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Rotation in Biphenyls with a Single Ortho-Substituent

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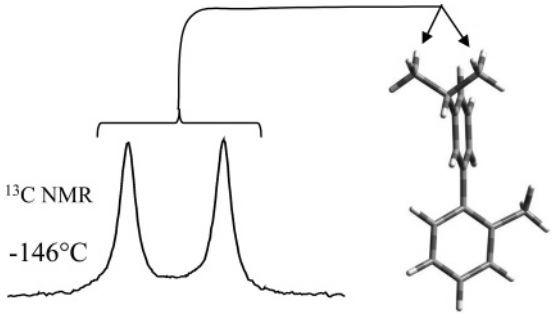

Barriers to rotation in a range up to 15.4 kcal mol^{-1} were determined by dynamic NMR spectroscopy for a series of biphenyl compounds **1a**−**1h** and **2a**−**2d** with a single ortho-substituent. Ab initio calculations reproduce these barriers satisfactorily and indicate the ground-state conformation of these molecules. Results are discussed in terms of the contribution of individual substituents to the barrier and of the buttressing of adjacent positions in a benzene ring by substituents.

Introduction

Hindered rotation about the central bond in ortho-substituted biphenyls and the consequences thereof are classical fields of study that led to an understanding of many aspects of stereochemistry and molecular conformations. In 1922, Christie and Kenner[3] prepared and isolated two diastereomeric brucine salts from the tetrasubstituted 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid, which they associated with the two enantiomeric structures now labeled **3M** and **3P** of the parent acid (see Chart 1). This and subsequent work[4,5] clarified the three-dimensional structure of these enantiomers as in these now familiar diagrams and demonstrated experimentally for the first time that there is a considerable barrier to rotation about a single bond, in this case the one joining the two rings. The term atropisomers was subsequently suggested to describe these enantiomeric structures,[4] which can be chemically separated since rotation about the central single bond that brings about their interconversion is slow on the chemical time scale. Following Christie and Kenner's first example, there were many further investigations[5,6] of such highly substituted biphenyls, based largely on measuring rates of racemization or mutarotation.[7] In practice, studies were thus limited to enantiomers with a lifetime of a minimum of a few minutes at room temperature, that is, with rotational barriers greater than about 20 kcal mol^{-1}.[8] This usually meant biphenyl derivatives with three or four ortho-substituents, although, it was soon shown that lifetimes are sufficiently long for study with only two suitably large ortho-substituents.[9] Ideas on the size of substituents were developed from these studies,[5,10b] together with consideration of the additivity of the contribution

(1) University of Bologna.
(2) University College London.
(3) Christie, G. H.; Kenner, J. *J. Chem. Soc.* **1922**, *121*, 964.
(4) Kuhn, R. In *Stereochemie*; Freudenberg, H., Ed.; Franz Deutike: Leipzig-Wien, 1933; pp 803−824.
(5) Adams, R.; Yuan. H. C. *Chem. Rev.* **1933**, *12*, 261.
(6) Oki, M. *Top. Sterochem.* **1983**, *14*, 1.
(7) A racemization study might involve, for example, preferential crystallization of a salt of one enantiomer of an acidic biphenyl derivative and a homochiral alkaloid base to give a more-or-less pure single diastereoatropisomer, the other one remaining in solution. Careful regeneration of the biphenyl derivative from the salt might yield the more-or-less pure optically active biphenyl. A solution of this material loses optical activity at a rate that can be measured and depends on the barrier to biphenyl rotation. The biphenyl derivative has racemized. If the rotation barrier is rather low, the precipitated salt itself may be studied. The initial optical rotation of a sample solution is observed to change, but does not vanish, settling eventually at a new value. Rotation about the biphenyl bond leads to a mixture of two diastereo-atropisomers, but there is residual optical activity, since different amounts of two diastereomers—salts of the homochiral base—are present and are eventually at equilibrium. This is mutarotation.
(8) In early work, results were discussed in terms of half-lives for racemization rather than barriers to rotation about the central biphenyl bond.

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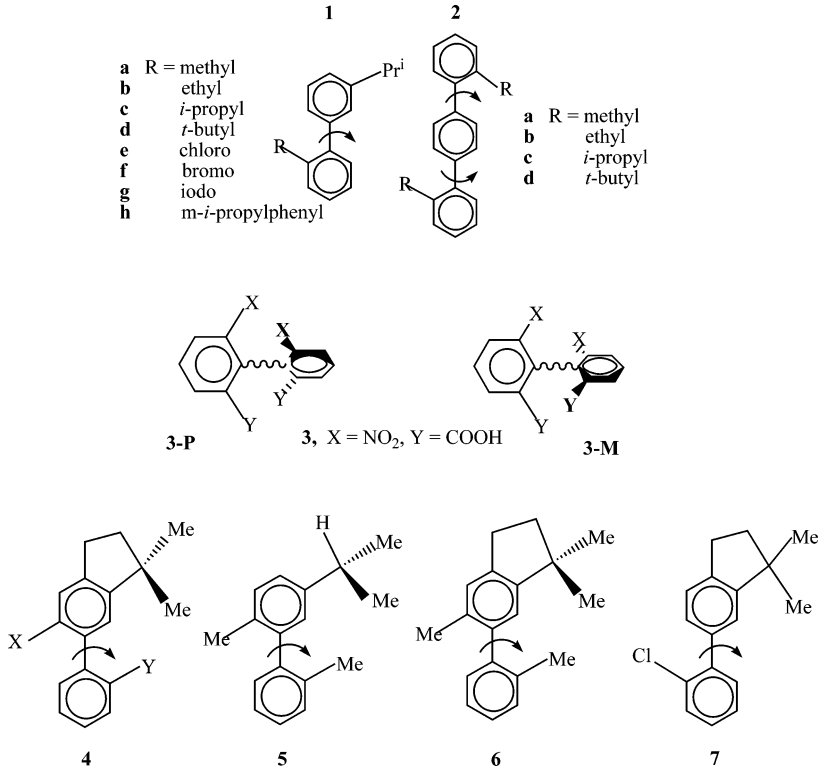
CHART 1



of each substituent to the barrier measured for a given compound. The subject was regularly reviewed[10] and became an important example in the teaching of stereochemistry by the middle of the 20th century.[10a,11] The measuring of large numbers of barriers and thus the systematic demonstration of substituent effects on barriers allowed one of the earliest physical−organic discussions of steric and electronic interactions and the complex interrelationship of these.[10,11]

From 1963 onward, with the advent of dynamic NMR spectroscopy, barriers much lower than 20 kcal mol^{-1} could be measured, without resolution of enantiomers, so many more compounds with one ortho-substituent in each ring were studied.[12] This phase culminated with the systematic study by Bott, Field, and Sternhell (BFS)[13] of a large series of biphenyls with one ortho-substituent in each ring (see **4**, in Chart 1) in which the relatively rigid five-membered ring serves as an NMR probe. They measured barriers in 26 compounds where X = methyl, and six compounds where X = methoxy. They examined the additivity of substituent effects on the size of the rotational barrier by dissecting the experimental barrier for a compound into contributions from each ortho-substituent, as we discuss below. Furthermore, on the basis of the contribution of each substituent to the experimental barrier, they proposed the concept of the effective van der Waals radius of a substituent, which has proved a useful steric quantifier, for such substituents that are not symmetrical.[14]

Interest in the subject has continued to develop with, for example, regular reports of naturally occurring biphenyl derivatives with two or more ortho-substituents,[15] where conformations and rotational barriers are of significance.

From the rotational barriers in disubstituted biphenyls that they measured experimentally, BFS had assigned an interference value I^{X-H} to each of a variety of ortho-substituents X interacting with an ortho-hydrogen atom H of the adjacent benzene ring, in the coplanar transition state for rotation of the biphenyl. When added together for two substituents, these *I*-values satisfactorily reproduced rotational barriers for a range of disubstituted biphenyls that they had studied,[16] plus examples from the work of others.[13] They also suggested an interference value for hydrogen as a substituent, that is I^{H-H}, from the rotational barrier of 2 kcal mol^{-1} in biphenyl itself.[17] This begs the question, is

(9) (a) Lesslie, M. S.; Turner, E. E. *J. Chem. Soc.* **1932**, 2021. (b) Lesslie, M. S.; Turner, E. E. *J. Chem. Soc.* **1932**, 2394. (c) Turner, E. E. *Chem. Ind.* **1932**, *51*, 435. (d) Corbellini, A.; Angeletti, A. *Atti Accad. Lincei* **1932**, *15*, 968. (e) Searle, N. E.; Adams, R. *J. Am. Chem. Soc.* **1933**, *55*, 1649. (f) Lesslie, M. S.; Mayer, U. J. H. *J. Chem. Soc.* **1962**, 1401.

(10) (a) Shriner, R. L.; Adams, R. Optical Isomerism. In *Organic Chemistry*, 2nd ed.; Gilman, H., Ed.; Wiley: New York, 1943; p 343. (b) Westheimer, F. H. *Calculation of the Magnitude of Steric Effects* in *Steric Effects in Organic Chemistry;* Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 12. (c) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Section 14.5 and *passim.*

(11) See, for example: Finar, L. Stereochemistry of Biphenyl Compounds. In *Organic Chemistry*, 5th ed.; Longman: New York, 1975; Chapter 5, Vol. 2, p 215. The first edition was 1956. Other mid-20th century textbooks deal with the subject at a similar length, while more modern ones almost invariably mention the topic, but more briefly.

(12) (a) Meyer, W. L.; Meyer, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2170. (b) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219. (c) Oki, M.; Akashi, K.; Yamamoto, G.; Iwamura H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1683 (d) House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815. (e) Colebrook, L. D.; Jahnke, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 4687. (f) Oki, M.; Yamamoto, G. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 266.

(13) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

(14) Science Citation Index reports over 200 citations of ref 13 by August 2005.

(15) (a) Leroux (*ChemBioChem* **2004**, *5*, 644) gives a brief summary of recent investigations as well as some ab initio calculations. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

(16) These barrier values were of course the source of the *I*-values, but some substituents appeared several times and there is a self-consistency about the *I*-value determined.

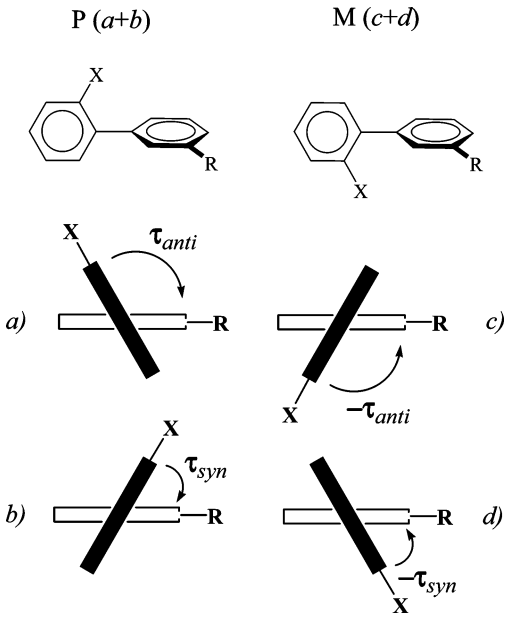
rotation in mono- and bisubstituted biphenyls similar enough that the rotational barrier in the former case can be deduced from the sum of the BFS interference values for the substituent and for hydrogen? There were no reports of barriers to rotation in biphenyls with only one ortho-substituent,[18,19a] so we set out to examine a series of such compounds with a range of common substituents. We will show by dynamic NMR studies that, experimentally, barriers are always significantly less than the BFS sum $I^{X-H} + I^{H-H}$.

Beyond the topic of substituent effects on rotational barriers and additivity when there is more than one ortho-substituent,[13] we will discuss the conformation of the central bond, that is to say the relative torsion of the two rings, and various aspects of substituent buttressing.[20]

The coplanar conformation for any biphenyl with a single ortho-substituent X has maximum destabilization from the steric interaction of X with the nearer ortho-hydrogen on the second phenyl ring and maximum stabilization from the $\pi-\pi$ interaction of the two rings. In the orthogonal conformation, these opposing contributions to the molecular energy are both at a minimum, so the overall lowest energy conformation for the biphenyl will be somewhere between these extremes, more or less near to orthogonal, depending on the size of X.[21,22]

That conformation can be conveniently defined by the C2−C1−C1′−C2′ torsion angle, τ. Inspection suggests and calculations confirm that the ground state has two doubly degenerate minima for the conformation of the biphenyl bond. These are the enantiomeric syn structures *b* and *d* and the enantiomeric anti structures *a* and *c* of Scheme 1. Librational motion that interconverts *a* with *b*, and *c* with *d*, via a transition state where the phenyl rings are mutually orthogonal, is rapid compared with the conventional biphenyl rotation that interconverts *a* with *c*, or *b* with *d*, via a coplanar transition state. Such libration, with different lifetimes in the two interconverting states, is implicit in our subsequent discussions, and biphenyl rotation is thus represented by the interconversion of enantiomeric structures M and P.

SCHEME 1



Results

We now report results for rotation in compounds with a single ortho-substituent, i.e., the two series **1a**−**1h** and **2a**−**2d**,[19a] and for compound **5** with two ortho-substituents (Chart 1). The latter was prepared to make a comparison with the equivalent disubstituted compound **6** in the BFS series (i.e. **4**, X = Y = Me). In the NMR spectrum of compounds **1**, the isopropyl methyl signals change from being isochronous to anisochronous as interconversion of atropisomers M and P changes from being fast to being slow on the NMR time scale as the temperature is lowered. Variation of the spectrum with temperature thus allows determination of the rotational barrier.

The 3-isopropyl group in **1** adopts two rapidly interconverting conformations with the methine hydrogen in the plane of the benzene ring. According to MM3 calculations, the conformation with that hydrogen pointing toward the 4-position is slightly more stable than that where it points to the 2-position, although ab initio calculations suggest that these two conformers have the same energy. Since the barrier to rotation of an isolated isopropyl group on a benzene ring is about 1.5 kcal mol^{-1},[23] interconversion of these conformations is rapid on the NMR time scale at all accessible temperatures. The possibility of these two isopropyl group conformations and of syn−anti libration will not be mentioned again, and both are implicit in our discussions henceforth.

In contrast, each of the terphenyls **1h** and **2a**−**2d** exists as a mixture of stereoisomeric cis and trans-conformations,[24] rather different[25] from the syn- and anti-conformations of Scheme 1, as shown in Figure 1. When interconversion of these, i.e., rotation about both phenyl−phenyl bonds,[19b] is slow on the NMR time scale, two sets of signals of different intensities are seen in the NMR spectrum, reflecting the relative population of these two conformations, and the rotation barrier can be derived from changes in the spectrum with temperature.[19a]

Buttressing, now widely recognized in many intramolecular situations, was first postulated as the indirect effect of substituents in the meta- and para-positions on the biphenyl rotation

(17) Katon, J. E.; Lippincott, E. R. *Spectrochim. Acta* **1959**, *19*, 627, with a temperature correction as described.[13]

(18) Mutarotation[7] of a camphorsulfonate salt of a biphenyl with a single ortho-substituent, trimethylarsonium, was reported at a surprisingly early date (Lesslie, M. S.; Turner, E. E. *J. Chem. Soc.* **1933**, 1588) but were not quantified.

(19) (a) A preliminary account of some of this work (compounds **2a**−**2d**) is given: Lunazzi, L.; Mazzanti, A.; Minzoni, M.; Anderson, J. E. *Org. Lett.* **2005**, *7*, 1291. (b) The $\Delta G^{\ddagger}$ values reported in ref 19a are obtained from the interconversion rates between the cis and trans atropisomers, an interconversion that can take place by rotation of either of the two terminal aryl groups. Comparison with compounds of type **1** requires the rate constant for rotation of only one of the two aryl groups, which is obviously half of the measured atropisomerization value. Thus the values to be used here for the comparison of **2a**−**2d** with **1a**−**1d** are $RT \ln 2 = 0.2-0.4$ kcal mol^{-1} higher (i.e., 7.0, 8.1, 10.2, and 15.0 kcal mol^{-1} for **2a**, **2b**, **2c**, and **2d**, respectively) than those reported in ref 19a.

(20) Rieger, M.; Westheimer, F. *J. Am. Chem. Soc.* **1950**, *72*, 19.

(21) When there is an ortho-substituent in each ring, the ground state conformation is expected to be close to orthogonal ($\tau = 90°$), except when both substituents are fluorine.[15a,22]

(22) Grein, F. *J. Phys. Chem. A* **2002**, *106*, 3823.

(23) Schaefer, T.; Sebastian, R.; Penner, G. H. *Canad. J. Chem.* **1988**, *66*, 1495.

(24) The central ring may be ortho-substituted (**1h**), para-substituted (**2a**−**2d**), or meta-substituted. There are two cis-structures (both-X-up and both-X-down) and two anti-structures (up, down and down, up)[25] but that need not be taken further account of in our discussions.

(25) In our preliminary communication[19a] we used syn and anti as labels for **2a**−**2d** stereoisomeric conformations, but with the use of these labels in Scheme 1, we have changed these labels as cis and trans (Figure 1) in the hope of avoiding confusion.

TABLE 1. Computed (ab initio) and Experimental Barriers (±0.2 kcal mol^{-1}) for the Interconversion of the Biphenyl Atropisomers 1a−1h and 5[h]

	barrier				
compound	$\Delta\nu$ (in Hz at 150.8 MHz)	experimental[a]	computed	interpolated[b]	τ^c
1a (X = Me)	41 at −146°	7.4 [−130°, −110°]	7.1	(9.7 + 1) = 10.7	127
1b (X = Et)	32 at −107°	8.7 [−100°, −90°]	8.6		118
1c (X = i-Pr)	28 at −75°	11.1 [−54°, −36°]	11.1	(12.6 + 1) = 13.6	122
1d (X = t-Bu)	39 at −7°	15.4 [+20°, +55°]	15.3	(18.3 + 1) = 19.3	95
1e (X = Cl)	22 at −131°	7.7 [−120°, −115°]	7.3	(9.1 + 1) = 10.1	126
1f (X = Br)	57 at −120°	8.75 [−100°, −90°]	7.7	(10.2 + 1) = 11.2	127
1g (X = I)	67 at −96°	9.9 [−73°, −67°]	not feasible	(10.9 + 1) = 11.9	NA
1h (X= 3-i-PrPh)	96 and 212 at −135°	7.7[d] [−120°, −100°]	7.4	(7.9 + 1)[e] = 8.9	129, −53
2a[f]		6.8 [−145°, −135°]	6.7		127
2b[f]		7.9 [−120°, −104°]	8.1		117
2c[f]		9.9 [−86°, −60°]	10.7		123
2d[f]		14.6 [−2°, +25°]	14.8		94
5	18 at +50°	18.7 [+81°, +86°]	16.7		90
6		19.3[g] [+64°, +87°]	17.1		91

[a] The values in square brackets represent the temperature range where line shape simulations yield the rate constants used for the determination of the barrier. [b] The sum ($I^{X-H} + I^{H-H}$) of the interference values[13] for substituent X and for hydrogen; see the text. [c] Computed dihedral angle. [d] Barrier for the transition major isomer to minor. [e] The interference value for the phenyl rather than for the *m*-isopropylphenyl is used. [f] Data from ref 19a (see also ref 19b). [g] Value from ref 13. [h] The chemical shift separations are those of the ^{13}C methyl signals of the isopropyl substituent in the meta position. Our earlier results for **2a**−**2d** and those of **6** discussed in the text are also reported.

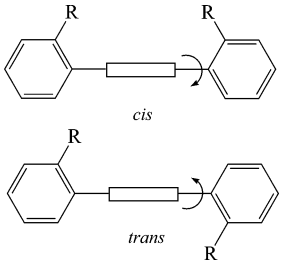


FIGURE 1. Conformation of terphenyls **2a**−**2d**. Each biphenyl bond undergoes libration as in Scheme 1.

barrier.[20,26] Such additional substituents bolster the substituent, or even the hydrogen atom, in the adjacent ortho-position, destabilizing a coplanar state and thereby raising the biphenyl rotational barrier.[13,20] We will comment on buttressing in our simply substituted biphenyls.

Dynamic NMR Studies. Barrier measurements for compounds studied are shown in Table 1. A typical example of the temperature-dependence of the ^{13}C NMR spectra of compounds **1a**−**1g** is shown, for the case of **1a**, in Figure 2 (left). The single line of the isopropyl methyl signal broadens below −100 °C and eventually splits into a pair of equally intense peaks at −146 °C. On the right are shown line shape simulations obtained with the rate constants indicated, from which the $\Delta G^{\ddagger}$ value (7.4 kcal mol^{-1} as in Table 1) was obtained.

The spectra of compound **1h** shows an additional feature to all other compounds **1**, since the cis- and trans-rotational conformers yield separate sets of signals of different intensity at low temperatures. Thus at −135 °C the ^{13}C signal of the isopropyl group appears as two doublets of relative intensity 60:40 with doublet separation of 96 and 212 Hz, respectively (see Figure 3 and Table 1).

On the basis of ab initio computations, wherein the trans-conformation is more stable than the cis- (albeit by only 0.02 kcal mol^{-1}, which is well below the uncertainty of the computed energy values), we tentatively assign the more intense signals to the trans-conformer of **1h**.

(26) Chien, S. L.; Adams, R. *J. Am. Chem. Soc.* **1934**, *56*, 1787.

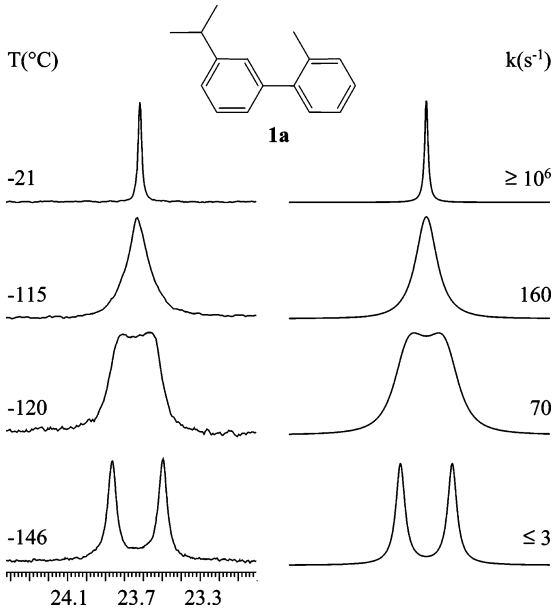


FIGURE 2. Left: temperature dependence of the ^{13}C NMR (150.8 MHz) isopropyl methyl signal of **1a** in $CHF_2Cl/CHFCl_2$. Right: selected examples of line shape simulation obtained with the rate constants indicated.

The terphenyl compounds **2a**−**2d** of ref 19a show spectral changes similar to those for **1h** and these give rise to the barriers reported in Table 1. The barrier in compound **5** is 18.7 kcal mol^{-1}, whereas in the equivalent BFS compound **6** it is 19.3 kcal mol^{-1}.

Molecular mechanics[27] and ab initio[28] calculations were carried out for ground state conformations and for rotation of the biphenyl bond in the compounds studied experimentally and some others. Table 1 shows relevant values of the barriers to rotation (the computed dihedral angles that define each ground state conformation are reported in Table 1).

Discussion

Ground-State Conformation. For the same ortho-substituent, the calculated torsion angles (Table 1) are not consistently

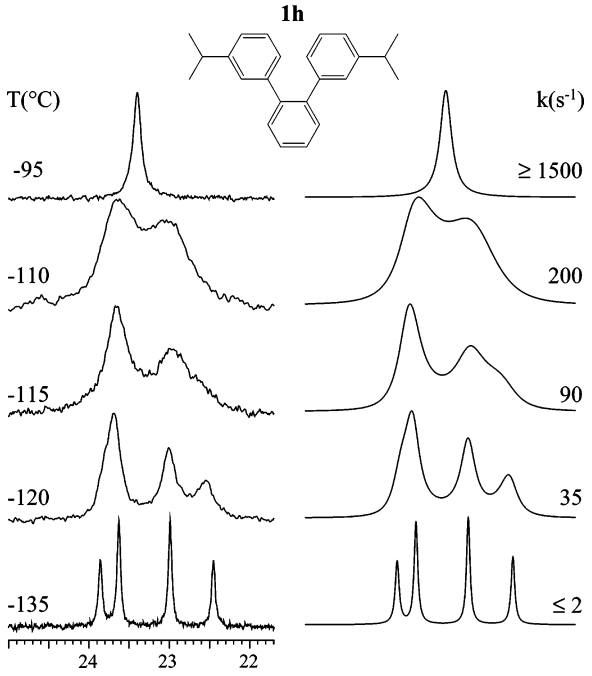


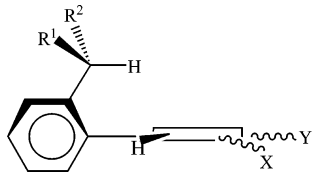
FIGURE 3. Left: temperature dependence of the ^{13}C NMR (150.8 MHz) isopropyl methyl signal of **1h** in $CHF_2Cl/CHFCl_2$ showing two conformers in a 60:40 ratio at −135 °C. Right: selected examples of line shape simulation obtained with the rate constants indicated.

different in the terphenyl series **2** and in the *m*-isopropyl series **1**. We determined the crystal structure conformation for compounds **2a** and **2d**, and the dihedral angles τ measured (55° and 99.5°) are in close agreement with the values calculated, 55° and 93°, respectively.[19a]

Except with the biggest *tert*-butyl substituent, i.e., **1d** or **2d**, the rings are quite far removed from orthogonal, showing that, in the monosubstituted biphenyls, there is a significant conflict between steric repulsion, favoring an orthogonal arrangement, and conjugative interaction of the two phenyl rings, favoring a coplanar system. It has been calculated[22] that in biphenyl itself (at the B3LYP/6-311+G(d) level) the ground-state torsion angle is 43°, and the coplanar and orthogonal states are 2.17 and 1.79 kcal mol^{-1} less stable, suggesting that these two effects are of a comparable size when the ortho-substituents are hydrogen atoms.

The barrier to rotation in a monosubstituted biphenyl should reflect somewhat the ground-state torsion angle τ, which

SCHEME 2



represents the rotation needed to reach the coplanar transition state. The smaller this torsion angle, the greater the relative steric strain already present in the ground state, so the smaller the steric contribution to the observed barrier. On the other hand, a small torsion angle represents enhanced $\pi-\pi$ stabilization in the ground state, so there is less additional electronic stabilization offsetting the steric interaction in the coplanar transition state. This would lead to a somewhat higher barrier, but since in all compounds studied, the steric strain of the planar conformation is greater than the electronic stabilization, the expectation is that the smaller the torsion angle in the ground state, the smaller the barrier; Table 1 shows that this is in fact the case (see also Supporting Information).

While all monosubstituted biphenyls, except **1d** and **2d**, are calculated to have ground-state torsion angles less than 90°, in the 50°−80° range, biphenyls with two ortho-substituents[22] usually have torsion angles close to 90°. These two tendencies mean that rotation has significantly different features in the mono- and disubstituted series.

Barriers in Monosubstituted Biphenyls. The steric interactions during rotation in a substituted biphenyl are not as simple as a transition-state diagram with coplanar rings might imply. It is well-known[29] that if structural constraints are great, the benzene ring is relatively easily distorted and also that exocyclic bond angles can be significantly altered by atom displacement in or out of the plane. Thus during rotation, the maximum interaction of the 2-position with the adjacent 2′-position need not coincide with the maximum interaction of the 6- and 6′-positions. Nonetheless, the size of the barriers along the series **1** clearly fits with widely accepted ideas of the steric size of substituents.

The variation of barriers is particularly marked—more than doubling—with the alkyl groups of **1a**−**1d** and **2a**−**2d**. Alkyl−phenyl bond rotation takes place relatively easily, and this helps to reduce congestion when the two phenyl groups are more or less coplanar. Further relief of strain comes from splaying apart of the C1−phenyl and C2−X bonds. As biphenyl rotation continues, reversal of the alkyl group rotation (or perhaps in the case of a methyl or *tert*-butyl group, completion of 120° of rotation) and relaxation of the bond splaying deliver the molecule to the enantiomeric ground state conformation.

When such an *o*-alkyl group is methyl, ethyl, or isopropyl in **1a**−**1c** and **2a**−**2c**, it no doubt points a hydrogen atom toward the biphenyl bond, as in Scheme 2.

This apparently similar arrangement leads however to different interconversion barriers of 7.4, 8.7, and 11.1 kcal mol^{-1} for **1a**, **1b**, and **1c** and 6.8, 7.9, and 9.9 kcal mol^{-1} for **2a**, **2b**, and **2c**, respectively.[19b] The increase in barrier in going along each series reflects the increasing difficulty of the postulated

(27) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551, 8566, 8576. (b) Allinger, N. L.; Li, F.; Yan, L.; Tai, J. C. *J. Comput. Chem.* **1990**, *11*, 868.

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(29) Qiao, X.; Padula, M. A.; Ho, D. M.; Vogelaar, N. J.; Schutt, C. E.; Pascal, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 741. This paper reports two extreme examples of distorted biphenyl-like structures, octaphenylnaphthalene and decaphenylanthracene, and discusses the distortions in their structures and earlier work.

TABLE 2. Rotational Barriers (kcal mol^{-1}) in Biphenyls with One and with Two Ortho-Substituents[a]

monosubstituted compd				disubstituted compounds		
	ortho-substituent exp barrier *U*		ortho-substituent exp barrier *Q*	barrier for disubstituted from monosubstituted ($U + Q - 2.0$)	exp barrier (ref 13) at the mean temp of columns 2,4	sum of interference values (ref 13) $I^{U,H} + I^{Q,H}$
1a	Me 7.4 [153]	**1g**	I 9.9 [203]	15.3	17.0 [178]	20.5
1a	Me 7.4 [153]	**1f**	Br 8.8 [178]	14.2	17.7 [165]	19.8
1a	Me 7.4 [153]	**1e**	Cl 7.7 [156]	13.1	14.9 [155]	17.8
1a	Me 7.4 [153]	**1a**	Me 7.4 [153]	12.8	15.7 [153]	19.2
1a	Me 7.4 [153]	**1c**	*i*-Pr 11.1 [228]	16.5	17.4 [190]	22.1
1a	Me 7.4 [153]	**1h**	Ar 7.7 [163]	13.1	13.4 [158]	17.5
1c	*i*-Pr 11.1 [228]	**1c**	*i*-Pr 11.1 [228]	20.2	25.5 [228][b]	25.0
1c	*i*-Pr 11.1 [228]	**1d**	*t*-Bu 15.4 [311]	24.5	30.8 [270][b]	30.8

[a] The values in square brackets are the absolute temperatures. [b] These experimental barriers are from ref 32 corrected to the temperature (*T*) shown using an entropy of activation of −11.0 eu.[32]

changes in the alkyl group conformation during biphenyl rotation, either by alkyl group rotation or by splaying. The hydrogen atom in the adjacent C3-position buttresses the alkyl group against both these changes in shape.

Rotation barriers also increase, although rather less markedly with the size of the halogen atom (see **1e**−**1g**). It is not uncommon[30] that the relative effect of chlorine, bromine, and iodine in rotations and in conformational equilibria is less marked than their covalent radii might suggest. Examples of alkyl group rotation in neopentylbenzenes with two halogen atoms as ortho-substituents give barriers[31] in exactly the same ratio as in the present biphenyls.

Barriers in Ortho-Disubstituted Biphenyls. It is interesting to compare the barriers for biphenyls with two ortho-substituents with those for the two corresponding monosubstituted compounds, and relevant results are shown in Table 2.

If rotational barriers in the disubstituted series are predicted from the sum of barriers in the appropriate monosubstituted cases, reduced by 2.0 kcal mol^{-1} (i.e., the rotational barrier in biphenyl itself due to the interaction of two pairs of coplanar hydrogen atoms), the outcomes are always markedly lower than the experimental values.[13] We believe that our monosubstituted biphenyl barriers serve for predicting only a lower limit for those in the disubstituted series.

There is however a problem associated with a comparison based on such experimental rotational barriers. From the nature of the dynamic NMR experiment, disubstituted biphenyl barriers are determined in a markedly higher temperature range ΔT than the two compared monosubstituted biphenyls. If there is a significant entropy of activation $\Delta S^{\ddagger}$ for rotation, one of the two barriers compared has to be adjusted to the temperature of the other by $\Delta T\Delta S^{\ddagger}$. We have found that free energies of activation for series **1** and **3**, inevitably determined over narrow temperature ranges, are essentially constant within the limits of experimental error,[33] so for lack of better information we take $\Delta S^{\ddagger}$ to be 0 in these series.

BFS on the other hand reported a mean $\Delta S^{\ddagger}$ value of −18.8 ± 6.7 eu for the series of disubstituted biphenyls that they measured.[13] The difficulties in determining $\Delta S^{\ddagger}$ from dynamic NMR experiments are well-known and lead to an excessively negative value.[34]

Activation entropies for rotation in biphenyls determined by classical methods shed light on this problem. Hall and Harris[35] have reviewed the literature[36] and showed that classically determined activation entropies for four disubstituted biphenyls averaged −6.6 eu while for eight trisubstituted and four tetrasubstituted biphenyls, the average values are −11.6 and −13.8 eu, respectively. These averages are striking and do confirm the need for caution in dynamic NMR derivations of activation entropies. Furthermore, the progression in the averages with substitution indicates that an activation entropy of near to zero in monosubstituted biphenyls is plausible.

If rotational barriers in monosubstituted biphenyls are derived from the sum of the BFS interference values for that substituent and for hydrogen, the predictions (see the interpolated values in the last column of Table 1) are invariably higher than experimental values, usually by much more than 1 kcal mol^{-1}. Since the BFS interference values do serve well for predicting results for further examples of disubstituted biphenyls, there must be some factor that differs between the disubstituted and monosubstituted series. This is buttressing, which is progressively greater with increasing substitution, but whose effects can be observed even in simply substituted compounds.

Buttressing. The structural phenomenon of buttressing was first demonstrated with polysubstituted biphenyls[26] and is particularly associated with benzene rings where the relative position of adjacent substituents on a rigid framework is well-

(30) Anderson, J. E.; Doecke, C. W.; Pearson, H. *J. Chem. Soc., Perkin Trans. 2* **1976**, 336.

(31) Nilsson, B.; Martinson, P.; Olsson, K.; Carter, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 3190.

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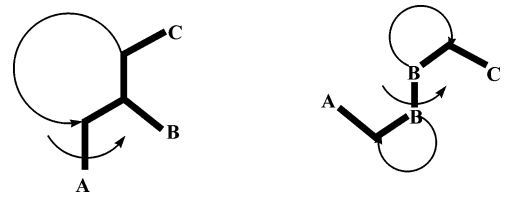
(33) As often observed in conformational processes, the $\Delta G^{\ddagger}$ value was found to be independent of temperature within the experimental uncertainty of the NMR measurements. See: Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484. Forlani, L.; Lunazzi L.; Medici, A. *Tetrahedron Lett.* **1977**, *18*, 4525. Bernardi, F.; Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron*, **1977**, *33*, 1337. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031. Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1990**, *112*, 2915. Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924. Garcia, M. B.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Orelli, L. R. *J. Org. Chem.* **2001**, *66*, 6679. Garcia, M. B.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Orelli, L. R. *Eur. J. Org. Chem.* **2002**, 4018. Casarini, D.; Rosini, C.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2003**, *68*, 1815. Casarini, D.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2004**, *69*, 345. Bartoli, G.; Lunazzi, L.; Massacesi, M.; Mazzanti, A. *J. Org. Chem.* **2004**, *69*, 821. Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A.; Rompietti, R. *J. Org. Chem.* **2004**, *69*, 5746.

(34) Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. *J. Am. Chem. Soc.* **1966**, *88*, 3185.

(35) Hall, D. M.; Harris, M. M. *J. Chem. Soc.* **1960**, 490. See also later classical measurements.[36]

(36) (a) Lesslie, M. S.; Mayer, U. J. H. *J. Chem. Soc.* **1961**, 611. (b) Cheung King Ling, C.; Harris, M. M. *J. Chem. Soc.* **1964**, 1825.

SCHEME 3



defined. It is essentially an effect of steric interaction of these substituents, although any one substituent may have an electronic effect as well.

In any system of three groups, A, B, and C, as in Scheme 3 (left), when a process at A is studied, the process being a chemical reaction or a movement (here the process is rotation about the bond to A), B has a direct steric effect on this process. Group C, as a meta-substituent in a biphenyl for example, is too distant from the rotating phenyl ring A to exert any direct steric compression (van der Waals repulsion), but the very presence of C, or introducing a larger substituent as C, may increase the effect that B has on the process at A, and this is known as the buttressing of B by C: the effect of the interaction between B and C on a process at A.

Although hydrogen as a substituent B or C is often taken as the starting point in discussing buttressing by larger substituents, it may itself be involved in buttressing. Thus, the experimental rotational barriers for the meta-substituted compounds **1a**−**1d** are each higher than in the para-substituted terphenyl compounds **2**, by 0.6 kcal mol^{-1} on average.[19b] Ab initio calculations for the same compounds suggest that the barriers are 0.45 kcal mol^{-1} higher on average in the meta-substituted series **1**. Molecular mechanics calculations for 2-chlorobiphenyl suggest that the barrier is 9.6 kcal mol^{-1}, whereas in meta-substituted analogues, **1e** and **7**, which also have a chlorine as a single ortho-substituent, the barrier is somewhat higher at 9.9 kcal mol^{-1}. In **5**, where there is an isolated isopropyl group as a meta-substituent, free to rotate so that its methyl groups need not be near the *o*-hydrogen atom, we measured a barrier of 18.7 kcal mol^{-1}. In compound **6**, whose structure around the biphenyl bond is superficially similar to **5** but has the meta-substituent held rigid with methyl groups toward the *o*-hydrogen atom, the barrier is 19.3 kcal mol^{-1}. This varied evidence suggests that the buttressing effect of an isolated meta-substituent (such as is used as an NMR probe for the biphenyl rotation) is small but real and is transmitted by the *o*-hydrogen atom.[37]

Given the size of this buttressing by an isolated meta-substituent, any intrinsic buttressing effect by an isolated para-substituent in series **2**, transmitted by intervening *m*- and *o*-hydrogens, should be negligible. An electronic effect on the rotation barrier might be expected,[38] but the *p*-phenyl substituent in series **2** is far from coplanar, which reduces any electronic interaction, and this does not necessarily change during the biphenyl rotation being observed. We thus suggest that the barriers measured in the series **2** are close approximations to the basic barriers, those to be expected in a biphenyl with an ortho-group as the only substituent.[19b] Similar basic barriers for *o*-halogen substituents can be obtained by reducing the series **1** barrier by 0.6 kcal mol^{-1}.

Another kind of buttressing occurs in a system like that in Scheme 3 (right) when the process is represented as B−B bond rotation. Groups A and C will not only affect the process at B by direct steric interaction, but each will also restrict distortion at B to accommodate the other. The A−B and B−C interactions will buttress each other to increase rotational barriers. A comparison with our results for monosubstituted compounds suggests that this is what happens in biphenyls with an ortho-substituent in each ring.

The experimental barrier values for such disubstituted compounds contain a substantial contribution from mutual buttressing that is inevitably much diminished in the monosubstituted case when one substituent is hydrogen. It is thus unlikely that there is a simple link between the rotational barriers of a series of monosubstituted biphenyls and of any member of the corresponding set of disubstituted biphenyls.

The extent to which the BFS interference value for a substituent, derived from disubstituted biphenyls, is greater than the monosubstituted biphenyl rotation barrier (see columns 3 and 5 of Table 1) can thus be taken as a measure of the buttressing effect of a substituent. On this basis, the phenyl group has a small effect (0.2 kcal mol^{-1}), halogen atoms have a similarly sized intermediate effect (1.0−1.4 kcal mol^{-1}), and alkyl groups have larger effects (1.5−2.9 kcal mol^{-1}).

Calculations. Computations of barriers to rotation in monosubstituted biphenyls have an unusual outcome. Molecular mechanics calculations (MM3) driving the inter-ring dihedral angle invariably lead to a rotational barrier that is significantly higher than experimental values. While it may be that driving the torsion angle needs to be accompanied by some rotation of the ortho-substituent to better reproduce what happens experimentally during rotation, this cannot be the case for simple ortho-substituents such as halogen, where the calculated barriers are also too high. In the chloro compound **1e**, for example, the calculated barrier is 9.9 kcal mol^{-1}, more than 25% higher than the experimental value of 7.7 kcal mol^{-1}.

If, however, the structure for the ground state and transition state are calculated by ab initio methods (B3LYP/6-31G(d) level[28]), optimization of these latter calculations leads to a calculated barrier that agrees well with the experimental values for the monoalkylbiphenyls and reasonably well for the monohalobiphenyls.[39]

Conclusions

A series of biphenyl compounds with a single ortho-substituent adopts a ground state conformation where the biphenyl dihedral angle varies between about 40° and 90°,

(37) Stoughton and Adams (*J. Am. Chem. Soc.* **1932**, *54*, 4426) considered the effect of an isolated *m*-methyl or methoxy substituent on rotation, but could detect no significant difference in the half-lives for racemization of appropriate chiral biphenyls. Confusingly, Chien and Adams[26] cited this paper shortly afterwards and stated that Stoughton and Adams "demonstrated that a group in the 5′-position increased the antipodal stability of the molecule."

(38) Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* **1988**, *43*, 173.

(39) A reviewer has suggested that for the series of chiral compounds **1a**−**1g**, the experimental $\Delta G^{\ddagger}$ include a $\Delta S^{\ddagger}$ contribution of $-R$ ln 2 from the loss of the entropy of mixing of the enantiomeric ground-state structures with a planar, achiral rotational trensition state. However, the two almost equivalent coplanar transition states should balance the ground-state degeneracy in such a way that the whole contribution becomes almost negligible. The reviewer suggests that the loss of entropy might be allowed for by correcting the experimental barrier by *RT* ln 2. This would affect the comparison of the barriers and would reduce the small discrepancy between the calculated activation enthalpies and the experimental activation energies for the series **1**. It would also reduce the difference between the experimental barriers for chiral series **1** with a meta-substituent and achiral series **2**, a difference that we have attributed to a buttressing effect of the meta-substituent.

reflecting the size of the substituent. Barriers to rotation between enantiomeric conformations reflect steric size. These barriers are somewhat smaller than expected from literature values for biphenyls with an ortho-substituent in each ring. Remote substituents in the meta-position affect the barrier somewhat. These last two observations are evidence of differing kinds of buttressing effects that are present even when three of the four ortho-positions carry hydrogen atoms.

Experimental Section

Materials. 3-Isopropylboronic Acid. To a solution of 1-bromo-3-isopropylbenzene (15 mmol in 100 mL of THF) cooled at −78 °C was added 10 mL (16 mmol) of BuLi (1.6 M in hexane). After 2 h the resulting 3-isopropylphenyllithium was transferred dropwise into a solution of triisopropylborate (45 mmol in 20 mL of THF) kept at −78 °C. (Note: the transferring line has to be cooled to avoid decomposition of the organometallic reagent.) When the addition was terminated, the reaction was maintained for 1 h at this temperature and subsequently warmed to room temperature for about 1 h. Finally, the reaction was quenched with aqueous HCl and extracted with Et_2O. The crude product was crystallized from hexane to yield 1.36 g (10 mmol) of 3-isopropylphenylboronic acid.

1-Bromo-2-*tert*-butylbenzene.[40] A solution of 2-*tert*-butylphenylamine (0.1 mol 15.6 mL) in 30 mL of 40% w/w hydrobromic acid was prepared in a 250-mL round-bottomed flask. After cooling to 5 °C by immersion in an ice/salt bath, diazotization was performed by gradual addition of a solution of 15.1 g (0.22 mol) of sodium nitrite in 20 mL of water, with stoppering of the flask after each addition and shaking until all red fumes were adsorbed. The temperature was kept between 5 and 10 °C for 2 h. When the diazotization was completed, 0.4 g of copper powder was added. **WARNING**: **the solution was refluxed very cautiously because of evolution of gas.** When the vigorous evolution of nitrogen moderates, the system was kept at 50 °C for 30 min and was then diluted with 80 mL of water and extracted with Et_2O. The organic layer was washed with 10% solution of KOH, and the crude purified by chromatography on silica gel (hexane) and distilled at 85 °C (3 mmHg) to obtain 6.0 g (28.3 mmol) of 1-bromo-2-*tert*-butylbenzene.

1-Bromo-*p*-cymene and 2-Bromo-*p*-cymene. To a 250-mL round-bottomed flask containing 63.9 g (0.475 mol) of *p*-cymene and 0.2 g of iron powder was added 64 g (0.40 mol) of Br_2 slowly under a nitrogen flux. During the addition the reaction can be monitored by the vigorous evolution of HBr, and the temperature should be kept between 50 and 60 °C. When the evolution of gas ends, the mixture was warmed to 70 °C for about 4 h and then quenched by addition of 100 mL of a 6 M KOH solution, and the resulting mixture was extracted with chloroform. The dried solution (Na_2SO_4) was evaporated at reduced pressure. The unreacted *p*-cymene was removed by distillation (bp 75 °C at 25 mmHg). The brown crude product was distilled at reduced pressure to obtain a mixture of the two isomers (bp 116 °C at 19 mmHg).[41]

(40) Hou, Y.; Meyers, C. Y. *J. Org. Chem* **2004**, *69*, 1186.

General Procedure for Compounds 1a−1h and 5. To a solution of the appropriate ortho-substituted bromobenzene (1 mmol in 6 mL of benzene) were added K_2CO_3 (2 M solution, 1.25 mL), 3-isopropylphenylboronic acid (2.5 mmol, suspension in 4 mL of ethanol), and $Pd(PPh_3)_4$ (0.2 mmol) at room temperature (in the case of **1h**, 7.5 mmol of 3-isopropylphenylboronic acid was added). The stirred solution was refluxed for 2−3 h, the reaction being monitored by GC−MS. Then $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude was prepurified by chromatography on silica gel (hexane). The analytically pure compounds were obtained from preparative HPLC on a Kromasil C18 column (250 mm × 10 mm, 5 μm, eluent CH_3CN/H_2O). The spectroscopic and analytical data for all the new compounds are reported in the Supporting Information.

NMR Measurements. NMR spectra were recorded at 600 MHz for ^1H and 150.8 MHz for ^{13}C. The assignments of the ^{13}C signals were obtained by DEPT and 2D experiments (gHSQC sequence[42]). The samples for the ^{13}C NMR low-temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the compound and some C_6D_6 for locking purpose and condensing therein the gaseous CHF_2Cl and $CHFCl_2$ under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out using a PC version of the DNMR-6 program.[43] At least five different temperature spectra were used for the simulations.

Computational Details. Ab initio computations were carried out at the B3LYP/ 6-31G(d) level by means of the Gaussian 03 series of programs[28] (the standard Berny algorithm in redundant internal coordinates and default criteria of convergence was employed). Harmonic vibrational frequency was calculated in order to ascertain the nature of all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas for each transition state the frequency analysis showed a single imaginary frequency. The corresponding optimized structures are reported in the Supporting Information.

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Supporting Information Available: Analytical and spectroscopic data for compounds **1a−1h** and **5**; Ab initio calculated ground state dihedral angles and computational details of compounds **1a−1h** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060205B

(41) Strubell, W. *Chem. Techn*. **1957**, *9*, 597.

(42) Wilker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem*. **1993**, *31*, 287.

(43) PC version of the QCPE program no. 633, Indiana University, Bloomington, IN.