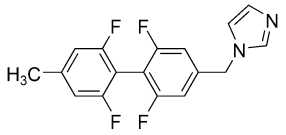
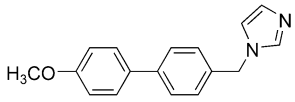
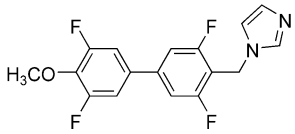
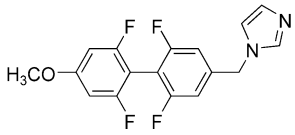
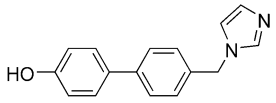
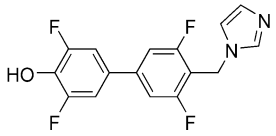
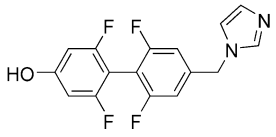
[a] Calculated by using the B3LYP6-311+G* formalism. [b] X-ray crystal structure data. [c] Average twist angle of biphenyl from X-ray crystal structures available in the Cambridge Structural Database. [d] Average twist angle of molecules with a 3,3′-dichlorobiphenyl unit as a substructure (from X-ray crystal structures available in the Cambridge Structural Database). [e] Measured gas-phase twist angle.

By relocating the fluorine atoms from the *meta* to the *ortho* positions, the two aryl rings of the biphenyl unit are forced to occupy distinctly separated planes. Single-crystal X-ray diffraction studies revealed twist angles of 59.5°[26b] and 64.1°[9d] for 2,2′,6,6′-tetrafluoro-substituted biphenyls. This was anticipated from the twist angle of 59.7° for perfluorobiphenyl[37] in comparison with the calculated value of 55.0°.[14]

4. Biological Study of Fluorinated versus Nonfluorinated Biphenyls

Fluorine substitution can have profound effects on the biological activity of small molecules. Fluorine is often introduced into molecules to mimic hydrogen with respect to steric requirements at binding sites on receptors and enzymes. In addition, due to flourine's electron-withdrawing power, fluorine substitution may cause stereoelectronic discrimination, may confer metabolic stability to natural and xenobiotic materials,

Table 8. *Inhibition of CYP 17 and CYP 19 by fluorinated biphenylmethylimidazoles in comparison to the nonfluorinated parent compounds.*[9d]

	Compound	% Inhibition of CYP 17 (IC_{50} [μM])	% Inhibition of CYP 19
1		>80 (0.96)	66
2		>80 (0.37)	57
3		73	66
4		36	51
5		39	66
6		38	72
7		43	62
8		46	53
9		4	48
10		>80 (0.31)	31
11		>80 (0.38)	29
12		75	68

may enhance the lipophilicity of these materials, and, as a corollary, may facilitate cell-membrane permeation.[11,38]

17α-hydroxylase-C17,20-lyase (P-450$_{17}$, CYP 17, androgen synthase), a cytochrome P450 monooxygenase, is the key enzyme of androgen biosynthesis. It produces androstenedione and dehydroepiandrosterone from progesterone and pregnenolone. As androgens are implicated in the development of prostate cancer, a promising alternative to treatment with antiandrogens would be to develop selective inhibitors of this enzyme. *N*-Imidazolylmethyl-substituted biphenyls are highly potent inhibitors of CYP 17 and CYP 19 (aromatase).[9] Unfortunately, the very encouraging in vitro results are contrasted by a lack of in vivo activity due to rapid degradation of the compounds by metabolic oxidation. The major metabolites were isolated and identified by means of biomimetic methods. They were found to be products formed by mono- and dihydroxylation at the *ortho* and *meta* positions of the biphenyl unit.[39] Sequential introduction of fluorine atoms increases the oxidation potential of an aromatic system and should increase the metabolic stability. Therefore, the metabolically sensitive positions of *N*-(4-biphenylmethyl)imidazoles were blocked by fluorine atoms. These compounds were tested for their inhibitory activity towards CYP 17 and CYP 19 and were compared with the nonfluorinated parent compounds. When the inhibitory activities exceeded 80%, the IC$_{50}$ values were determined (see Table 8).[9d]

The fluorinated biphenyl derivatives exhibit poor to moderate inhibitory activity towards CYP 19. However, 3,3′,5,5′-tetrafluoro-substituted biphenylmethylimidazoles are potent inhibitors of CYP 17. Their inhibitory activity generally equalled or surpassed the inhibitory activity of the unfluorinated parent compounds. The 4′-unsubstituted compound (entry 2, Table 8) showed an almost threefold higher activity towards CYP 17 (IC$_{50}$ value of 0.37 μM) than the nonfluorinated analogue (entry 1, Table 8, IC$_{50}$ value of 0.96 μM). In contrast, 2,2′,6,6′-tetrafluoro-substituted congeners generally did not match the activity of the halogen-free derivatives.

The different biological activity can be explained with the different torsion angles in both cases. The strongly twisted *ortho*-fluoro-substituted biphenyls (see Section 3, Table 6) seem to be too "bulky" to interact well with the active site of the target enzyme. In addition, the rotational barrier for planarization of the biphenyl unit is too high (26 kcal mol^{-1}, see Section 2) to be surmounted in the enzyme pocket. In contrast, the *meta*-fluoro-substituted congeners are only slightly twisted (see Section 3, Table 7) and adopt a conformation comparable to the nonfluorinated parent compounds. Thus, one benefits from the metabolism-retarding ability of the fluorine atoms without modifying the conformation of the biphenyl unit.

In an additional study, the effect of fluorine substitution on the metabolic stability of the biphenylmethylimidazoles was investigated. The two fluorinated hydroxy isomers with the highest inhibitory activity towards CYP 17 (entries 11 and 12 in Table 8) were tested for their metabolic stability in an in vitro study. Phenol and the unsubstituted analogues were used as reference compounds (Figure 1). The *ortho*-tetrafluoro-substituted compound was metabolized faster than the unfluorinated parent compound, whereas the *meta*-tetrafluoro-substituted derivative showed a reduced in vitro metabolism relative to its nonfluorinated congener (see Figure 1).

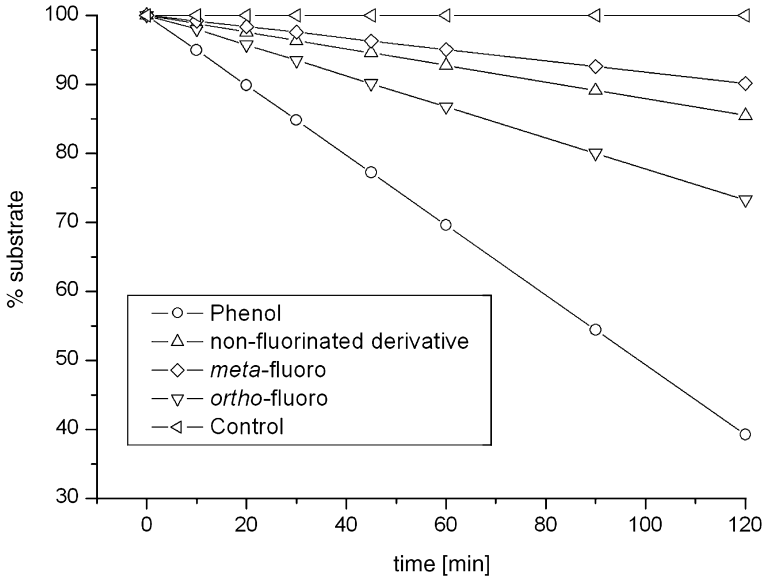


Figure 1. *In vitro biodegradation of 3,3′,5,5′-tetrafluoro-4′-(1*H*-imidazole-1-ylmethyl)-1,1′-biphenyl-4-ol (*meta*-fluoro-substituted) and 2,2′,6,6′-tetrafluoro-4′-(1*H*-imidazole-1-ylmethyl)-1,1′-biphenyl-4-ol (*ortho*-fluoro-substituted) compared with the unfluorinated parent compound and phenol.*[9d]

Acknowledgements

This work was supported by the Swiss Federal Institute of Technology Lausanne (EPFL), the Swiss National Science Foundation, and the COST-D12 action 0004/98.

Keywords: atropisomerism · biaryls · fluorine · rotational barriers · twist angles

[1] a) K. B. G. Torssell, *Natural Product Chemistry*, Taylor and Francis, New York, **1997**; b) G. Bringmann, F. Pokorny in *The Alkaloids, Vol. 46* (Ed.: G. A. Cordell), Academic Press, New York, **1995**, p. 127; c) T. Okuda, T. Yoshida, T. Hatano in *Prog. Chem. Org. Nat. Prod., Vol. 66* (Eds.: W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm), Springer, Vienna, **1995**, p. 1.

[2] a) D. H. Williams, B. Bardsley, *Angew. Chem.* **1999**, *111*, 1264–1286; *Angew. Chem. Int. Ed.* **1999**, *38*, 1172–1193; b) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem.* **1999**, *111*, 2230–2287; *Angew. Chem. Int. Ed.* **1999**, *38*, 2096–2152; c) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Brian, *J. Am. Chem. Soc.* **1973**, *95*, 1335–1336.

[3] a) C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis* **1992**, 503–517; b) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494; c) K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry, M. Yamanaka, *Synlett* **2002**, 1561–1578; d) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369–3400; e) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297–3344.

[4] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl: a) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; b) R. Noyori, *Chemtech* **1992**, *22*, 360–367.

[5] Meo-BIPHEP = 6,6′-bis(diphenylphosphanyl)-2,2′-dimethoxy-1,1′-biphenyl: a) R. Schmid, J. Foricher, M. Cereghetti, P. Schönholzer, *Helv. Chim. Acta* **1991**, *74*, 370 – 389; b) R. Schmid, *Chimia* **1996**, *50*, 110 – 113.
[6] a) P. J. Collings, M. Hird, *Introduction to Liquid Crystals Chemistry and Physics*, Taylor and Francis, London, **1997**; b) J. W. Goodby, N. A. Clark, S. T. Laggerwall, *Ferroelectric Liquid Crystals: Principles, Properties and Applications*, Gordon and Breach, Philadelphia, **1991**.
[7] A. A. Patchett, R. P. Nargund, "Privileged Structures" in *Topics in Drug Design and Discovery* (Ed.: G. L. Trainor), *Annu. Rep. Med. Chem. (Section IV)* **2000**, *35*, 269 – 298.
[8] a) A. Kleemann, J. Engel, *Pharmaceutical Substances: Syntheses, Patents, Applications*, Thieme, Stuttgart, **1999**, pp. 306 – 307, 1116 – 1119, 1024 – 1025, and 1984 – 1985; b) H. Ji, M. Leung, Y. Zhang, K. J. Catt, K. Sandberg, *J. Biol. Chem.* **1994**, *269*, 16533 – 16536; c) H. T. Schambye, S. H. Hjorth, J. Weinstock, T. W. Schwartz, *Mol. Pharmacol.* **1995**, *47*, 425 – 431; d) S. Perlman, H. T. Schambye, R. A. Rivero, W. J. Greenlee, S. A. Hjorth, T. W. Schwartz, *J. Biol. Chem.* **1995**, *270*, 1493 – 1496; e) V. Nirula, W. Zheng, R. Sothinathan, K. Sandberg, *Br. J. Pharmacol.* **1996**, *119*, 1505 – 1507; f) V. Nirula, W. Zheng, K. Krishnamurthi, K. Sandberg, *FEBS Lett.* **1996**, *394*, 361 – 364.
[9] a) R. W. Hartmann, *Eur. J. Pharm. Sci.* **1994**, *2*, 15 – 16; b) B. G. Wachall, M. Hector, Y. Zhuang, R. W. Hartmann, *Bioorg. Med. Chem.* **1999**, *7*, 1913 – 1924; c) Y. Zhuang, B. G. Wachall, R. W. Hartmann, *Bioorg. Med. Chem.* **2000**, *8*, 1245 – 1252; d) F. Leroux, T. Hutschenreuter, C. Charrière, R. Scopelliti, R. W. Hartmann, *Helv. Chim. Acta* **2003**, *86*, 2671 – 2686.
[10] J. P. Van Wauve, P. A. J. Janssen, *J. Med. Chem.* **1989**, *32*, 2231 – 2239.
[11] a) M. Schlosser, *Tetrahedron* **1978**, *34*, 3 – 17; b) M. Schlosser, *Angew. Chem.* **1998**, *110*, 1538 – 1556; *Angew. Chem. Int. Ed.* **1998**, *37*, 1496 – 1513; c) "The Chemical and Physiological Size of Fluorine" M. Schlosser in *Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedicinal Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**, pp. 613 – 659.
[12] G. H. Christie, J. Kenner, *J. Chem. Soc.* **1922**, *121*, 614 – 620.
[13] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley and Sons, **1994**, pp. 1142 – 1145.
[14] F. Grein, *J. Phys. Chem. A* **2002**, *106*, 3823 – 3827.
[15] a) A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441 – 451; b) A. Bondi, *J. Phys. Chem.* **1966**, *70*, 3006 – 3007.
[16] G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc.* **1980**, *102*, 5618 – 5626.
[17] a) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 1552 – 1556; b) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 6159 – 6161; c) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 6472 – 6473; d) M. Charton, *J. Org. Chem.* **1976**, *41*, 2217 – 2220; e) M. Charton, *J. Org. Chem.* **1977**, *42*, 2528 – 2529; f) M. Charton, *Prog. Phys. Org. Chem.* **1973**, *10*, 81 – 204; g) R. Gallo, *Prog. Phys. Org. Chem.* **1983**, *14*, 115 – 163.
[18] B. E. Smart in *Chemistry of Organofluorine Compounds* (Ed.: M. Hudlicky), American Chemical Society, Washington DC, **1995**, p. 25.
[19] Y. H. Zhao, M. H. Abraham, A. M. Zissimos, *J. Org. Chem.* **2003**, *68*, 7368 – 7373.
[20] The author is very grateful to one of the referees for pointing out this fact.
[21] M. Schlosser, D. Michel, *Tetrahedron* **1996**, *52*, 99 – 108.
[22] a) A. Mannschreck, L. Ernst, *Chem. Ber.* **1971**, *104*, 228 – 247; b) W. J. E. Parr, T. Schaefer, *Acc. Chem. Res.* **1980**, *13*, 400 – 406; c) T. Schaefer, R. P. Veregin, R. Laatikainen, R. Sebastian, K. Marat, J. L. Charlton, *Can. J. Chem.* **1982**, *60*, 2611 – 2616.
[23] a) R. Cosmo, S. Sternhell, *Aust. J. Chem.* **1987**, *40*, 35 – 47; b) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, G. H. Wahl, *J. Am. Chem. Soc.*, **1964**, *86*, 1710 – 1733; c) O. Yamamoto, H. Nakanishi, *Tetrahedron* **1973**, *29*, 781 – 787.
[24] R. Adams, H. C. Yuan, *Chem. Rev.* **1933**, *12*, 261 – 338.
[25] T.-H. Tang, M. Nowakowska, J. E. Guillet, I. G. Csizmadia, *J. Mol. Struct.* **1991**, *232*, 133 – 146.
[26] a) N. Hasaka, M. Okigawa, I. Kouno, N. Kawano, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3828 – 3830; b) F. Leroux, M. Maurin, N. Nicod, R. Scopelliti, *Tetrahedron Lett.* **2004**, *45*, 1899 – 1902.
[27] H. Jendralla, C.-h. Li, E. Paulus, *Tetrahedron: Asymmetry* **1994**, *5*, 1297 – 1320.
[28] O. Desponds, M. Schlosser, *Tetrahedron Lett.* **1996**, *37*, 47 – 48.
[29] C. Wolf, W. A. König, C. Rouzssel, *Liebigs Ann.* **1995**, 781 – 786.
[30] H. Cailleau, A. Girard, F. Moussa, C. M. E. Zeyen, *Solid State Commun.* **1979**, *29*, 259 – 261.
[31] Rajnikant, D. Watkin, G. Trunter, *Acta Crystallogr. Sect. C* **1995**, *51*, 1452 – 1454.
[32] B. Aldridge, G. De Luca, M. Edgar, J. W. Emsley, M. I. C. Furby, M. Webster, *Liquid Cryst.* **1998**, *24*, 569 – 581.
[33] C. Romming, H. M. Seip, I.-M. A. Oymo, *Acta Chem. Scand. Ser. A* **1974**, *28*, 507 – 514.
[34] D. D. MacNeil, A. Decken, *Acta Crystallogr. Sect. C* **1999**, *55*, 628 – 630.
[35] H. Bock, M. Sievert, Z. Havlas, *Chem. Eur. J.* **1998**, *4*, 677 – 685.
[36] A. Almenningen, O. Bastiansen, L. Fernholt, S. Gundersen, E. Kloster-Jensen, *J. Mol. Struct.* **1985**, *128*, 77 – 93.
[37] W. B. Gleason, D. Britton, *Cryst. Struct. Commun.* **1976**, *5*, 483 – 488.
[38] a) D. Michel, M. Schlosser, *Tetrahedron* **2000**, *56*, 4253 – 4260; b) M. Schlosser, L. Guio, F. Leroux, *J. Am. Chem. Soc.* **2001**, *123*, 3822 – 3823; c) B. K. Park, N. R. Kitteringham, *Drug Metab. Rev.* **1994**, *26*, 605 – 643.
[39] R. W. Hartmann, T. Hutschenreuter, unpublished results.

Received: December 15, 2003 [M906]

