Atropisomerism in Hindered Naphthyl Sulfones Investigated by Dynamic NMR and Dynamic HPLC Techniques[1]

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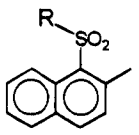
The existence of asymmetric conformations, leading to a pair of conformational enantiomers, has been observed by variable temperature NMR in hindered naphthyl sulfones, either monitoring the signals of prochiral groups or the signals of non-prochiral groups in a chiral environment. The corresponding enantiomerization barriers were determined by line shape analysis. In a sulfone featuring two stereogenic axes, the presence of both meso and racemic conformers has been detected and, by means of an appropriately cooled (−80 °C) enantioselective column, the three expected conformational stereoisomers have been physically separated, allowing assignment of the meso structure to the most stable species. MM calculations were also employed to describe the stereodynamic processes.

1-Naphthyl sulfones bearing a methyl group in the position 2 of the naphthalene ring (**1**–**4**) adopt a conformation lacking any element of symmetry, thus displaying a pair of *R*,*S* enantiomers (atropisomers) created by the restricted rotation about the stereogenic axis between the sulfur atom and the C-1 carbon of the naphthalene ring. A similar behavior had been observed in analogous ketones[2a] and sulfoxides.[2b]



R = Me, **1**
= Et, **2**
= Pr^i, **3**
= Bu^t, **4**

We discovered this feature by observing the low temperature ^{1}H NMR spectra of **2** and **3**. The *gem*-methylene hydrogens of the ethyl moiety in **2** and the *gem*-methyl groups of the isopropyl moiety in **3** become diastereotopic, thus yielding anisochronous NMR signals, below −140 °C and −80 °C, respectively. The exchange rates between the resulting *R* and *S* conformational enantiomers (Scheme 1) could be determined by computer line shape simulation, allowing the corresponding free energy of activation[3] (Table 1) to be obtained.

As an example the case of **2** (R = Et) is illustrated in Figure 1. The absence of prochiral probes[4] in **1** (R = Me) and **4** (R = Bu^t) does not allow the enantiomerization process to be observed, in that identical NMR spectra are expected for both enantiomers in solution. However, distinguishable signals are predicted to occur in a suitable chiral environment. This was checked by recording the spectrum of **3** in the presence of an excess (20:1 molar ratio) of *S*-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol[5] (TFAE). At −80 °C two equally intense lines for the methyl group in the position 2 of the naphthalene ring were actually detected, due to the presence of the *R* and *S* enantiomers. The rate constants, measured by computer simulation of these lines, afforded a barrier essentially equal (within the ±0.15 kcal mol^{-1} experimental error of these determinations) to that previously determined by monitoring the anisochronous methyl isopropyl signals in a nonchiral environment (i.e. 10.6_5 vs 10.5 kcal mol^{-1} for the former and the latter, respectively), indicating that addition of TFAE does not affect, in practice, the enantiomerization process of these sulfones. Accordingly the 600 MHz spectrum of **4**, taken at −35 °C in analogous conditions, displays a pair of equally intense lines for both the *tert*-butyl and the 2-methyl groups (Figure 2). On raising the

Scheme 1

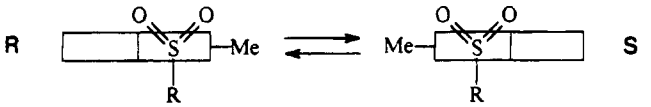


Table 1. Free Energies of Activation (ΔG^* in kcal mol^{-1}) Measured by Dynamic NMR for the Exchange Processes of 2–5

compd	ΔG^*	solvent	temp range (°C)[a]
2	7.2	CHF_2Cl	−136, −120
3	10.5	CD_2Cl_2	−60, −50
	10.6_5	CD_2Cl_2 + TFAE[b]	−60, −50
4	14.6	CD_2Cl_2 + TFAE[b]	−13, +15
	14.7	$CDCl_3$ + TFAE[b]	−23, −18
5	14.6	CD_2Cl_2	−38, −26
	14.8	toluene-d_8	−22, −10

[a] Range of temperature where line shape simulation was performed. [b] TFAE stays for the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-(9-anthryl)ethanol (see text).

[⊗] Abstract published in *Advance ACS Abstracts*, July 15, 1995.

(1) Conformational Studies by Dynamic NMR. 53. For Part 52 see: Casarini,D.; Lunazzi, L.; Foresti, E.; Macciantelli, D. *J. Org.Chem.* **1994**, *59*, 4637.

(2) (a) Casarini,D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521. (b) Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org.Chem.* **1993**, *58*, 5674.

(3) As often reported in the case of restricted rotation, the ΔG^* values are independent of temperature, indicating a negligible ΔS^*. Thus the free energy of activation is, in practice, equal to ΔH^*, allowing reliable comparisons to be made amongst ΔG^* values obtained in different temperature ranges.

(4) (a) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1. (b) Jennings, W. B. *Chem Rev.* **1975**, *75*, 307.

(5) Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837.

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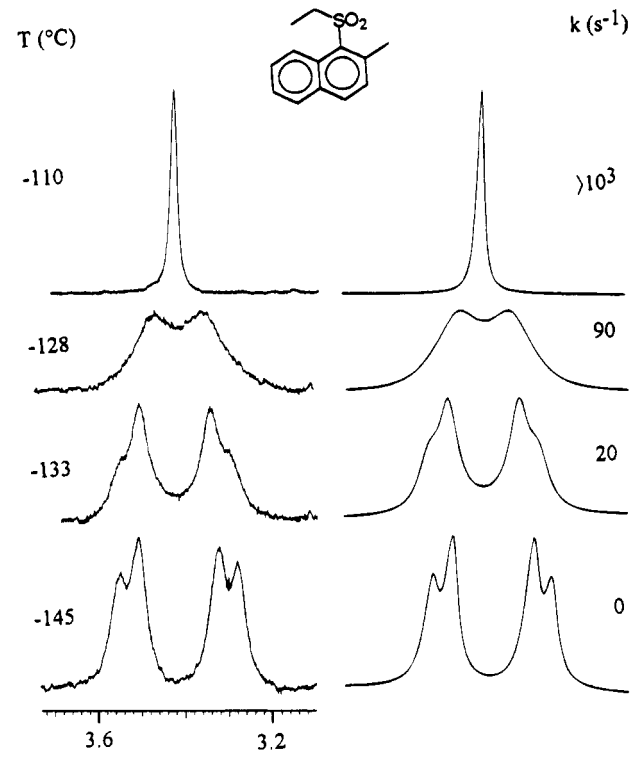


Figure 1. Left: experimental ^1H signal of the CH_2 group of **2** (R = Et) as function of temperature (300 MHz in CHF_2Cl). The spectrum has been decoupled at the frequency of the triplet signal of the corresponding methyl group. Right: computer simulation obtained with the rate constants (k, s^{-1}) indicated.

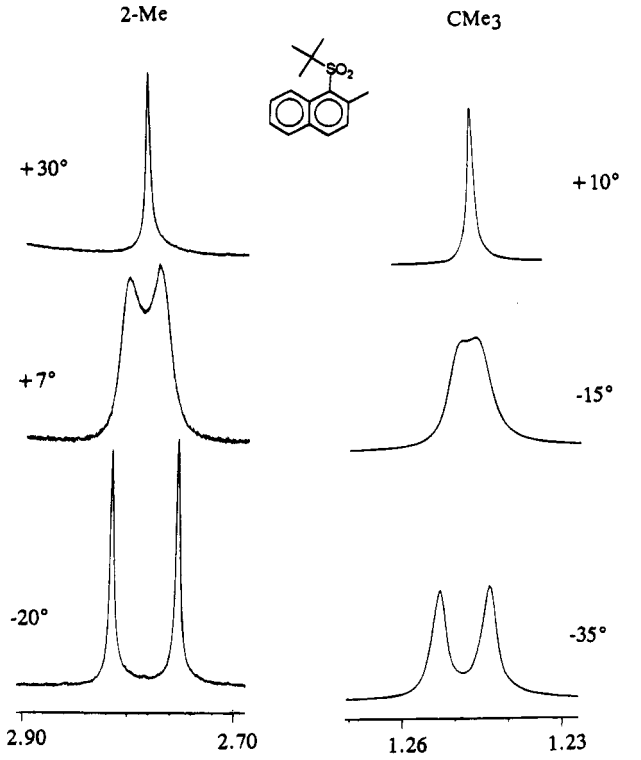


Figure 2. Temperature dependence of the aliphatic region of the ^1H spectrum (600 MHz in CD_2Cl_2) of **4** (R = Bu^t) in the presence of a 20:1 molar excess of an enantiomerically pure chiral agent (TFAE, see text), showing the presence of two exchanging conformational enantiomers. The horizontal scale of the *tert*-butyl signal (right) has been enlarged by a factor of five with respect to that of the 2-methyl signal on the left (the vertical scales are arbitrary).

temperature these signals coalesce in a reversible manner yielding (line shape simulation) a ΔG^* value (14.6 kcal mol^{-1}) higher than those of **3** (R = Pr^i) and **2** (R = Et), the increasing enantiomerization barrier reflecting the increasing bulkiness of the substituents R (Table 1). As a consequence the barrier for **1** (R = Me) is expected to be lower than that measured (7.2 kcal mol^{-1}) for **2** (R = Et). This accounts[6] for the absence of any NMR observable dynamic behavior in the spectrum of **1**, even at −135 °C (in the presence of TFAE). Barriers lower than about 6−7 kcal mol^{-1}, in fact, are NMR detectable at temperatures too low (≤−140 °C) to keep this sulfone (and the excess of TFAE as well) in solution.

When two equivalent sulfonyl groups are present in the symmetric positions 1,5 (and two methyl groups are also symmetrically placed in positions 2,6), such as in **5**, the chirality created by the pair of stereogenic naphthyl−sulfur axes makes possible the existence of two conformational diastereoisomers (Scheme 2).

That with a center of symmetry corresponds to a meso form (**5a**), the other to a racemic form (**5b**, **5b′**). Both species were observed in unequal proportions below −40 °C (for instance in toluene-d_8 the ratio is 4:1, as shown in Figure 3). The ΔG^* value for the interconversion of the more into the less stable form[7] was found equal to that of **4** in the same solvent (both are 14.6 kcal mol^{-1} in CD_2Cl_2, Table 1). For it is conceivable to expect a barrier for **5** nearly equal to that of **4** since the second sulfonyl and the second methyl substituents lie so farther away that they should not appreciably interfere with the rotation about the other naphthyl−sulfur bond.

The assignment of the meso and racemic structure to these conformers cannot be safely made using the NMR shifts: a possible approach could be that based upon the different polarity of the racemic conformer **5b, 5b′** (which does not have a negligible dipole moment) with respect to the meso conformer **5a** (which has a null dipole moment owing to the symmetry). The conformer ratios of **5** were thus determined at −60 °C in solvents of increasing dielectric constants, i.e. toluene-d_8, $CDCl_3$, CD_2Cl_2, and acetone-d_6 (the corresponding dielectric constants[8] being, respectively, 2.5, 6.5, 13.5, and 30.5). The respective conformers ratios turned out to be 4.0, 3.5, 2.5, and 2.0: thus, it appears reasonable to suggest that the nonpolar meso conformer **5a** is the more stable form since its proportion *decreases* with the *increasing* solvent polarity. This result also agrees with the MM calculations[9] that predict the meso (**5a**) to be more stable than the racemic (**5b,5b′**) form (see further). These

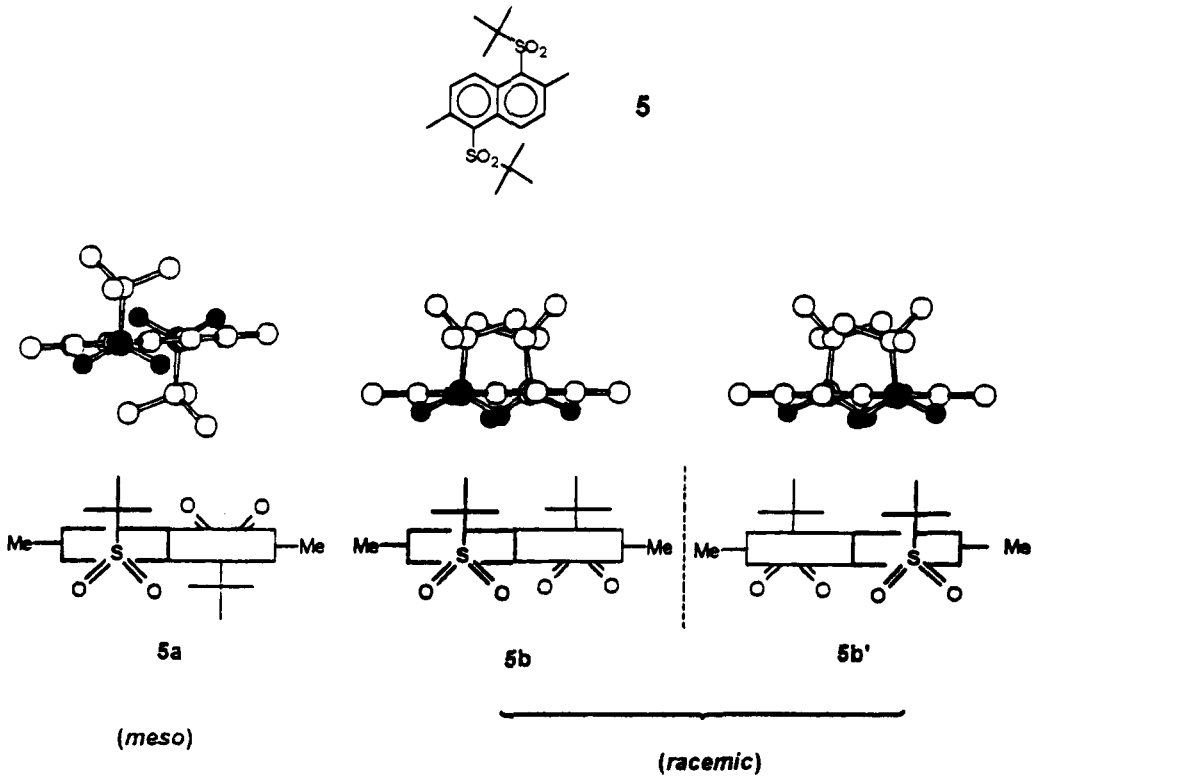
(6) Such a negative result might be alternatively explained by assuming that 1 adopt a symmetric conformation, unable to generate conformational enantiomers, contrary to the case of the other sulfones (for instance the naphthyl moiety of 1 might lie in a plane bisecting the SO_2 angle). However MM calculations that had correctly predicted asymmetric conformations for **2**−**4** indicate that the same type of conformation should also be adopted by **1**.

(7) A transmission coefficient of 2 was employed in the calculation of ΔG^* for **5** to account for the possibility that rotation of each of the two *t*-Bu-SO_2 moiety allows for the meso−racemic exchange.

(8) Landolt-Börnstein, Band II, Teil 6, Springer Verlag: Berlin, 1959.

(9) Still, W. C.; Mohamadi, F.; Richards, N. J. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T. Macromodel V4.5; Chemistry Department: Columbia University, New York, NY 10027.

Scheme 2



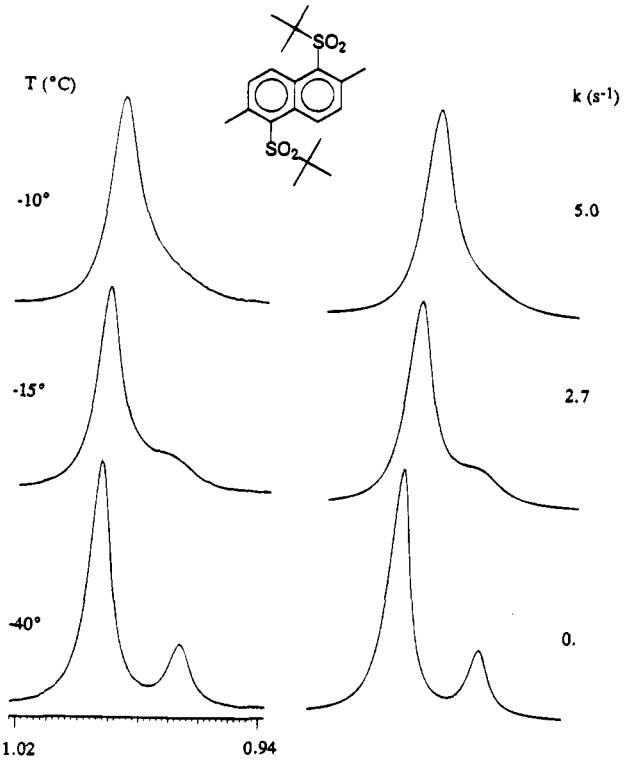


Figure 3. Experimental ^1H lines (left) of the *tert*-butyl group of **5** (300 MHz in toluene-d_8) at various temperatures, showing the presence of the exchanging meso (major) and racemic (minor) conformers. The computer simulation (right) has been obtained with the rate constants (k, in s^{-1}) indicated.

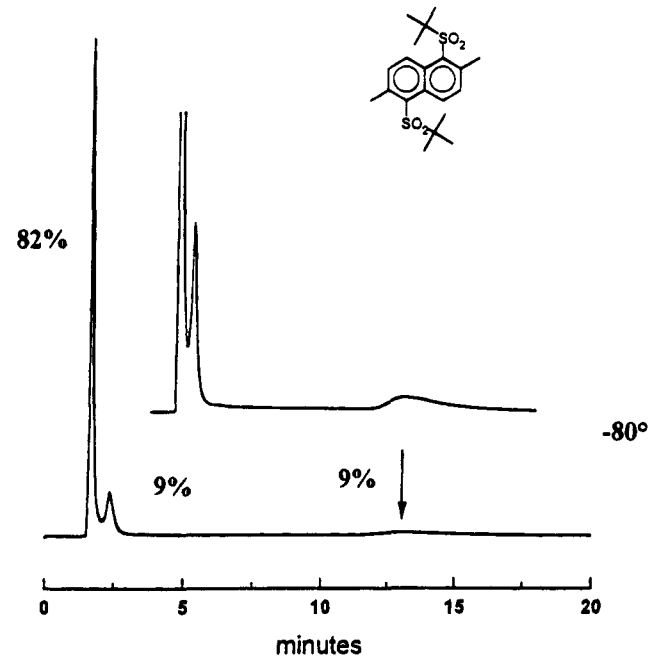


Figure 4. Low temperature (−80 °C) enantioselective chromatogram of **5** under slow exchange conditions, showing the three resolved conformational stereoisomers **5a**, **5b**, **5b'** with a relative intensity 82:9:9 (the inset is a vertically expanded trace). The retention factors for the three peaks are 0.24, 0.74, and 8.68, respectively.

conclusions, however, would appear more convincing if confirmed by a rigorous experiment, not requiring any kind of assumptions.

For this purpose derivative **5** was analyzed by low temperature HPLC on a brush type chiral stationary phase which has recently been used to separate interconverting atropisomers of aromatic compounds featuring hindered Ar−SO and Ar−CO bond rotations.[10] The NMR-determined rate constants indicate that, at temperatures approaching −80 °C, the half-life of the conformers of **5** would become longer than 1 h, thus allowing,

(10) Villani, C.; Pirkle, W. H. *Tetrahedron: Asymmetry* **1995**, *6*, 27 and references quoted therein.

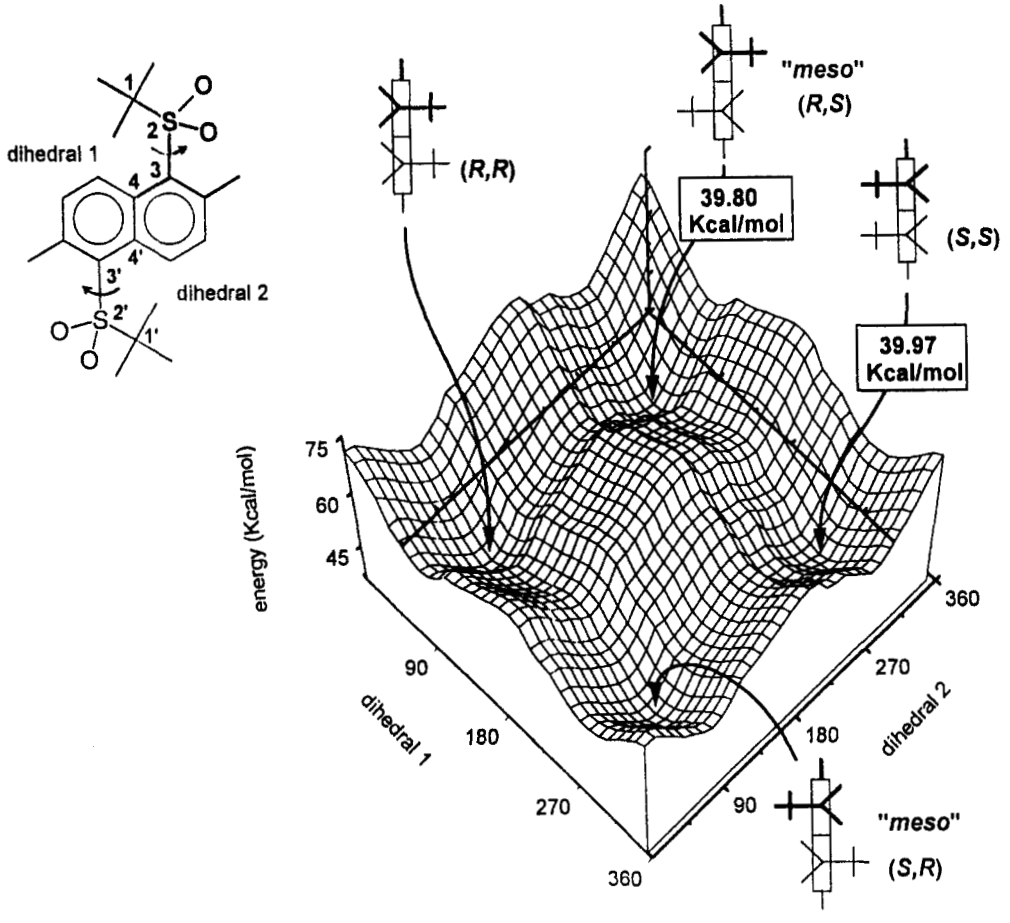


Figure 5. *MM-computed potential energy surface for the complete rotation about the two* $Ar-SO_2$ *bonds of* **5**.

in principle, a physical separation of **5a**, **5b**, **5b'** at that temperature. Indeed the chromatograms of **5**, obtained at temperatures between −60 °C and −80 °C (with eluent flow rates between 1.0 and 2.0 mL/min) display temperature- and flow-dependent deformations of peak shapes, indicating the occurrence of an on-column exchange process. When the maximum allowed flow rate (2.0 mL/min) is reached, the UV detected signal of **5** comprises a single, narrow peak at temperatures above −60 °C which broadens between −65 °C and −75 °C and eventually splits, at −80 °C, into three signals with a 82:9:9 relative intensity (Figure 4). Obviously the most intense peak corresponds to the meso (**5a**) form whereas the less stable racemic form yields the pair of equally intense peaks (9% each) due to the *RR* and *SS* enantiomers. By means of this experiment, therefore, the assignment has been unambiguously established.

The internal motions of **5** were also studied by molecular mechanics calculations using the MacroModel (Amber*) program:[9] both the distribution of the conformers (computed energy difference equal to 0.17 kcal mol^{-1}, favoring **5a**) and the rotational activation energies available for the meso−racemic interconversion are in the same range as the experimental values. A three-dimensional potential energy surface for a 360° rotation of both the $Ar-SO_2$ bonds of **5** is displayed in Figure 5. All the stable conformations are predicted to have the *tert*-butyl groups almost perpendicular to the plane of naphthalene (computed values 83°) and the two possible pathways for the interconversion process, in which one of the *tert*-butyl groups remains static while the other undergoes a 180° rotation past H-8 (H-5) or, alternatively, past Me-2 (Me-6), were predicted to have barriers of 15.8 and 13.8 kcal mol^{-1}, respectively (experimental $\Delta G^* =$ 14.6−14.8 kcal mol^{-1}, Table 1). According to this theoretical approach the second pathway (involving the passage of the *tert*-butyl moiety over the methyl groups in position 2 or 6) might be considered as more favored since it exhibits a 2 kcal mol^{-1} lower activation enthalpy.

Experimental Section

Material. Naphthyl sulfones **1**−**5** were obtained by 3-chloroperbenzoic acid oxidation of the corresponding sulfoxides:[2b,11] chromatography on silica gel (CH_2Cl_2/MeOH 99/1) gave pure compounds in 80−85% yields.

1-(Methanesulfonyl)-2-methylnaphthalene (1). IR (KBr): 1319, 1296, 1146, 1134 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$): δ 2.95 (s, 3H), 3.25 (s, 3H), 7.38 (d, 1H), 7.54 (t, 1H), 7.66 (t, 1H), 7.88 (d, 1H), 7.96 (d, 1H), 8.97 (d, 1H). Anal. Calcd for $C_{12}H_{12}O_2S$: C 65.43; H 5.49; S 14.55. Found: C 65.45; H 5.52; S 14.53.

1-(Ethanesulfonyl)-2-methylnaphthalene (2). IR (KBr): 1322, 1294, 1146, 1128 cm^{-1}. ^1H NMR (200 MHz; CD_2Cl_2): δ 0.95 (t, 3H), 2.70 (s, 3H), 2.75 (q, 2H), 6.95 (d, 1H), 7.20 (t, 1H), 7.37 (t, 1H), 7.56 (d, 2H), 8.97 (d, 1H). Anal. Calcd for $C_{13}H_{14}O_2S$: C 66.64; H 6.02; S 13.68. Found: C 66.59; H 5.98; S 13.57.

2-Methyl-1-(propane-2-sulfonyl)naphthalene (3). IR (KBr): 1321, 1127 cm^{-1}. ^1H NMR (300 MHz; CD_2Cl_2): δ 1.3 (d, 6H), 2.90 (s, 3H), 3.50 (m, 1H), 7.40 (d, 1H), 7.53 (t, 1H), 7.63 (t, 1H), 7.88 (d, 1H), 7.98 (d, 1H), 8.96 (d, 1H). Anal. Calcd for $C_{14}H_{16}O_2S$: C 67.70; H 6.49; S 12.90. Found: C 67.73; H 6.47; S 12.87.

2-Methyl-1-(2-methylpropane-2-sulfonyl)naphthalene (4). IR (KBr): 1285, 1115 cm^{-1}. ^1H NMR (300 MHz;

(11) Casarini, D.; Lunazzi, L.; Gasparrini, F.; Villani, C.; Cirilli, M.; Gavuzzo, E. *J. Org.Chem.* **1995**, *60*, 97.

$CDCl_3$): δ 1.4 (s, 9H), 2.98 (s, 3H), 7.40 (d, 1H), 7.50 (t, 1H), 7.62 (t, 1H), 7.82 (d, 1H), 7.98 (d, 1H), 9.30 (d, 1H). Anal. Calcd for $C_{15}H_{18}O_2S$: C 68.67; H 6.91; S 12.22. Found: C 68.64; H 6.94; S 12.24.

2,6-Dimethyl-1,5-bis(2-methylpropane-2-sulfonyl)naphthalene (5). IR (KBr): 1312, 1119 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ 1.4 (s, 9H), 2.98 (s, 3H), 7.50 (d, 1H), 9.58 (d, 1H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.2 (Me), 25.1 (Me), 64.3 (q), 128.3 (q), 131.9 (CH), 132.2 (q), 132.7 (CH), 143.4 (q). Anal. Calcd for $C_{20}H_{28}O_4S_2$: C 60.57; H 7.12; S 16.17. Found: C 60.62; H 7.09; S 16.15.

The HPLC chiral separation was carried out with a 250 × 4.6 mm (*S,S*) Whelk O-1 column (Regis Chemical Co., Morton Groove, IL). The low temperature experiments (−80 °C) were performed by placing the column into a Dewar flask containing dry ice/2-propanol; eluent CH_2Cl_2/MeOH 98:2, flow rate 2 mL/min, UV detection at 300 nm. Variable temperature NMR spectra were obtained at 200 or 300 MHz, except for **5** where a 600 MHz spectrometer was employed to enhance the separation of the signals of the *tert*-butyl groups. The samples for the low temperature spectra of **1** and **2** were prepared by connecting the NMR tubes, containing a C_6D_6 solution of the compounds, to a vacuum line and condensing the gaseous CHF_2Cl by means of liquid nitrogen. The tubes were subsequently sealed *in vacuo* and introduced in the precooled probe of the spectrometer. The line shape simulations were performed with a computer program based on the Block equations.[12] The chemical shift separation of the anisochronous methylene hydrogens of **2** (0.234 ppm at −145 °C in CHF_2Cl) decreases on rising the temperature by approximately 0.025 ppm every 10 °C and that of the isopropyl methyl groups of **3** (0.38 ppm at −80 °C in CD_2Cl_2) decreases by 0.02 ppm every 10 °C. The vicinal *J* couplings involving the diastereotopic groups of **2** and **3** were found equal for each pair of anisochronous signals. However, the low temperatures required to make these lines anisochronous also broaden the spectral width, so that the errors in the measurements of these *J* values (which in principle should not be exactly equal) are probably larger than the expected differences.

Acknowledgment. Thanks are due to the High Field NMR Laboratory of the University of Florence and to Mr. M. Lucci for the 600 MHz spectra. This work was carried out with the financial support of the Ministry of the University and Scientific Research (MURST) and the National Research Council (CNR), Rome.

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(12) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org.Chem.* **1986**, *51*, 517.