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Conformation and Stereodynamics of Symmetrically Ortho-Disubstituted Aryl Carbinols and Aryl Ethers

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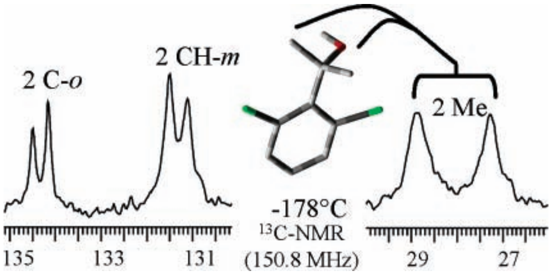

By making use of low-temperature dynamic NMR spectroscopy, the rotation barriers about the sp^3−sp^2 bond have been determined in a number of hindered benzyl alcohols symmetrically substituted in the ortho positions, the substituents being F, Cl, Br, and Me. The free energies of activation covered the range 4.6−10.1 kcal mol^{-1}. Ab initio computations matched satisfactorily the trend of these values and predicted the conformation adopted by these compounds. In one case, this result could be also confirmed by the X-ray diffraction structure. In the case of the corresponding methyl ethers two barriers could be measured, corresponding to the passage across two distinguishable transition states: the higher barriers covered the range 5.0−8.1 kcal mol^{-1} and the lower ones the range 4.7−6.2 kcal mol^{-1}.

Introduction

Restricted rotation about the bond connecting the aryl groups with the sp^3 carbon atoms has been observed in a variety of aryl carbinols, and the corresponding barriers were determined by means of variable-temperature NMR spectroscopy.[2−10] In particular, when the aryl moiety does not exhibit a 2-fold symmetry axis two atropisomers with different populations were detected and their structure assigned.[3,8] In the case of very crowded derivatives bearing, as substituents, the *tert*-butyl or the adamantyl groups, the atropisomers could be also separated.[5−8] The majority of the compounds studied so far had the aryl moiety substituted by one or by two different groups. Here we present an investigation about aryl carbinols bearing two equal substituents in the ortho positions, as those shown in Chart 1.

In this type of derivative, four possible situations could, in principle, be considered: in Scheme 1 are displayed, as an example, the possible conformers one might expect in the case of compounds **1**−**4** (R = Me). In order to decide whether they actually correspond to ground-state structures, theoretical calculations were employed. The theoretical approach is also helpful for providing indications about the relative stability of these conformers.

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(2) Newsoroff, G. P.; Sternhell, S. *Tetrahedron Lett.* **1967**, *8*, 2539. Baas, J. M. A.; Sinnema, A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 899. Baas, J. M. A.; van der Toorn, J. M.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 173.

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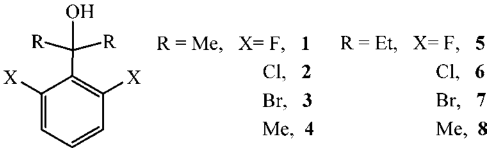
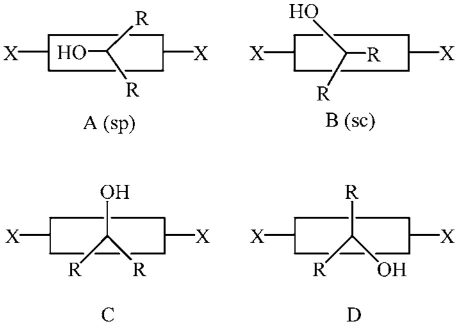
CHART 1



SCHEME 1



Results and Discussion

Ab initio[11] computations (and Molecular Mechanics[12] as well) of **1** (X = F, R = Me) indicate that the conformations of type C (anticlinal[13]) and D (synclinal[13]) do not correspond to energy minima (actually they represent transition states[14]) and that the minimum corresponding to conformation A (synperiplanar[13]) has an energy higher (by 0.65 kcal mol^{-1}, according to ab initio) than that of conformation B (synclinal[13]), indicating that the latter should be the more populated species at low temperature. The asymmetry of the most stable conformer B implies the existence of two enantiomeric forms (+sc and −sc), but the barrier for their interconversion, involving the passage through the scarcely populated conformer A (sp), is predicted to be very low: for instance, the ab initio computed value for **1** is 3.15 kcal mol^{-1}, as shown in Scheme 2.[15]

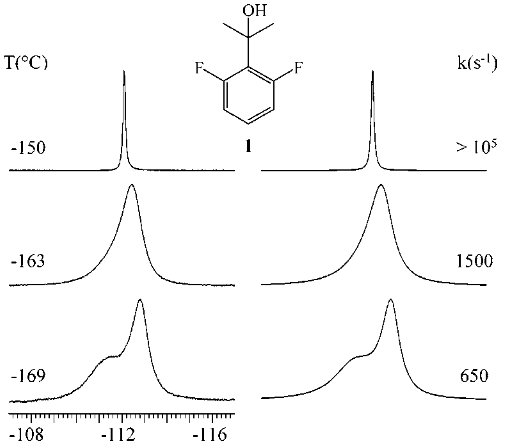
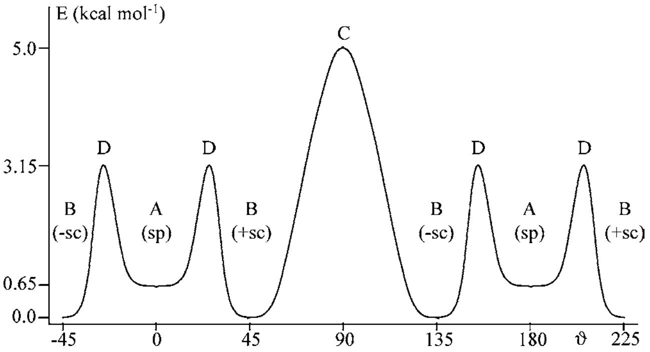


FIGURE 1. Temperature dependence (left) of the ^{19}F NMR signal (564.3 MHz) of compound **1** in CHF$_2$Cl/CHFCl$_2$. The shifts are referred to the signal of C_6F_6 at −163 ppm. On the right is displayed the simulation obtained with the rate constants indicated.

SCHEME 2. Schematic Energy Profile of 1 (*E* in kcal mol^{-1}) as a Function of the Dihedral Angle ϑ between the Aromatic Ring and the Plane of the C1−C−O Moiety



Such a low barrier does not allow the corresponding enantiomerization process to be frozen in an NMR experiment in the case of **1**, so that, even at the lowest attainable temperature, a dynamic C_s symmetry (i.e., the same type of symmetry displayed by the syn periplanar conformer A) will be actually observed. Thus, the two methyl groups of **1** will appear equivalent (enantiotopic) in the NMR time scale, even when the atoms in the ortho and meta positions become diastereotopic.

The low-temperature ^{19}F spectra of **1** (Figure 1) show indeed how the single signal of the two ortho fluorine atoms broadens on cooling and eventually decoalesces at −169 °C into a pair of partially overlapping signals exhibiting a quite different line width:[16] their integrated intensities indicate that the ratio is 1:1.[14] From the rate constants derived from line shape simulation,[17] the free energy of activation ($\Delta G^{\ddagger} = 4.6 \pm 0.3$ kcal mol^{-1}) for the rotation that makes the ortho positions equivalent (homotopic) could be obtained.[18] The corresponding ab initio calculated barrier is 5.0 kcal mol^{-1} (Scheme 2), a value in good agreement with the experiment. These calculations indicate that

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(11) Program Gaussian 03, Revision D.01. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

(12) MMX force field as in PC Model v 7.5, Serena Software, Bloomington, IN.

(13) Eliel, L. E.; Wilen, S. H.; *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; p 21.

(14) This result is at variance with the hypothesis of Schaefer et al., which arbitrarily assumed conformation C to be the ground state. See: Schaefer, T.; Sebastian, R.; Penner, G. H.; Salman, S. R. *Can. J. Chem.* **1986**, *64*, 1602.

(15) As shown in Scheme 2, the computed dihedral angle between the aromatic ring and the plane defined by the C1−C−O moiety of **1** is 48° for the most stable conformer B and 28° for the transition state interconverting B into A, i.e., the process which is responsible for the too fast interconversion of the +sc and −sc enantiomers.

(16) Also, the ortho and meta ^{13}C signals of **1** should likewise split into a pair of lines: this feature, however, was not observed since the corresponding shift separations were smaller than the line width, which is very broad below −160 °C.

(17) PC version of QCPE program DNMR 6 no. 633, Indiana University, Bloomington, IN.

(18) The relatively large experimental error of the barrier of **1** (±0.3 kcal mol^{-1}) is a consequence of the great uncertainty in determining the intrinsic line width of the two ^{19}F lines at such low temperatures.

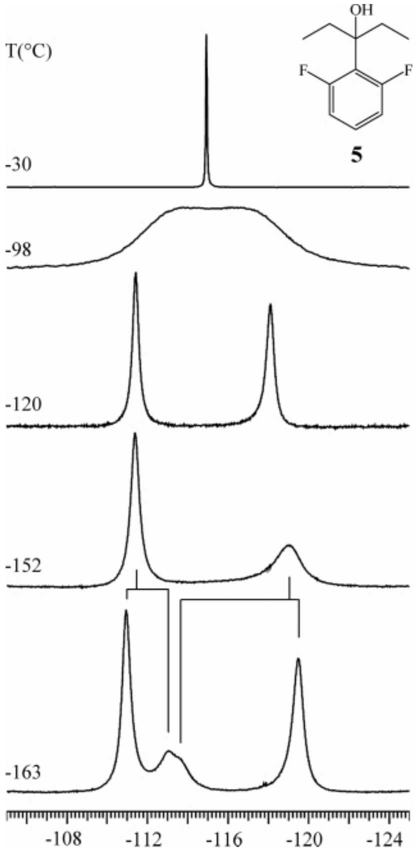

FIGURE 2. Temperature dependence of the ^{19}F NMR signal (564.3 MHz) of compound **5** in $CHF_2Cl/CHFCl_2$. The shifts are referred to the signal of C_6F_6 at −163 ppm.

the transition state for this process corresponds to the structure C (anticlinal), as shown in the rotation pathway reported in Scheme 2.

The larger width observed at −169 °C (Figure 1) for one of the two ^{19}F signals might suggest that the process which interconverts the unequally populated conformers A (sp) and B (sc) of Scheme 1 has a rate sufficiently slow for broadening this line, but still too fast to show the expected decoalescence, in agreement with the quite low computed barrier of 3.15 kcal mol^{-1} predicted for **1** (Scheme 2). According to this interpretation, the greater steric hindrance of the corresponding ethyl derivative **5** should make possible the detection of this second process at an attainable temperature. Indeed, Figure 2 shows that at −120 °C the two fluorine atoms of **5** display two equally intense lines, due to the freezing of the same rotation process observed in **1**, the corresponding barrier being higher than that of **1**, as anticipated (6.9 rather than 4.6 kcal mol^{-1}). On further cooling, these lines broaden selectively, as observed in the case of **1**, but now they split into a pair of unequally populated peaks at −163 °C (Figure 2). These signals correspond, therefore, to the conformers B (sc) and A (sp) of derivative **5**, their relative proportion being approximately 80:20. Line shape simulation yields the free energy of activation required to interconvert the major into the minor conformer (5.0 kcal mol^{-1}).

Contrary to the case of **1**, ab initio computations predict that the conformer A (sp) of **5** is 0.47 kcal mol^{-1} more stable than the conformer B (sc),[19] a result in agreement with the corresponding ^{13}C spectrum (Supporting Information, Figure S-1). At a temperature of −172 °C, in fact, the methylene carbon signal of **5** appears as a single line superimposed to a pair of equally intense lines, the single line being more intense (about 80%) than the other ones (10% each). The single major line thus corresponds to the two CH_2 carbons of the equivalent (enantiotopic) ethyl groups of conformer A (sp), whereas the two distinct lines with lower intensity are due to the two CH_2 carbons of the diastereotopic ethyl groups of conformer B (sc) of Scheme 1.[20]

In the case of compounds without fluorine substituents, the exchange process was followed by monitoring the decoalescence of the ^{13}C signals of the quaternary ortho and CH meta carbons:[21] Figure 3 displays, for instance, the temperature dependence of these lines in the case of derivative **2** (X = Cl, R = Me). In Table 1 are collected the barriers,[22] measured by line shape simulation,[17] for all of the compounds investigated.

As in the case of **1** and **2**, also in the other methyl alcohols investigated (**3** and **4**), the ^{13}C signals of the methyl groups bonded to the COH moiety remained equivalent (enantiotopic) at any attainable temperature, in agreement with the mentioned expectation of the related enantiomerization process having a barrier too low to be experimentally detected.

It should be pointed out that, according to calculations, the ground state (i.e., the B-type conformer of Scheme 1) of compounds **3** and **4** (X = Br and Me, respectively) has a value for the dihedral angle ϑ between the aryl ring and the C1−

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(19) The inversion of the relative stability of two conformers when the ethyl groups substitute the methyl groups had been well documented in analogous cases (see ref. 10).

(20) The interconversion between the two conformers of type A and B also involves a simultaneous rearrangement of the two ethyl groups: such a rearrangement contributes to determine the value of the measured barrier of 5 kcal mol^{-1} (the corresponding ab initio computed barrier of 4.4 kcal mol^{-1} agrees well with the experiment). In the more stable conformer of type A, in fact, the two ethyl groups adopt a symmetric relative disposition (see the computed structure in the Supporting Information, Figure S-2), in agreement with the observation of a single CH_2 line in the mentioned ^{13}C spectrum at the −172 °C. In the less stable conformer of type B, on the other hand, one of the two ethyl groups adopts a disposition different form that of its companion (also this the computed structure is displayed in the Supporting Information, Figure S-2). The existence of symmetric and asymmetric conformers due to the relative disposition of two ethyl groups has been also detected by supersonic jet mass resolved excitation spectroscopy (see: Breen, P. J.; Bernstein, E. R.; Seeman, J. I. *J. Chem. Phys.* **1987**, *87*, 3269). A situation analogous to the present one had been also observed in the case of 3-(1-naphthyl)pentan-3-ol.[8]

(21) Owing to the poor solubility of **4** and **11** at temperatures lower than −120 °C, these barriers were measured by monitoring the ^{1}H signal (600 MHz) of the *o*-methyl substituents.

(22) As often observed in conformational process, the $\Delta G^{\ddagger}$ value was found 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.

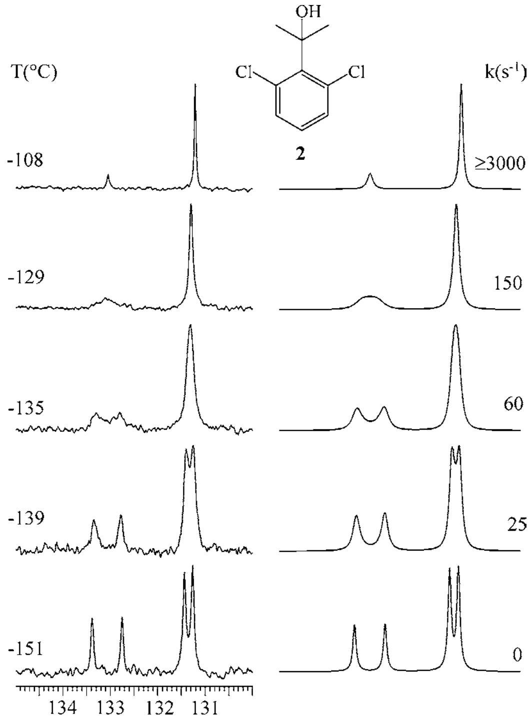

FIGURE 3. Left: temperature dependence of the ^{13}C signals (150.8 MHz in $CHF_2Cl/CHFCl_2$) of the two quaternary ortho and of the two CH meta carbons of **2**. Right: simulation obtained with the rate constants indicated.

C−O plane smaller than 30°. Rather than 48° as in **1** or 40° as in **2**, this angle is predicted to be 18° in **3** and 27° in **4**: for this reason, the corresponding conformer B should be indicated, in these cases, as syn periplanar (sp) rather than synclinal (sc).[13]

Single-crystal X-ray diffraction of **4** (Figure 4, left) shows indeed that the dihedral angle ϑ between the average plane defined by the aryl group (the shape of the aromatic ring deviates from a perfect planarity by 6° in the crystal) and that identified by the C1−C−O moiety is 24°, a value very close to that (ϑ = 27°) computed for the isolated molecule (Figure 4, right).

In the case of compounds **3** and **4**, computations also indicate that the A-type conformer of Scheme 1 (i.e., that having ϑ = 0°) corresponds to a low energy transition state rather than a ground state, as in **1** and **2**. Consequently, the corresponding energy profile is of the type displayed, as an example, in Scheme 3 for the case of **4** (R = X = Me).

In the aryl carbinols with two ethyl substituents bonded to the COH moiety (compounds **5**−**8**), the interconversion barrier was found to be consistently larger (by 2.45 ± 0.15 kcal mol^{-1}) than in the analogous methyl-substituted derivatives **1**−**4**. This is a consequence of the greater bulkiness of the ethyl with respect to the methyl group. In addition, in derivatives **1**−**3** and **5**−**7** the barriers increase with the dimension of the halogen substituent: this parallels the trend of the corresponding van der Waals radii (1.47, 1.75, 1.85 for F, Cl, Br, respectively).[23]

As shown in Table 1, the barriers measured for compounds **4** and **8** (having two methyl groups as ortho substituents) are lower than those of the corresponding derivatives **2** and **6** that have two chlorine atoms as ortho substituents (the average difference is 0.7 kcal mol^{-1}). This trend suggests that the steric hindrance exerted by the methyl group upon the rotation process is lower than that of the chlorine atom. This is in a qualitative agreement with the trend recently reported[24] for a pair of ortho-substituted biphenyl derivatives, where the Ar−Ar rotation barrier was found slightly lower for the methyl than for the chlorine substituent (i.e., 7.4 vs 7.7 kcal mol^{-1}, respectively).[25]

The present finding is at variance with the trend of the van der Waals radii indicated by Bondi,[23] who proposed a larger value for methyl with respect to chlorine (i.e., 2.0 vs 1.75), but is in keeping with that proposed by Charton,[26] if the minimum van der Waals radius for methyl is taken into account (i.e., 1.715 for methyl vs 1.75 for chlorine).

As previously mentioned, the process that would make diastereotopic the methyl groups is too fast in the alcohols **1**−**4** to be experimentally observed. However, if the OH is substituted by the OMe group (as in compounds **9**−**12** of Chart 2), the greater steric requirement should increase the corresponding barrier, making this process amenable to an experimental detection. This prediction is supported by Molecular Mechanics calculations[12] of the energy surface as function of the previously defined dihedral angle ϑ (related to the torsion about the Ar−C(Me$_2$) bond, and of the dihedral angle φ formed by the C1−C(Me$_2$)−O and (Me$_2$)C−O−Me planes (this angle is related to the torsion about the C−OMe bond). As an example, such a surface is displayed in Figure 5 for the case of **10** (X = Cl). The computed barrier involving the transition state which renders diastereotopic the ortho and meta positions (full square in Figure 5) is larger than that involving the transition state which renders diastereotopic the two methyl groups (full circle in Figure 5): the more accurate ab initio computations (Table 2) indicate these two values to be 9.4 and 5.5 kcal mol^{-1}, respectively.[27] These calculations therefore support the hypothesis that even the lower of these two barriers should be sufficiently high for obtaining an experimental determination (barriers larger than 4 kcal mol$^{-1,}$ in fact, are amenable to NMR measurements[28]).

The temperature dependence of the ^{13}C signals of **10** (X = Cl), reported in Figure 6, shows that at −144 °C the single lines of the two ortho and of the two meta carbons split into 1:1 pairs, since the same type of process observed in the corresponding alcohol **2** has been frozen. The signal of the two methyl groups bonded to the C−OMe moiety is still a single

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[23] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

[24] Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J. E. *J. Org. Chem.* **2006**, *71*, 5474.

[25] It should be outlined that the present result is at variance with the report of another pair of biphenyl derivatives, where the *o*-methyl-substituted compound displayed a rotation barrier 0.5 kcal mol^{-1} higher than that of the corresponding chlorine derivative. See: Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

[26] Two values were indicated for the van der Waals radii of the methyl group: a minimum of 1.715 and a maximum of 2.23; see: Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615.

[27] Ab initio calculations of the whole energy surface exceeded the capabilities of our computing facilities; thus, only the optimized singular points (ground and transition states) were computed (see the Experimental Section and Supporting Information).

[28] Examples of NMR determinations of very low barriers can be found in: Anet. F. A. L.; Chmurny, G. N.; Krane, J. *J. Am. Chem. Soc.* **1973**, *95*, 4423. Anet, F. A. L.; Yavari I. *J. Am. Chem. Soc.* **1977**, *99*, 6752. Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 4573. Brown, J. H.; Bushweller, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8153. Pawar, D. M.; Noe, E. A. *J. Am. Chem. Soc.* **1998**, *120*, 41485. Pawar, D. M.; Wilson, K. K.; Noe, E. A. *J. Org. Chem.* **2000**, *65*, 1552. Casarini, D.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2001**, *66*, 2757. Anderson J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, S. *J. Am. Chem. Soc.* **2001**, *124*, 6706. Lunazzi, L.; Mazzanti, A.; Minzoni, M. *Tetrahedron* **2005**, *61*, 6782. Lunazzi, L.; Mazzanti, A.; Minzoni, M. *J. Org. Chem.* **2005**, *70*, 456. Pawar, D. M.; Brown, J., II; Chen, K.-H.; Allinger, N. L., Noe, E. A. *J. Org. Chem.* **2006**, *71*, 6512.

TABLE 1. **Experimental Rotation Barriers (kcal mol^{-1})^{a} for Compounds 1−8 and ab Initio Computed Barriers for Compounds 1−4**

compd	**1** R = Me (X = F)	**2** R = Me (X = Cl)	**3** R = Me (X = Br)	**4** R = Me (X = Me)	**5**^{b} R = Et (X = F)	**6** R = Et (X = Cl)	**7** R = Et (X = Br)	**8** R = Et (X = Me)
exptl	4.6	6.8	7.4	6.2	6.9	9.4	10.1	8.6
computed	5.0^{c}	7.0^{d}	7.9^{d}	7.8^{c}				

^{a} In $CHF_2Cl/CHFCl_2$. ^{b} In **5** a second barrier of 5.0 kcal mol^{-1} has been also measured (see text). ^{c} B3LYP/6-31G(d) level. ^{d} B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level.

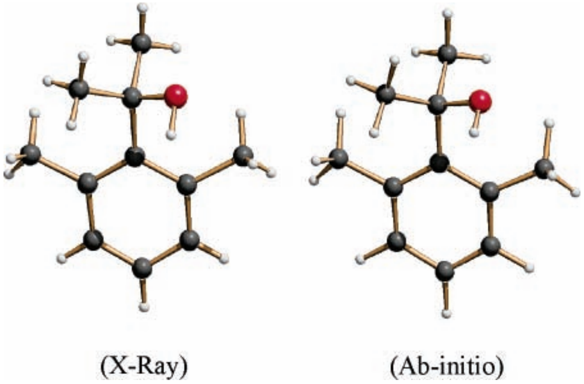


FIGURE 4. Experimental (left) and computed (right) structure of compound **4**.

SCHEME 3. **Schematic Energy Profile of 4 (*E* in kcal mol^{-1}) as a Function of the Dihedral Angle ϑ between the Aromatic Ring and the Plane of the C1−C−O Moiety**

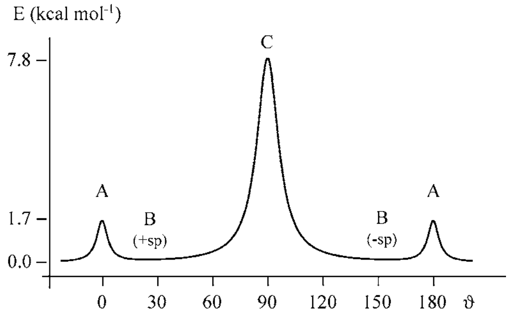
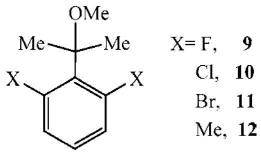


CHART 2



line at −144 °C, but on further lowering the temperature to −178 °C splits into a 1:1 pair of lines, because also the second process, with the lower barrier, has been frozen at this temperature. Analogous results were obtained for **11** and **12** (X = Br and Me, respectively): the corresponding barriers are collected in Table 2.

Also in the case of **9** (X = F), the methyl groups become diastereotopic at low temperature, as predicted by calculations: within the experimental uncertainty (±0.15 kcal mol^{-1}), however, the corresponding barrier was found equal to that measured by monitoring the ^{19}F signals of the ortho fluorine substituents (5.0 and 4.7 kcal mol^{-1}, respectively, as in Table 2). This means that in compound **9** the barrier for rendering diastereotopic the ortho and meta positions is very close to that required to make diastereotopic the two methyl groups. This agrees with the ab initio calculations predicting quite similar values for these two barriers (5.5 and 4.9 kcal mol^{-1}, respectively, as in Table 2).

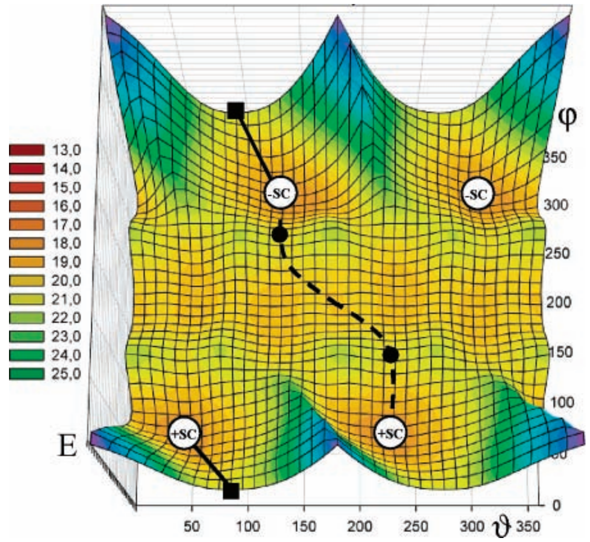


FIGURE 5. MM-computed energy (kcal mol^{-1}) surface of **10** as function of the dihedral angles ϑ and φ defined in the text. The solid line describes the passage across the higher energy transition state (full square) and the dashed line that across the lower energy transition state (full circle). The ground states are indicated as +sc and −sc.

TABLE 2. **Experimental Values of the Two Barriers (kcal mol^{-1}) Measured^{a} for the Rotation Processes Occurring in Ethers 9−12 (the Computed Values Corresponding to the Transitions States TS-1 and TS-2 Are Shown in Parentheses)**

compd	**9** (X = F)	**10** (X = Cl)	**11** (X = Br)	**12** (X = Me)
higher barrier (TS-1)	5.0 (5.5^{b})	6.9 (9.4^{c})	8.1 (10.2^{c})	7.0 (10.0^{b})
lower barrier (TS-2)	4.7 (4.9^{b})	4.8 (5.5^{c})	5.0 (5.9^{c})	6.2 (5.5^{b})

^{a} In $CHF_2Cl/CHFCl_2$. ^{b} B3LYP/6-31G(d) level. ^{c} B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level.

The higher of the two barriers measured in the ethers **9**−**11** increases regularly (5.0, 6.9, 8.1 kcal mol^{-1} as in Table 2) with the dimension of the halogen substituent, as already observed in the corresponding alcohols **1**−**3** and **5**−**7** (Table 1): this trend is also predicted by the computed values of Table 2. The pathway responsible for this effect is due to the restriction of the Ar−C bond rotation that drives the C-OMe bond into a perpendicular position to the aryl ring (i.e., a situation analogous to that of type C of Scheme 1): the corresponding ab initio computed transition states (indicated as TS-1) are reported in Figure S-3 of the Supporting Information. On the contrary, the values of the lower barriers measured for the ethers **9**−**11** are equal within the experimental uncertainty (4.7−5.0 kcal mol^{-1} as in Table 2) and do not depend, therefore, on the dimension of the halogen substituents. This suggests that the lower barriers measured by NMR are essentially determined by the rotation process about the C−OMe bond (i.e., that indicated by the angle

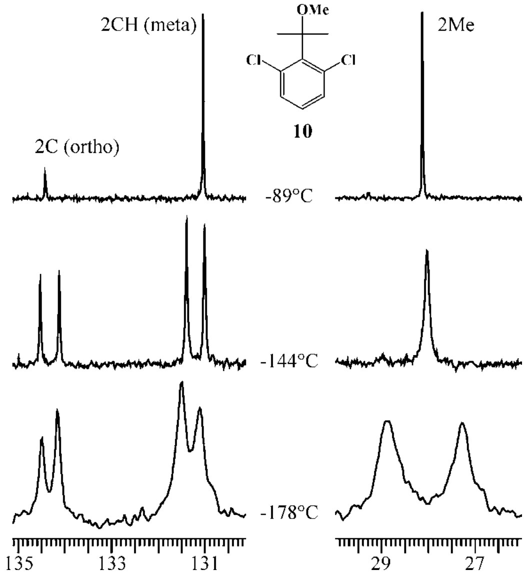


FIGURE 6. Temperature dependence of ^{13}C signals (150.8 MHz) of the two ortho, two meta, and two methyl carbons (bonded to the C−OMe moiety) of **10** in $CHF_2Cl/CHFCl_2$.

φ in Figure 5), the related transition state (TS-2) being described by the O−Me bond eclipsing one of the two C−Me bonds (this situation corresponds to the point identified by the full dot in Figure 5 for compound **10**). It is quite evident that this process cannot be affected by the dimension of the halogen groups in the ortho position, thus accounting for the observed invariance of the lower barriers in **9**−**11**: these TS-2 transition states, resulting from ab initio computations, are displayed in Figure S-3 of the Supporting Information.

Such an interpretation also accounts for the fact that in the alcohols **1**−**4** the diastereotopicity of the two methyl groups could not be observed in the NMR spectra, even at the same low temperatures where it was detected in the corresponding methyl ethers **9**−**12**: the rotation barrier about the C−OH bond of the alcohols is in fact conceivably lower than that about the CO−Me bond of the corresponding ethers.

Conclusion

As anticipated by computations, the low-temperature NMR spectra of symmetrically ortho disubstituted aryl carbinols display a barrier due to the restricted rotation about the sp^2−sp^3 Ar−C bond, the threshold mechanism being that where the C−OH bond becomes perpendicular to the aryl ring: this barrier increases with the increasing dimension of the halogen substituents. In the corresponding methyl ethers a second additional barrier, due to the C−OMe bond rotation, could be also measured, the latter barrier being independent, as conceivable, of the type of the halogen groups in the ortho positions.

Experimental Section

Materials: General Procedure for 1−3 and 5−7. A solution of lithium diisopropylamide (LDA) was prepared in 1 h by addition of 12.5 mL of *n*-butyllithium (20 mmol, 1.6 M in hexane) to a stirred solution of 2.02 g of diisopropylamine (20 mmol in 12.5 mL of anhydrous THF) kept at −5 °C. The solution was then slowly transferred into a solution of the appropriate 1,3-dihalobenzene (20 mmol in 12.5 mL of anydrous THF), kept at −78 °C. After 1.5 h, the suspension of the resulting lithiate[29] was treated either with acetone (for compounds **1**−**3**, 40 mmol, neat) or diethyl ketone (for compounds **5**−**7**, 40 mmol, neat). The temperature was immediately raised to ambient temperature, and the mixture treated with aqueous NH_4Cl, extracted with Et_2O, and dried (Na_2SO_4). After removing the solvent, the crude was prepurified by a silica gel chromatography column (petroleum ether/Et_2O 8/2). Yields: 73% for **1**[30], 52% for **2**, 8% for **3**, 66% for **5**, 44% for **6**, 10% for **7**. Analytically pure samples were obtained by semipreparative HPLC on a Synergi Polar-RP column (4 μm, 250 × 10 mm, 4 mL/min, $MeOH/H_2O$ 80:20 v:v). See the Supporting Information for details.

2-(2,6-Dimethylphenyl)propan-2-ol (4) and 3-(2,6-Dimethylphenyl)pentan-3-ol (8). A 12.5 mL portion of BuLi (20 mmol, 1.6 M in hexane) was added to a solution of 1-bromo-2,6-dimethylbenzene (20 mmol in 15 mL of dry THF) at −78 °C. The solution was stirred for 60 min and then treated with acetone or diethyl ketone (40 mmol in 5 mL of dry THF). After being stirred for 10 min, the mixture was warmed to 25 °C, treated with aqueous NH_4Cl, extracted with Et_2O, and dried (Na_2SO_4). The crude obtained after removal of the solvent was purified by a silica gel chromatography column (petroleum ether/Et_2O 8/2) to give **4** (65%)[31] and **8** (58%). Analytically pure samples were obtained by semipreparative HPLC on a Synergi Polar-RP column (4 μm, 250 × 10 mm, 4 mL/min, $MeOH/H_2O$ 80:20 v/v). In the case of compound **4**, crystals suitable for X-ray diffraction were obtained by slow evaporation from $CHCl_3$. See the Supporting Information for details.

General Procedure for 9, 10, and 12. To a suspension of NaH (95% powder, about 10 mmol in 5 mL of dry THF), kept at 0 °C, was added dropwise a solution of the appropriate alcohol (2 mmol in 2 mL of dry THF). After 10 min, the stirred suspension was treated with excess MeI (1 mL). After being warmed to ambient temperature, the reaction was cautiously quenched with aqueous NH_4Cl, extracted with Et_2O, and dried (Na_2SO_4). After removal of the solvent, the crude was prepurified by a silica gel chromatography column (petroleum ether/Et_2O 20/1) to give **9** (72%)**, 10** (65%), and **12** (58%). Analytically pure samples were obtained by semipreparative HPLC on a Synergi Polar-RP column (4 μm, 250 × 10 mm, 4 mL/min, $MeOH/H_2O$ 80:20 v/v) in the case of compound **10**, and on a Luna C18(2) column (5 μm, 250 × 10 mm, 4 mL/min, ACN/H_2O 95:5) in the case of compounds **9** and **12**. See the Supporting Information for details.

1,3-Dibromo-2-(2-methoxypropan-2-yl)benzene (11). A solution of LDA was prepared in 1 h by addition of 12.5 mL of *n*-butyllithium (20 mmol, 1.6 M in hexane) to a stirred solution of 2.02 g of diisopropylamine (20 mmol in 12.5 mL of anhydrous THF) kept at −5 °C. The solution was then slowly transferred into a solution of 1,3-dibromobenzene (20 mmol in 12.5 mL of anhydrous THF) kept at −78 °C. After 1.5 h, the suspension of the resulting lithiate was treated with acetone (40 mmol, neat). The temperature was immediately raised to 25 °C, and the mixture transferred into a solution of MeI (1 mL) in anhydrous DMF (10 mL). After 1 h, the solvents and DMF were removed by distillation at reduced pressure and the crude was prepurified by a silica gel chromatography column (petroleum ether/Et_2O 20/1) to obtain **11** (overall yield: 3%, ∼30% on the intermediate alcohol). Analytically pure samples were obtained by semipreparative HPLC on a Luna C18(2) column (5 μm, 250 × 10 mm, 4 mL/min, ACN/H_2O 80:20 v:v). See the Supporting Information for details.

NMR Spectroscopy. The spectra were recorded at 300, 400, and 600 MHz for ^1H and 75.45, 100.6, and 150.8 MHz for ^{13}C, and 564.3 MHz for ^{19}F. The external standard C_6F_6 (neat, set at −163.0 ppm) in the ^{19}F spectra was used as reference. The assignments of the ^{13}C signals were obtained by DEPT and

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bidimensional experiments (gHSQC[32] and gHMBC[33] sequences). The samples for obtaining spectra at temperatures lower than −100 °C 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 $CHFCl_2$ (4:1 v/v) 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 Cu/Ni thermocouple before the measurements.

Calculations. Computations were carried out at the B3LYP/6-31G(d) or at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[11] (see the Supporting Information): the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency.

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Supporting Information Available: Variable-temperature NMR spectra of compound **5**, optimized structures of the two ground-state conformations of **5**, optimized TS-1 and TS-2 transition-state structures for compounds **9**−**11**, X-ray diffraction data of compound **4**, analytical and spectroscopic data of compounds **1**−**12**, ^{1}H and ^{13}C NMR spectra of compounds **1**−**12**, mass spectra of compounds **3**, **7**, and **11**, HPLC traces of compounds **1**−**12**, and computational data for compounds **1**−**5** and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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