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Structure, Conformation, and Dynamic Processes of the Stereolabile Atropisomers of Hindered Terphenyl Hydrocarbons

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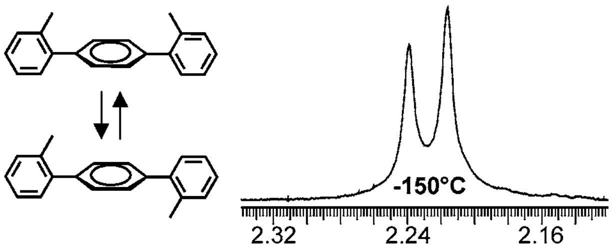
ABSTRACT



Ortho-substituted *p*-terphenyl hydrocarbons exist as trans and cis atropisomers that were identified by low-temperature NMR spectroscopy. The interconversion barriers increase with the dimensions of the ortho substituents, the experimental values being matched by ab initio calculations. X-ray diffraction shows that only the trans atropisomer is present in the solids. Spectra of a *tert*-butyl derivative in nonequilibrium conditions indicate that the cis is more populated than the trans atropisomer in solution, favored by attractive interactions.

A benzene ring bearing two identical ortho-substituted phenyl groups in para positions is expected to involve two types of atropisomers because the ortho substituents can adopt either a trans disposition (with the alkyl groups on the opposite side of the plane of the para-substituted phenyl ring) or a cis disposition (with the alkyl group on the same side).[2,3] These two forms are unlikely to be configurationally stable and would rapidly interconvert at ambient temperature. The stereodynamic consequences of such an interconversion−rotation of a biphenyl bond with only one ortho substituent are investigated here for *p*-terphenyl compounds (**1**−**4** of Figure 1) with alkyl groups of increasing dimensions as ortho substituents.

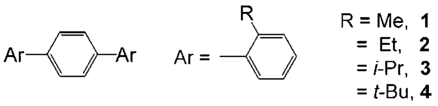


Figure 1.

Owing to the competition between conjugative and steric effects, the two *o*-alkylphenyl moieties of compounds **1**−**3** would display dihedral angles with the para-substituted phenyl ring somewhat intermediate between 0° (coplanarity) and 90° (orthogonality). As a consequence, both the trans and cis atropisomers would comprise a pair of rotational conformers, since in each atropisomer the *o*-alkyl groups can be either in a *syn* or in an *anti* relative position. In Figure 2

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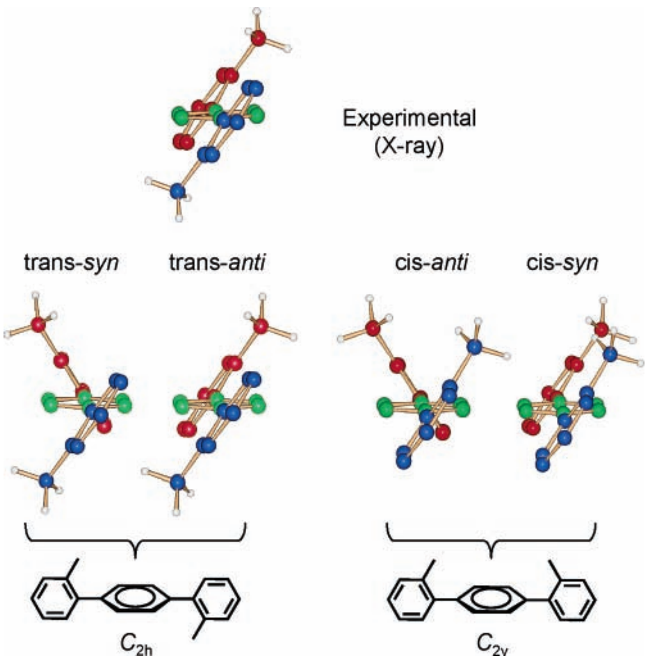

Figure 2. Representation of the four rotamers of **1** as derived by ab initio calculations (for convenience only the methyl hydrogens are reported). The carbons of the para-substituted phenyl group are green, and those of the *o*-methylphenyl group are blue when directed toward the observer and red when away from the observer. The shape of the two atropisomers (trans on the left and cis on the right) resulting from the rapid interconversion of the corresponding pair of rotamers is sketched underneath. On the top is also shown the structure obtained by X-ray diffraction in the solids, which is very similar to that of the computed trans-*anti* rotamer.

these four rotamers, which correspond to the four energy minima resulting from ab initio computations,[4] are displayed for compound **1** (R = Me), the mentioned dihedral angles being 55° for all the rotamers. The corresponding energies can be considered essentially equal within the computing approximations because their differences are less than 0.01 kcal mol^{-1}.[5]

Single-crystal X-ray diffraction shows that the structure of **1** is of the trans-*anti* type (Figure 2, top); the measured dihedral angle of 54.9° matches that anticipated by calculations (55°). Since this rotamer has essentially the same computed energy as the other three, the preference for this structure in the solids should be attributed to a particularly stable crystal packing.

The barrier for the mutual interconversion between the trans-*syn* and trans-*anti* rotamers (as well as between the cis-*syn* and cis-*anti*) is expected to be very small, since corresponds to the passage of one *o*-alkylphenyl group across the plane perpendicular to that of the central, para-substituted phenyl ring. Computations[4] predict that this barrier is as low as 0.63 kcal mol^{-1} in the case of **1** and is therefore too low to be determined by dynamic NMR measurements. This fast motion generates, consequently, a dynamic symmetry, so that the trans atropisomer should display the time averaged symmetry of the C_{2h} point group: likewise, the cis atropisomer has the symmetry of the C_{2v} point group.

The interconversion between the "dynamic" trans (C_{2h}) and cis (C_{2v}) atropisomers, defined as above, requires that in the transition state an *o*-alkylphenyl group becomes coplanar with the central para-substituted phenyl ring. In the case of **1** this energy has been calculated[4] to be 6.7 kcal mol^{-1} higher than that of the ground state (Table 1), a value which should be amenable to an experimental verification.

In Figure 3 a few selected NMR spectra (^{1}H at 600 MHz) of the aliphatic region of **1** are reported as a function of temperature. Below −120 °C the methyl signal begins to broaden and eventually decoalesces into a pair of lines with a 48:52 intensity ratio at −150 °C,[6] making the existence of cis and trans atropisomers experimentally observable.

From the rate constants derived by line shape simulation,[7] the free energy of activation ($\Delta G^{\ddagger} = 6.8 \pm 0.2$ kcal mol^{-1}, as in Table 1) was determined:[8] the experimental value is essentially equal to that predicted by calculations.

When the dimension of *o*-alkyl substituent R increases, the measured barriers become progressively higher owing to the larger steric effects, as anticipated by calculations (Table 1). Also the population of the more stable atropisomer increases regularly with the dimension of the substituents (Table 1).

The *tert*-butyl group is large enough as to make the adjacent phenyl rings essentially orthogonal, the dihedral angle predicted by calculations[4] being, in this case, 93°. For this reason, compound **4** has only two energy minima (rather than the four minima of **1**−**3**), indicating that the cis and

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(4) (a) Ab initio computations were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 programs[4b] (the standard Berny algoritm in redundant internal coordinates, and default criteria of convergence were employed). Harmonic vibrational frequency were 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 optimised structures are reported in the Supporting Information. (b) Gaussian 03, Revision C.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; 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.

(5) Also in the cases of **2** (R = Et) and **3** (R = *i*-Pr) the four rotamers have essentially the same computed energies, their differences lying within 0.03 and 0.04 kcal mol^{-1}, respectively. The dihedral angles between the aromatic rings were computed to be 64° for the four rotamers of **2** and 60° for those of **3**.

(6) 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 a spectrometer operating at 600 MHz. The temperatures were calibrated by substituting the sample with a Cu/Ni thermocouple before the measurements.

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

Table 1. Experimental and Computed Barriers (in kcal mol^{-1}) for the Interconversion of the More into the Less Stable Atropisomer of Compounds **1**−**4**

compd	solvent	atropisomer ratio	$\Delta G^{\ddagger}$ (exptl)	ΔE (computed)
1 (R = Me)	$CHF_2Cl/CHFCl_2$	52/48 (at −150 °C)	6.8 ± 0.2	6.7
2 (R = Et)	$CHF_2Cl/CHFCl_2$	53/47 (at −125°C)	7.9 ± 0.15	8.1
3 (R = *i*-Pr)	CD_2Cl_2	55/45 (at −90 °C)	9.9 ± 0.15	10.7
4 (R = *t*-Bu)	CD_2Cl_2	67/33 (at −30 °C)	14.6 ± 0.15	14.8

trans atropisomers adopt structures (Figure 4) that correspond to static C_{2v} and C_{2h} symmetries, respectively. The energies calculated (ab initio) for the two atropisomers are very similar, the cis being more stable than the trans by only 0.1 kcal mol^{-1}.[9]

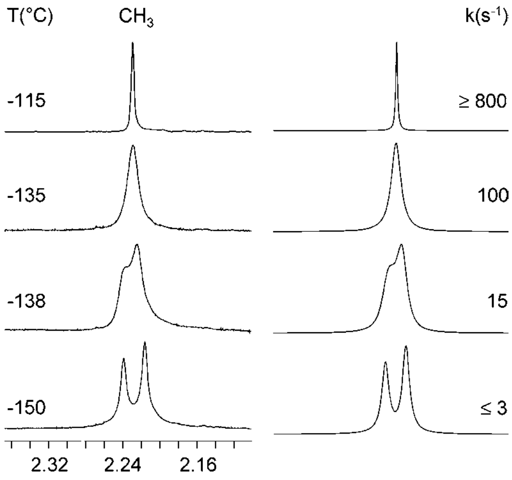

Figure 3. Experimental (left) and computer-simulated (right) ^{1}H NMR spectrum (600 MHz) of the methyl signal of **1** as a function of temperature in $CHF_2Cl/CHFCl_2$.

Single-crystal X-ray diffraction of **4** shows that the crystal cell comprises two identical molecules (actually four-half molecules related by a center of symmetry) having the structure trans. The mentioned dihedral angle is 99.5° (Supporting Information), the difference with respect to the computed value of 93° being due to a slight structural distortion occurring in the crystal.

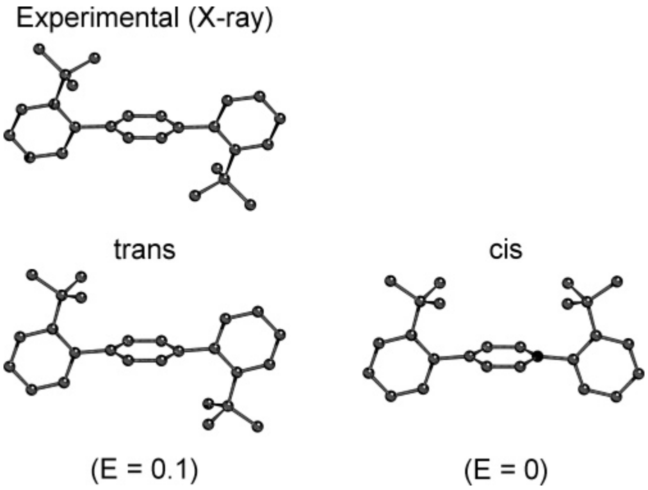

Figure 4. Ab initio computed structures of the trans (left) and cis (right) atropisomers of **4**. The relative energies (*E*) obtained by ab initio computations are in kcal mol^{-1}. On the top is also displayed the structure (trans) of **4**, as obtained by X-ray diffraction.

Whereas in compounds **1**−**3** the two atropisomers have very similar populations, in derivative **4** there is a substantially difference in their relative proportions. To achieve a structural assignment in the latter case, the following experiment was performed.

A few crystals of **4**, known by X-ray diffraction to contain only the trans atropisomer, were dissolved at −80 °C in CD_2Cl_2 and the spectrum recorded at −90 °C without ever raising the temperature. From the measured value of the interconversion barrier (14.6 kcal mol^{-1}, as in Table 1) the half-life of the atropisomers of **4** is predicted to be almost 2 h at this temperature. Under these conditions, the system has not had enough time to reach the conformational equilibrium in solution, so that the observed NMR signals should mainly correspond to those of the trans form. The relative proportion of the two NMR signals measured in these conditions (0.51) is indeed reversed with respect to the value observed at the equilibrium (2.03, Table 1). In other words, the major signal

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[8] In the restricted temperature range where this dynamic process could be monitored, the free energy of activation was found essentially constant within the experimental errors, suggesting a negligible value for the activation entropy, as often observed in conformational processes. 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. 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.

[9] Also, Molecular Mechanics calculations (MMX force field as in PC Model v 7.5, Serena Software, Bloomington, IN) indicate that the cis should be more stable than the trans atropisomer by 0.2 kcal mol^{-1}.

detected in this experiment corresponds to the minor signal observed at equilibrium and *vice versa*. On raising the temperature, the minor signal increases its proportion, becoming the major one (and the major diminishes becoming the minor signal) until the equilibrium is eventually attained (Figure 5). Thus, the cis structure should be assigned to the more stable atropisomer in solution. That the crystal conformation is trans implies a more stable crystal lattice when molecules are in that conformation.

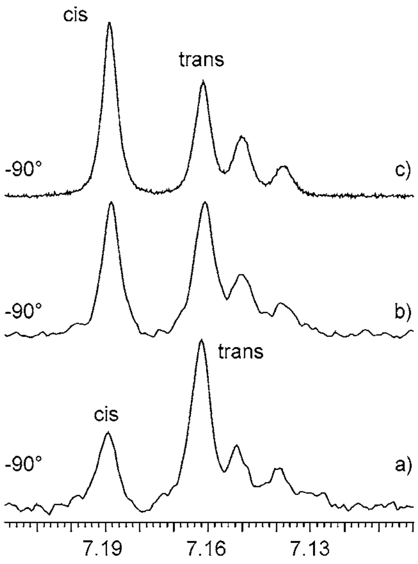

Figure 5. ^{1}H NMR (600 MHz in CD_2Cl_2 at −90 °C) single lines due to the four equivalent hydrogens of the para-substitued phenyl group of the cis and trans atropisomers of **4** (at this temperature the line at 7.162 ppm overlaps some of other aromatic hydrogens signals). Trace a: spectrum obtained by dissolving **4** at −80 °C and recorded without ever raising the temperature. Trace b: spectrum recorded after having raised the temperature for a few minutes at −70 °C. Trace c: spectrum obtained after equilibration at room temperature.

The preference for the cis with respect to the trans atropisomer in solution can be explained on the basis of the attractive interactions,[10,11] which have been observed to affect conformational equilibria when many-atom groups such as pairs of *tert*-butyl groups[12] are so distant that they do not repel each other (in the present case the smallest distance between the *tert*-butyl hydrogens is computed to be as large as 3.4 Å in the cis conformer of **4**).

Hindered rotation about biphenyl bonds is the founding epitome for atropisomerism,[13] and since 1922, many examples have been studied by a range of techniques.[14] Surprisingly, the present series represents the first systematic study of such bonds in compounds with a single ortho substituent hindering rotation.

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Supporting Information Available: Experimental procedures and computational data for compounds **1**−**4**. Crystal data for compounds **1** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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