Conformational Studies by Dynamic NMR. 99.[1] Experimental and Computed Determination of Rotation Barriers in the Crystalline State: The Case of Naphthylphenylsulfoxide

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Abstract: The ^{13}C NMR CP-MAS spectrum of 2-naphthylphenylsulfoxide in the solid state displays line broadening effects due to the restricted rotation about the Ph−S bond. Line shape simulation of the temperature-dependent traces allowed the corresponding barrier to be determined in the solids (14.7 kcal mol^{-1}). By making use of the information obtained from single-crystal X-ray diffraction, this barrier could be satisfactorily reproduced by theoretical calculations (14.5 kcal mol^{-1}) that take into account the correlated phenyl motion involving a large set of molecules in the crystalline state

The rotational processes that allow the interconversion between conformers (or topomers) have been widely investigated by dynamic NMR spectroscopy in solution.[3] These studies are often accompanied by theoretical calculations that usually reproduce quite satisfactorily the experimental barriers.[4] This is because the approximation of considering an isolated molecule model does not conflict too severely, in the majority of cases, with the actual situation. The solvent effects upon the barrier are relatively modest and, if necessary, can be accounted for by introducing in the calculations appropriate parameters related to the dielectric constant of the medium.

The situation is quite different when dealing with molecules in the solid state, where the corresponding conformers often cannot even interconvert as a result of the severe constraints of the crystalline environment.[5] When interconversion processes can be observed, the barriers involved are much higher than in solution,[6–11] because of the restrictions to the internal motions brought about by the surrounding lattice. For these reasons computations that treat the molecule as an isolated entity cannot reproduce the values of the barriers measured in the solid state. There are, however, computational approaches that take into account the situation of a molecule in the crystal[5a,12–14] and that have been applied to describe the conformation of polymers in the solids[15] and the dynamics of reorientation within the lattice.[5,12,14–16] However, there are not available examples where theory and experiment have been both applied to investigate the interconversion of conformers (or topomers) of organic molecules in the crystalline state. We thus searched for a case where the barrier for such a process could be measured in the solids with the purpose of reproducing this value by theoretical methods.

The title compound (2-naphthylphenylsulfoxide, **1**) turned out to be appropriate for this scope. MM computations,[17] which treat the molecule as an isolated object, provide the energy map as a function of the rotation about the phenyl−S and naphthyl−S bonds (*x*- and *y*-axis, respectively, as in Figure 1). The rotation about the phenyl−S bond (dashed line of Figure 1) corresponds to a topomerization process that exchanges the ortho, ortho′ and meta, meta′ positions with a computed barrier

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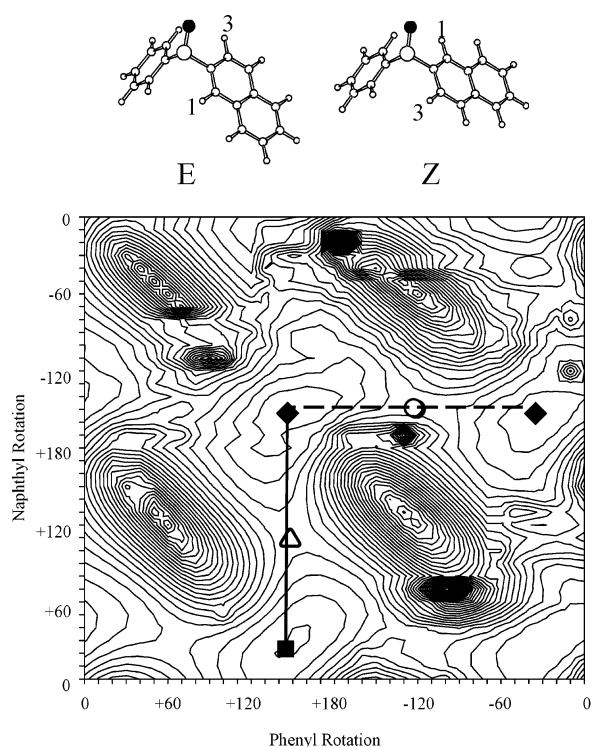
FIGURE 1. Energy map of **1** (considered as an isolated molecule) computed as a function of the rotation about the naphthyl−SO and phenyl−SO dihedral angles. The two lines represent the pathways connecting the ground states. The diamonds and the square identify the grounds states of the *E* and *Z* conformers, respectively. The circle and the triangle identify the two possible transition states (relative energies 1.9 and 1.8 kcal mol^{-1}, respectively).

of 1.9 kcal mol^{-1}. The rotation about the naphthyl−S bond (solid line of Figure 1) corresponds to the exchange of the conformer where the C1-C2-S-O dihedral angle is 29.5° (thus *Z*-conformer) with the nearly equally stable (within the computing approximations) conformer where this angle is −150.4° (*E*-conformer). This second computed barrier (1.8 kcal mol^{-1}) is almost equal to the previous one, as conceivable for the case of an isolated molecule. According to this model, the two rotation processes are not correlated but take place independently of each other, as indicated by the fact that the two lines of Figure 1 are parallel to the respective axes.[18,19]

Even allowing for the approximation involved in this theoretical approach, the computed barriers are predicted to be too low for an experimental determination by NMR spectroscopy; even at −160°C, in fact, we could not detect any evidence of such a motion in solution (see Experimental Section).

Effects due to a rotation process could be, however, observed in the crystals of **1** near ambient temperature by means of CP-MAS NMR spectroscopy. This suggests that the corresponding barrier has increased in the crystal with respect to the value expected in solution. As
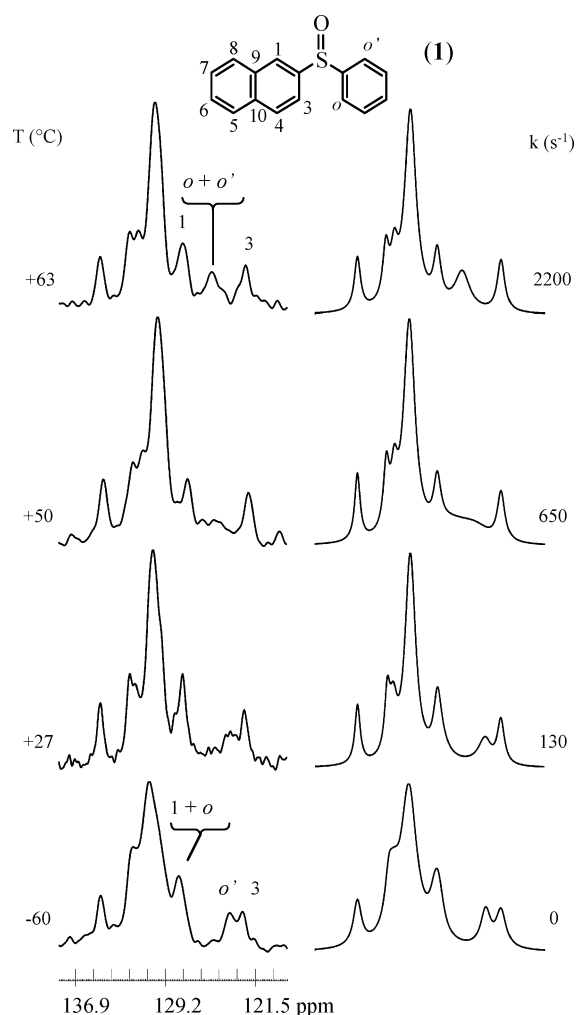
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FIGURE 2. (Left) Relevant region of the solid-state CP MAS ^{13}C NMR spectrum of **1** (75.5 MHz) as function of temperature. (Right) Spectra simulated with the rate constants indicated.

displayed in Figure 2, where the relevant portion of the solid-state spectrum of **1** is reported as a function of temperature, the two ortho carbons of the phenyl ring exhibit a single signal (125.0 ppm)[20] at +63°C since in these conditions the Ph−S rotation is fast in the NMR time scale. This line broadens considerably on cooling and eventually splits, below −30°C, into a pair of lines at 123.3 and 127.6 ppm, the latter being accidentally coincident with that of carbon C-1 of the naphthalene ring (in Figure 2 these two lines are indicated[21] as *o* and *o'*). Such a spectral behavior is completely analogous to that reported for the intramolecular motions occurring in the solid state (e.g., bond rotation,[7,8a,b,9a−e,11a] ring inversion,[6a,11e] tautomerism,[22]): in the cases reported in the mentioned references these spectra were interpreted by the same
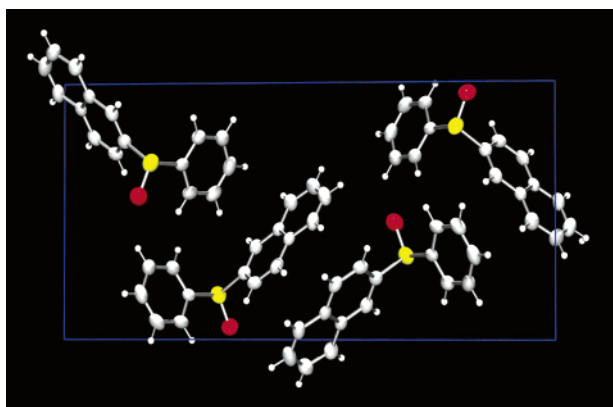
FIGURE 3. Plot of the unit cell content view along the 100 direction.

type of line shape simulation used for the dynamic exchange in solution.[23] The spectra of Figure 2 thus provide evidence that the rotation rate of the phenyl group varies with temperature, rendering the ortho carbons inequivalent, thus anisochronous, at low temperature (the analogous splitting expected for the meta carbon line could not be observed because of overlapping with a number of the naphthalene carbon signals). All of the lines of the naphthyl carbons, on the contrary, remain sharp, indicating the lack of a detectable rotation process about the naphthyl–S bond and suggesting, therefore, that the naphthyl moiety appears to be firmly packed in the lattice. Line shape simulations[24] (Figure 2, right) yield the rate constant for the Ph–S rotation process at various temperatures. The corresponding $\Delta G^{\ddagger}$ value (14.7 ± 0.4 kcal mol^{-1})[25] shows that the barrier in the solids is, as conceivable, much higher than that computed for the isolated molecule.

The structure obtained by single-crystal X-ray diffraction (Figure 3) corresponds to the *E*-conformer whose shape, apparently, fits the crystal cell better than the essentially isoenergetic *Z*-conformer. It should be also outlined that although the chirality of the sulfur atom implies the existence of a pair of enantiomers, the examined crystal contains only the enantiomer with the

configuration *S* since compound **1** crystallizes as a conglomerate of enantiomorphic crystals. This was ascertained by means of an enantioselective HPLC determination where a random mixture of a great number of crystals yielded two distinct peaks, having the same enantiomer ratio (2:1) as that determined by the ^{13}C NMR solution spectrum in a chiral environment[26] (the enrichment is due to the use of enantiopure menthol in the synthetic procedure, as reported in Supporting Information). On the contrary, examination of a single crystal in the HPLC experiment yielded a single peak, corresponding to only one of the two enantiomers. In addition use was made of the X-ray powder spectrum (see Supporting Information) to ensure that the bulk phase employed for the solid-state CP-MAS NMR experiment is the same as that for which the crystal structure was derived.

The data obtained from the X-ray diffraction determination were instrumental for calculating the Ph–SO rotation barrier in the crystal. These computations were performed by employing a local version of the MM3 program, upgraded in order to deal with crystal lattices.[13] Minimization was carried out with the Newton–Raphson algorithm using the standard MM3(92) force field.[27]

To estimate the rotational barrier of the phenyl group in the solid state, we used the DRIVE option of the MM3 program to force the phenyl of the reference molecule (RM) to rotate within the field generated by 256 surrounding molecules (SMs) positioned in accord with the (time and space) averaged structural parameters observed in the X-ray crystal structure determination. The SMs have been chosen on the basis of a cutoff radius of 20 Å from the RM. In this first attempt the rotation of the phenyl was hampered by its clashing with a nearby molecule.

Indeed, as highlighted in Figures 3 and 4, the structure can be formally "cut" in layers perpendicular to the *c*-axis because both naphthyl and phenyl groups are "segregated", i.e., they mainly interact with (are close to) themselves. In a second run, we have followed the phenyl rotation by allowing the first enclosure shell (ES) of the RM (i.e., a cluster of nine nearest-neighbors molecules surrounding the RM; see Figure 4) to relax. This approximation is obviously valid only if, upon rotation of the phenyl of the RM, all molecules of the ES return to their original position and if the set of SMs is large enough (here 247 molecules) to contain at least a second shell of rigid next-nearest neighbors to ensure that the ES is not allowed undue freedom of motion. Within this approach, on applying the suitable DRIVE option, the phenyl smoothly rotates about the S–C bond (Figure 5), the RM and the ES return on themselves, and the computed barrier (14.5 kcal mol^{-1}) matches that measured in the solid-state CP MAS NMR experiments (14.7 kcal mol^{-1}). When applied to the naphthyl–SO bond rotation these calculations showed that this motion had such an exceedingly high activation energy as to prevent

(21) The assignment of the upfield signal to the carbon syn to the oxygen of the SO moiety (labeled *o'* in Figure 2) is the result of a B3LYP/6-31+G(2d,p) ab initio calculation, as implemented in the Gaussian98 A.9 program (courtesy of Prof. D. Nanni, University of Bologna). Because of the analogous values observed in the case of **1** for the shifts in solution and in the solids, the assumption was made that the sequence of the two ortho and ortho' ^{13}C signals, computed for the isolated molecule, is the same as that occurring in the crystal. It has to be stressed, however, that such an assignment is immaterial for the experimental determination of the rotation barrier, since the opposite assignment would obviously yield the same $\Delta G^{\ddagger}$ value.

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(23) Above +63 °C, the averaged line of the ortho carbons does not sharpen further, as would occur in the solution spectra, but begins to broaden because the motional frequency moves from the site exchange regime to the dipolar broadening regime,[7,9b,e] a feature typical of NMR dynamics in the solids (see also: Frey, M. H.; DiVerdi, J. A.; Opella, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 7311. Ripmeester, J. A. *J. Inclusion Phenom.* **1988**, *6*, 31. Ratcliffe, C. I.; Ripmeester, J. A.; Buchanan, G. W.; Denike, J. K. *J. Am. Chem. Soc.* **1992**, *114*, 3204.). Above this temperature this type of line shape analysis[24] could not be applied anymore.

(24) QCPE program 633; Indiana University: Bloomington, IN.

(25) Within the experimental uncertainty the $\Delta G^{\ddagger}$ value was found to be independent of temperature, indicating that the $\Delta S^{\ddagger}$ term must be quite small.

(26) The ^{13}C spectrum was obtained at 150.9 MHz (CDCl$_3$ as solvent) in the presence of a nearly equimolecular amount of the enantiopure (*R*)-*l*-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837).

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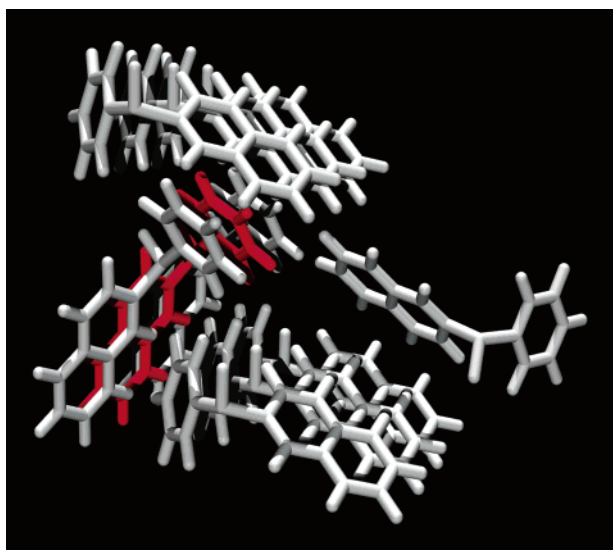
FIGURE 4. Plot of the reference molecule (red) and of its enclosure shell (9 molecules, gray)
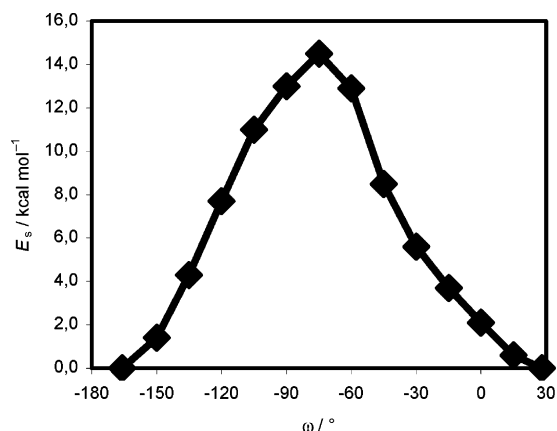

FIGURE 5. Computed relative energy of **1** in the crystalline state (see text) as function of the Ph–S rotation angle (ω).

the possibility of a rotation process, thus indicating that the naphthyl ring is firmly locked within the crystal lattice, in agreement with the experimental NMR observation.

In conclusion, these results indicate that it is possible, in suitable conditions, to interpret satisfactorily the conformational processes occurring in the solid state by means of an appropriate theoretical approach. The barrier involved in the present case has been, in fact, reproduced with an excellent accuracy.

Experimental Section

2-Naphthylphenylsulfoxide[28] (**1**) has been obtained by means of the general procedure reported in the literature[29] (see Supporting Information).

NMR Spectroscopy. The ¹H and ¹³C assignments in solution were obtained by means of DPFGSE-NOE, COSY, DEPT, gHSQC, and gHMBC sequences. The very low temperature (−160° C) experiment, which failed to show the effects of restricted rotation in solution, was carried out on a sample prepared by connecting to a vacuum line the NMR tube containing compound **1** dissolved in C_6D_6 (for locking purpose) and condensing therein the gaseous solvents CHF_2Cl and $CHFCl_2$ (in a 4:1 proportion) by means of liquid nitrogen. The tube was 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. The ¹³C NMR solid-state CP-MAS measurements have been obtained at 75.45 MHz. The sample was tightly packed in a 7 mm zirconia rotor and spun about the magic angle at a speed of 3.8−4.2 kHz. The cross polarization was achieved using a ¹H-90 and a ¹³C-90 pulse of 4.5 μs, as required by the Hartmann−Hahn conditions. A contact time of 2 ms, a recycle delay of 10 s, and 2 K data points were used during the acquisition, and the number of scans ranged from 512 to 2000. The temperature in the rotor was allowed to stabilize for at least 15−20 min before the acquisition. The chemical shifts were calibrated by replacement, with respect to the lower frequency signal (29.4 ppm) of the adamantane.

HPLC analysis was performed at +20 °C on an enantioselective column (5 μm), 250 mm × 4.6 mm i.d., UV detected at 254 nm, flow rate 1 mL/min (hexane/*i*-Pr₂O 90:10), retention times 16.16 and 17.82 min.

Supporting Information Available: Synthetic methods, crystallographic data, X-ray powder spectrum, and molecular mechanics parameters for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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