

Multitechnique Investigation of Conformational Features of Small Molecules: the Case of Methyl Phenyl Sulfoxide

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The conformational distribution of methyl phenyl sulfoxide (a molecule representative of a very important class of reagents widely used in asymmetric synthesis) has been studied in two different phases of matter (gas phase and solution) by a comprehensive approach including theoretical calculations, microwave spectroscopy, liquid crystal NMR experiments, and atomistic molecular dynamics computer simulations. The aim was to investigate the combined action of intra- and intermolecular interactions in determining the molecule's conformational equilibrium, upon which important physicochemical properties (inter alia, the chemoselectivity) significantly depend. Basically, the results converge in describing the tendency of the molecule to favor stable conformations governed by intramolecular interactions (in particular, the expected optimization between steric repulsion and conjugation of π systems). However, significant solvent effects (whose "absolute" magnitude is actually difficult to assess, due to a certain "method-dependence" of the results) have been also detected.

1. Introduction

The study of conformational equilibrium of flexible molecules traditionally represents a central topic of chemistry (vide, for example, ref 1 where a wide selection of contributions and references concerning different techniques to investigate internal rotation in molecules is collected). Obtaining information about stable conformations, and, if possible, about the complete Conformational Distribution Function (CDF) is indeed very important, not only from a fundamental point of view but also for practical purposes, since physicochemical features of the molecules (such as acidity, basicity, lipophilicity, polarity, "spatial occupancy" and, in particular, chemoselectivity)² can depend, to a large or small extent, on their conformational equilibrium. This, in turn, automatically implies that any element influencing the molecular CDF could, in principle, play a role in determining the molecular properties. In the light of these considerations (and as a final link in this "chain" of effects), the following pivotal question arises: what are the factors affecting the distribution of rotational conformers (rotamers) of flexible molecules? The problem is, of course, very complex and many-sided, so that a fully exhaustive answer cannot be given in few words. Conformational equilibrium is ruled by the combined action of intramolecular and intermolecular interactions, their respective roles being more or less important according to the state of matter. In solids, intermolecular

interactions are very important, whereas the gas phase is the realm of intramolecular interactions. In between, there is the liquid state, where the molecular CDF is dictated by a balance between intra- and intermolecular interactions. In order to avoid misunderstandings, it is worth emphasizing that that which was said above does not automatically imply that stable conformations of a flexible molecule necessarily have to be different in different phases; however, one needs to be cautious in extrapolating results about stable conformations from one phase to another (regarding this, an intriguing example of dramatic conformational "sensitivity" to the phase is represented by the biphenyl molecule).³ Nowadays, the development of effective theoretical methods and the increasing power of computers make it possible to carry out sophisticated calculations able to quite accurately predict the stable conformations of molecules; anyway, the theoretical calculations are usually performed in vacuo, by considering an isolated molecule. The results so obtained can be compared directly with experimental data from gas-phase techniques, such as microwave spectroscopy (MW); on the contrary, the uncritical assumption that the same results hold also in solution (so ignoring solvent effects, in particular when nonaqueous or non-highly polar media are used) can be very treacherous. There exist, of course, quantum chemical methods treating also solvated molecules;⁴ that said, the theoretical treatment of solutes in a medium certainly does not pertain exclusively to quantum chemistry (QC). Indeed, an effective way to treat this kind of problem is represented by Monte Carlo (MC) and molecular dynamics (MD) computer simulation techniques.¹⁰ These methods are particularly useful as the resulting simulated conformational "scenarios" can be compared with experimental data giving information about the molecular CDF in fluid condensed phases. Among the experimental techniques available for this purpose, an important place

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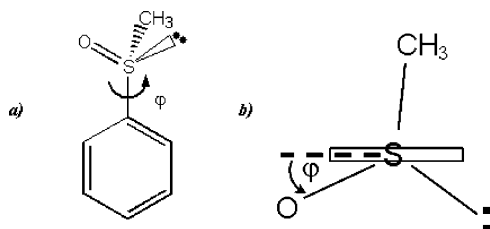


Figure 1. (a) Structure of Methyl Phenyl Sulfoxide (MPS) and the torsional angle φ with its positive sense of rotation; (b) top view of the molecule (the value $\varphi = 0^\circ$ is assumed when the $\text{S}=\text{O}$ bond is on the ring plane).

is occupied by NMR in liquid crystal solvents (LXNMR), a well-established experimental approach whose reliability is widely supported by literature.¹¹ In order to address systematically some of the general questions raised above about the conformational problem, in the present work, the molecule methyl phenyl sulfoxide (MPS, Figure 1) has been studied in gas phase and in solution. Several techniques, both experimental (MW, LXNMR) and theoretical (QC calculations, atomistic MD simulations) have been used and the results compared in order to better understand the nature of the underlying conformational mechanisms. The MPS molecule has been chosen as representative of a very important class of reagents widely used in asymmetric synthesis.¹²

The paper is organized as follows: in the next two sections, the results obtained by QC calculations and MW experiments will be described; subsequently, the conformational predictions from LXNMR and atomistic MD computer simulations will be presented; then, in order to get a comprehensive picture of the problem, all of the obtained data will be compared and discussed as a whole before developing our final considerations in the Conclusions section.

2. Quantum Chemical Calculations

The problem of the internal rotational potential in the MPS molecule has already been addressed by quantum chemical techniques. The early study,¹³ carried out at the HF/STO-3G and HF/3-21G* levels, suggested the most stable conformation is that characterized by having the $\text{S}=\text{O}$ group almost in the plane of the phenyl ring, the predicted value of the optimal torsional angle φ (defined in Figure 1) being 7° . Subsequent studies carried out at a higher level of theory (including approximate electron correlation, such as MP2/6-31+G*^{14,15} and B3LYP/6-311G*¹⁶) gave an optimized φ value in agreement with that obtained in ref 13. The different methods also provided similar predictions about the conformation of highest torsional energy: this has been predicted to be that in which the methyl group is almost on the plane of the phenyl ring ($\varphi \approx 110^\circ$). On the contrary, the different QC treatments give quite different values of the height of torsional barrier. In ref 13, a value of 34.7 kJ/mol was obtained, whereas smaller values were found by the aforementioned electron correlated techniques. In particular, a barrier of 21.3 kJ/mol resulted from refs 14 and 15, whereas Figure 5 of ref 16 shows a value of about 25.1 kJ/mol. The value reported in the quoted literature^{14,15} is in agreement with an experimental observation, suggesting the energy barrier should be smaller than 21 kJ/mol.¹⁷ In the present work, the potential energy curve for the internal rotation in MPS has been calculated at the B3LYP/6-31+G** level of theory.¹⁸ As shown in Figure 2, the molecular geometries corresponding to the most stable conformation ($\varphi_{\min} = 4.5^\circ$) and to the transition state ($\varphi_{\text{trs}} = 108^\circ$) agree quite well with the previous calculations.

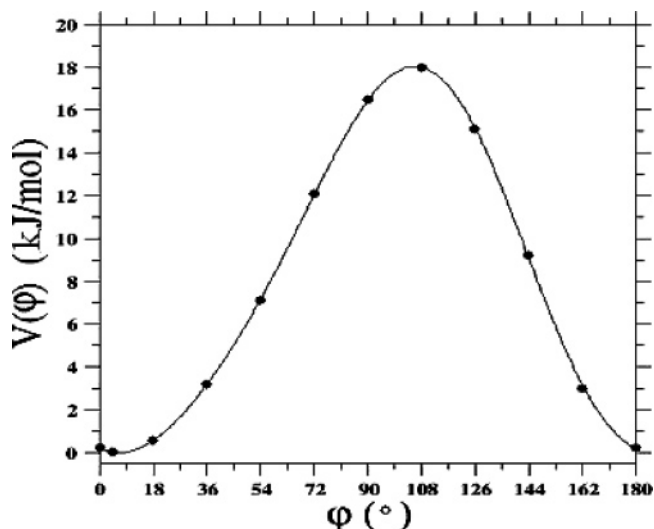


Figure 2. Theoretical torsional potential energy curve of methyl phenyl sulfoxide (MPS) calculated at B3LYP/6-31+G** level. Dots are the quantum chemical calculations while the curve is the fit to them.

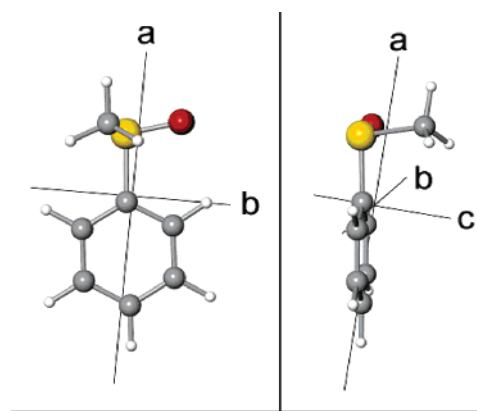
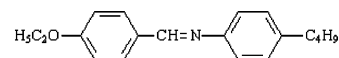


Figure 3. Two different views of MPS in its molecular frame defined by the inertia tensor principal axes.

EBBA



ZLI-1132

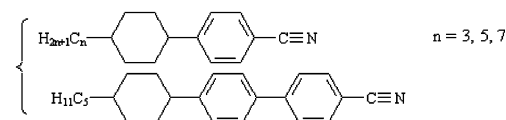


Figure 4. Chemical structure of used nematic solvents.

Figure 2 also shows that the calculated energy barrier (at this level of theory) amounts to 18 kJ/mol. This is in reasonable agreement with the previous MP2 result^{14,15} and fully consistent with the observation of ref 17. The QC data have been successfully fitted by the formula:

$$V(\varphi) = V_0 + V_2\{1 - \cos[2(\varphi - \varphi_2)]\} + V_4\{1 - \cos[4(\varphi - \varphi_4)]\} \quad (1)$$

The optimized value of the parameters of eq 1 are reported in Table 1.

The fit gives a value of $\varphi = 6.5^\circ$ for the most stable conformation, while it locates the transition state (18 kJ/mol higher with respect to the ground state) at $\varphi = 106^\circ$.

3. MW Experiment

Early experimental information on the potential energy surface associated with the torsional motion of the $\text{SO}(\text{CH}_3)$

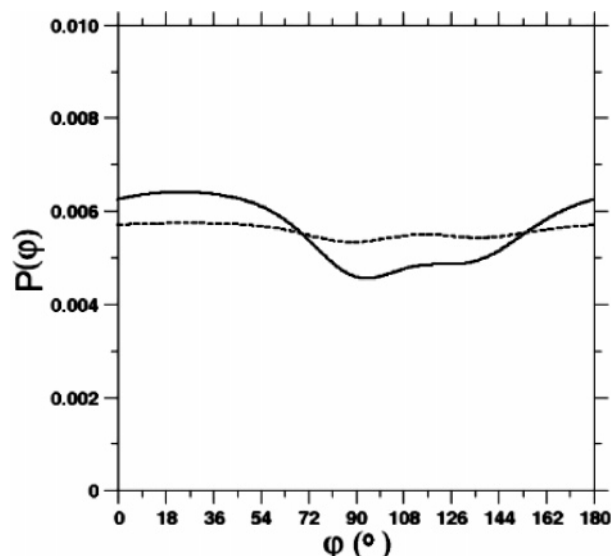


Figure 5. Conformational probability distribution $P(\varphi)$ of MPS in ZLI1132 (solid line) and EBBA (dashed line), produced by Maximum Entropy interpretation of LXNMR data.

TABLE 1: Parameters of the Fit of the B3LYP/6-31+G Data by eq 1**

k	V_k (kJ/mol)	φ_k (deg)
0	0.500	
2	8.909	12.06
4	−0.903	25.32

group in the MPS molecule were obtained from vibrational spectroscopic data.^{20–22} The most extended vibrational study is that by Gherseti et al.,²² in which the authors report the observation of bands at very low wavelengths and assign the torsion of the CH_3 group to the band at 203 cm^{-1} and the torsion of the OSCH_3 group to the band at 115 cm^{-1} . To our knowledge, beside the theoretical studies (mentioned in the above section) characterizing the geometry and the electronic potential surface of MPS, no direct experimental data on the structure of the isolated molecule are available. Rotationally resolved spectroscopy performed in free jet expansions is a valuable technique for the determination of molecular geometries and the investigation of conformational equilibria. Very low rotational temperatures are easily accomplished in the jet plume, allowing for a facile assignment of the spectrum, compared to spectroscopy performed at room temperature. Furthermore, the conformational distribution in the vapor prior to expansion (established at room or higher temperature) remains basically unaltered if conformational relaxation is prevented by a high energy interconversion barrier. This is due to the different relaxation rates that the various degrees of freedom achieve during the adiabatic expansion; it has been shown²³ that the upper limit of the barrier for which relaxation takes place in Ar is around 400 cm^{-1} . Additionally, the same study²³ has shown that the expansion conditions can be tuned to prevent or enhance relaxations: for example, when using He, the conformational relaxation is quenched because collisions are less effective. Thus, if different conformations are possible and if they are significantly populated at the temperature established prior to the expansion, then different rotational spectra can be observed and assigned, and the molecular geometries can be determined. The Stark and pulse-modulated free jet absorption millimeter-wave spectrometer used in this study and working in the range 60–78.3 GHz has been previously described.^{24,25} Solid MPS (purchased from Aldrich and used without further purification) was heated to about $50\text{ }^\circ\text{C}$ ahead of the nozzle while a stream of the carrier

TABLE 2: Spectroscopic Constants of MPS

A/MHz	3136.80(1)
B/MHz	965.05(1)
C/MHz	824.52(1)
D_J/kHz	0.047(7)
D_{JK}/kHz	0.17(2)
D_K/kHz	0.14(5)
N^a	36
σ/kHz	7

^a Number of observed transitions.

TABLE 3: MW-Refined Structure of MPS

	r_e (B3LYP 6-31+G**)	r_0 (structural fit)
$\text{O}\hat{\text{S}}\text{C}_{\text{ar}}/\text{deg}$	107.1	94.(2)
$\varphi_{(\text{CCSO})}/\text{deg}$	4.7	5.(1)
$\text{C}_{\text{me}}\hat{\text{S}}\text{O}/\text{deg}$	106.2	100.(1)
A/MHz	3084.7	3137.0
B/MHz	943.0	965.1
C/MHz	805.0	824.5

gas (Ar or He) at a pressure of $\sim 240\text{ mbar}$ was flown over it. In this way, the concentration of MPS in the mixture was estimated to be between 1 and 2%. The mixture was then expanded to about $5 \times 10^{-3}\text{ mbar}$ through a continuous nozzle with a diameter of 0.35 mm. The accuracy of the frequency measurements is estimated to be better than 0.05 MHz. The global minimum quantum chemical geometry (vide section above) indicates that MPS is a prolate near symmetric top, with components of the dipole moment in all three directions of the principal axes of the inertia tensor of the molecule (Figure 3).

Given the frequency range in which our spectrometer operates, we estimated the μ_a R-type transitions as too weak to be observed (because of the high rotational quantum numbers involved), and thus we searched for μ_b and μ_c R-type spectrum. The first assigned lines were those associated with low J high K_a quantum numbers, which degenerate for μ_b and μ_c . Then, we progressively assigned lower K_a transitions resolving the single μ_b and μ_c lines. The measured rotational transitions (given in Table SI-1 of the Supporting Information) were fitted with Watson's semirigid Hamiltonian in the "S" reduction and I' representation.²⁶ The rotational and centrifugal distortion constants are reported in Table 2.

The experimental rotational constants are in agreement (within 2%) with those calculated at the optimized geometry with the B3LYP/6-31+G** method, and only small adjustments of the structure were needed to exactly reproduce the observed rotational constants. The molecule has a shallow potential energy surface for the φ torsion around the $\text{S}-\text{C}_{\text{ar}}$ bond and also the geometry of the $\text{SO}(\text{CH}_3)$ group is very sensitive to electronic effects. For these reasons, starting from the QC geometry, we adjusted slightly the $\text{O}\hat{\text{S}}\text{C}_{\text{ar}}$ angle, the $\varphi_{(\text{CCSO})}$ angle and the $\text{C}_{\text{me}}\hat{\text{S}}\text{O}$ angle, in order to reproduce the observed rotational constants. The results of the fit are reported in Table 3. It can be seen that in the observed conformation, the $\text{S}=\text{O}$ of the methylsulphonyl group is only slightly twisted (φ_{min} is about 5°) with respect to the phenyl ring, so confirming that this is the global conformational minimum. As stated above, different conformational species could be observed in the free jet plume if the conformational population prior to the expansion is not negligible and relaxation is prevented. This can be achieved by using a lighter carrier gas: for this reason, a second free jet spectrum was recorded using He as carrier gas, instead of Ar. No new lines were observed, probably because no other conformations are significantly populated at the stagnation temperature. Another attempt has been made to observe torsional vibrational satellites, by using a conventional microwave

TABLE 4: LXNMR Optimized Torsional Parameters for MPS Nematic Solutions

	MPS in ZLI1132	MPS in EBBA
$\varphi_{\min}/\text{deg}$	16 ± 11	44 ± 2
$V_2/\text{kJ mol}^{-1}$	4.0 ± 0.3	15 ± 4
$\text{Car}\widehat{\text{S}}\text{C}_{\text{me}}/\text{deg}^a$	94.0 ± 1.0	

^a Assumed the same for both the solvents.

spectrometer equipped with a heated Stark cell, but the high-temperature spectrum resulted too weak. Such a weak spectrum at high temperature is an indication of the presence of low-lying energy levels over which the molecular population is spread.

4. Conformational Analysis by LXNMR Methods

The NMR spectra of 10% w/w solutions of MPS in ZLI1132 and EBBA nematic solvents (Figure 4) were recorded at room temperature on a Bruker AC 300 (working at 7.04 T) and on a Bruker AVANCE 500 (working at 11.7 T); then, the spectra were analyzed and the obtained dipolar coupling constants D_{ij} (given in Table 1 of ref 27) were interpreted by making use of the Additive Potential (AP) Model,²⁸ in order to get orientational and conformational information concerning the solute [the interested reader is referred to ref 27 and, in particular, to its Supporting Information (SI), for all experimental and theoretical details].

MPS has been assumed as composed by two “rigid” subunits (the phenyl ring and the methylsulphonyl group) keeping a fixed internal structure as they rotate relative to each other. The fragments’ geometries were, as usual, borrowed from other experimental techniques and/or from theoretical calculations; then slightly adjusted, when necessary, to fit the data. Following a simplifying assumption commonly found in literature,^{11,29} the solute’s sub-structures were considered basically solvent-independent; then, MPS shares common subunits geometries (reported in Table A2 of SI of ref 27) in both the used solvents. In the frame of the AP analysis of LXNMR data, the CDFs of MPS in the two solvents were described by the following simple twofold torsional potential:

$$V(\varphi) = V_2\{1 - \cos[2(\varphi - \varphi_{\min})]\} \quad (2)$$

The best-fit values of V_2 and φ_{\min} for the two solvents, together with the adjusted common $\text{Car}\widehat{\text{S}}\text{C}_{\text{me}}$ angle, are given in Table 4. Looking at the AP-LXNMR results of Table 4, it is possible to realize at once that both the position of the minimum and the height of the barrier of the MPS torsional potential are significantly affected by the nature of solvent. In ZLI1132, the obtained φ_{\min} (within its large range of standard deviation) is safely compatible with theoretical calculations and MW results (as already reported at p. S9 of SI of ref,²⁷ fixing $\varphi_{\min} \sim 7^\circ$ implies only a slight worsening of the fit of D_{ij} s), even though the barrier is significantly lower than that predicted by calculations in vacuo (so confirming what already emphasized in early studies,¹³ by comparing theoretical predictions with experimental results from ^{13}C NMR in isotropic solutions¹⁷). On the contrary, the most stable conformation for MPS in EBBA ($\varphi_{\min} \cong 44^\circ$) corresponds to a quite unexpected, very large displacement of the $\text{S}=\text{O}$ group with respect to the aromatic ring. This apparent anomaly induced us to reanalyze the same LXNMR dipolar coupling data sets by making use of another well-established model based on the statistical principle of maximum entropy,³⁰ originally proposed in the context of information theory: the so-called maximum entropy (ME) method.^{31,32} The ME method,

providing the “least-biased” estimate possible on the given information, is able to directly produce the probability distribution curves for the MPS rotamers. Unfortunately, it is well-known^{11,32} that ME, in its original formulation,^{31,32} suffers of an intrinsic “physiological” limitation: since its effectiveness is based on the “content of information” available from the data, when the data are “poor” the estimates suggested by ME tend to be quite “uninformative” about constant curves. In the case of dipolar couplings, the content of information is intrinsically related to the degree of ordering of the solute: this is the reason why solutes with low orientational order lead to “unrealistic” very flat ME-predicted distributions. Correctives to the ME (as the so-called “constrained” ME³³ and “mixed” a priori-ME³⁴ approaches) have been proposed to overcome this limitation; anyway, this inevitably implies the introduction of “biases” in the treatment. In the present work, we did not utilize these modified-ME approaches, since our intention was that of testing the AP results by using another method, chosen to be “conceptually” as different as possible from the “biased” AP model; thus, the ME in its original formulation^{31,32,35} has been applied. The resulting probability distributions are shown in Figure 5.

Both curves are basically flat as the MPS is not strongly ordered in these nematic solvents, and *prima facie* they do not exhibit particular features and/or predominant conformations (even though the profile of MPS in ZLI1132 is slightly wavier than that in EBBA, where $P(\varphi)$ is about constant). The conformational equilibrium of MPS in ZLI1132 is characterized by a distribution where the rotamers within the range $-15^\circ < \varphi < 60^\circ$ are basically equi-probable and slightly more populated than other conformations. The ME-result for MPS in EBBA is even less revealing, and can hardly be used alone for answering our question about the reliability of $\varphi_{\min}(\text{AP}) \cong 44^\circ$. Anyway, the ME method can be useful from a qualitative point of view, as it may disclose certain subtle details of the CDF (in this respect, good past examples are represented by the finding, in ethylbenzene, of a local minimum corresponding to the conformation with the ethyl fragment coplanar with the phenyl ring, and the coupled rotations in ethoxybenzene: both features have been later confirmed by quantum chemical calculations).³² The undulating CDF corresponding to MPS dissolved in ZLI1132, as well as that corresponding to MPS in EBBA, which in the scale of Figure 5 appears essentially flat, is characterized by a maximum around 25° and a minimum around 100° which is followed by a smooth plateau around 130° . It can be accurately fitted with a function proportional to $\exp[-V(\varphi)/kT]$ with $V(\varphi)$ given by eq 1. Thus, the ME method, in agreement with the quantum chemical calculations presented above, suggests that the effective torsional potential possesses a weaker 4-fold term, besides the largely dominant 2-fold term. The 2-fold term, however, is so dominant that the addition of a 4-fold term in the eq 1 does not produce, in the AP treatment of the LXNMR data, a significant improvement of the fitting (in other words, the inclusion of the 4-fold term in the context of the AP analysis is basically unnecessary and, of consequence, unjustified). Finally, as a general comment, while the AP approach has the advantage of being independent of the orientational order of the solute and, once a proper ansatz for the functional form of the effective torsional potential is assumed, is able to give a reliable CDF, the ME method results often helpful in suggesting this ansatz in the absence of other pieces of information.³²

5. Computer Simulations

Solutions of MPS dissolved in the isotropic phase of two nematogenic solvents have been simulated with the MD

technique.¹⁰ The “simulated” media were EBBA (the solvent also used in the “real” LXNMR experiments) and PCH7 (*trans*-4-heptyl-(4-cyanophenyl)-cyclohexane, also known as ZLI1115). As shown in Figure 4, PCH7 is a component of the ZLI1132 eutectic mixture used in the LXNMR experiments. It has been chosen for simulations in place of ZLI1132 because its dissolving and orienting properties are quite similar to those of ZLI1132, but it has the advantage to be a pure compound. Both solute and solvent molecules have been modeled at the atomistic, chemically detailed level. The model molecules are formed by a collection of interacting sites located on certain of the constituent atoms. While all heavy atoms have been explicitly considered, only hydrogens bonded to an unsaturated carbon atom have been taken explicitly into account, aliphatic hydrogens being condensed together with the saturated carbon atom to which they are bonded, i.e., a united-atom (UA) approach has been adopted for them. Understandably, the UA approach permits a considerable saving of computer time. The intramolecular bonded interactions considered have been bond angle (1,3) interactions and dihedral angle (1,4) interactions, bond (1,2) interactions being excluded as bond lengths are constrained at their equilibrium values during the simulations. This has been accomplished by the usual SHAKE method,³⁷ and has permitted the usage of a time step of 1 fs in the integration of the equations of motion using the leapfrog version of the Verlet algorithm.¹⁰ Each bond angle interaction has been represented by an harmonic term, while dihedral angle interactions have been given as a sum of sinusoidal terms. The bonded interactions’ parameters have been taken from the AMBER force-field,³⁸ except those used to model the torsional potential energy in MPS, obtained from the above-discussed B3LYP/6-31+G** calculations. The intramolecular and intermolecular nonbonded interactions have been represented by a sum of Coulombic and Lennard–Jones terms. The nonbonded interactions’ parameters have been taken from the OPLS force-field³⁹ (the complete list of interaction sites, together with their masses and the equilibrium geometry of solute and solvent molecule, as well as the list of the parameters entering the expression of the bonded and nonbonded interactions, are given in the Supporting Information). The two investigated solutions have been prepared by immersing a single MPS molecule in a sea of 243 solvent molecules. Initially, these 244 molecules have been taken in their equilibrium geometry and arranged in a simple cuboid lattice, with the MPS molecule placed at the center and the solvent molecules aligned along the Z axis of the laboratory frame of reference. This configuration has been expanded to a very small density and used to start a MD simulation run of 1 ns. This first run has been carried out in an effective isothermal–isobaric ensemble, working at a pressure (P) of 1 atm and a temperature (T) of 298 K. Pressure and temperature have been kept at their pre-selected values using the method proposed in ref 40. This first run aimed at completely isotropizing the sample. It has been then followed by an MD–NPT run of 1 ns performed at $P = 100$ atm and $T = 298$ K, during which the sample has been compressed. This second run has been followed by a further equilibration MD–NPT run of 2 ns performed at $P = 1$ atm and $T = 298$ K. The final fourth MD–NPT run, performed at ambient conditions and lasted 3 ns, has constituted the production run, during which the data necessary to compute the MPS CDF have been acquired. All simulations have been performed with the scalar version of the freely available program MOSCITO 4.⁴¹ The computed CDFs are shown in Figure 6.

Although, at least at a qualitative level, the simulations support the idea of a certain sensitivity of the CDF of MPS on

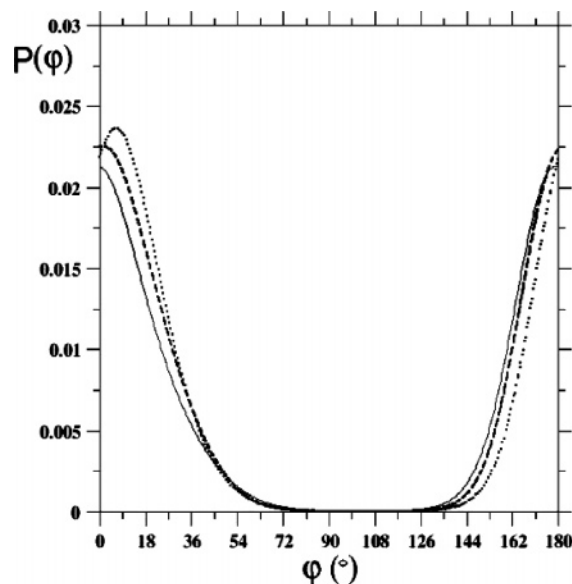


Figure 6. Conformational distribution function of MPS in the isotropic phase ($T = 298$ K) of PCH7 (solid line) and EBBA (dashed line) from the atomistic MD simulations. The conformational distribution of MPS in vacuo at the same temperature is also shown for comparison (dotted line).

the nature of the solvent (two different probability distributions are in fact obtained for the two different media), nevertheless both the solvents have the marked tendency to favor the conformations where the S=O group lies in the plane of the phenyl ring. Finally, from the computer simulation of isotropic MPS/EBBA solution, there is no evidence of highly twisted stable conformations. This result can probably be generalized to the case of MPS dissolved in the nematic phase of EBBA, because several past studies¹¹ lead to the quite general evidence that small solutes (in particular when they are only slightly oriented, as is the case of MPS in EBBA²⁷) show only a low (safely negligible) dependence of the conformational equilibrium on the solute’s ordering.

6. Discussion

The outcomes described in the previous sections lend themselves to interesting considerations and comments we will try to develop exhaustively in this section. Gas-phase experiments (MW) and in vacuo calculations agree in indicating the stable MPS conformation is that with the S=O group only slightly twisted (of about 5°) with respect to the plane of the ring. The found good agreement is not surprising, since the conformational equilibrium of isolated molecules exclusively depends on intramolecular interactions. Although the conformational results for the “rarefied” MPS are basically unambiguous (and therefore highly reliable), the same cannot be said for MPS in solution, where a series of not fully concordant, method-dependent conformational results exist (in our opinion, these not-univocal results should be also understood as a clear symptom of the intrinsic difficulties of treating complex conformational problems in fluid phases). The location of the torsional minimum predicted by the AP-LXNMR approach for MPS in ZLI1132 is in practice the same found by MW and calculations, so indicating just a small effect of this solvent on the φ_{\min} value (note, however, that our present discussion is restricted to the position of the minimum only; the problem of the influence of the solvent on the height of the barrier is not treated here). This result seems to be confirmed by atomistic MD computer simulations, where not only the MPS “virtually”

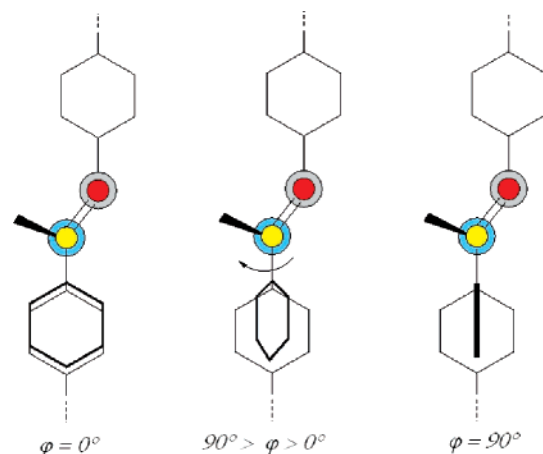


Figure 7. Possible scheme of MPS-EBBA specific interaction (see text for explanation). In the figure, the rigid (assumed planar) fragment of the EBBA (N in blue and C in gray) is represented as lying below MPS (S in yellow and O in red).

dissolved in isotropic PCH7, but also the MPS in isotropic EBBA exhibit the maximum of probability at $\varphi_{\min} \approx 0^\circ$ (Figure 6). Alternatively, for both solvents, the “experimental” ME-LXNMR method suggests (at least at a qualitative level) wide ranges of φ values, where the MPS rotamers are basically equiprobable (Figure 5). This means that the maximum entropy approach cannot exclude, in principle, the possibility of finding more twisted conformational solutions. Finally, the AP-LXNMR analysis of MPS in EBBA strongly supports a stable conformation where the S=O is significantly twisted ($\varphi_{\min} \approx 40^\circ$). In the present paper, the possibility of solute–solvent specific interactions has not yet been considered (computer simulations, described in the section above, are not able to account for specific interactions when they are not explicitly given in the mapping of interactions). This hypothesis, in our opinion, should not be underestimated (or even neglected) because mutually specific interactions could generate solute–solvent particular arrangements where more twisted MPS conformations could be favored. There are several sites, both in EBBA and MPS, that represent good candidates to mutually (specifically) interact. The presence of oxygen, nitrogen and sulfur atoms (involved in strong bond dipoles) as well as the presence of rings (also involved, in EBBA, in conjugated arrangements with the C=N double bond) could give rise to significant electrostatic and/or dispersion interactions. More in detail, it is well established⁴² that benzene dimer possesses two, almost equally energetic (about 11 kJ/mol at the equilibrium geometry) favored configuration; namely, T-shaped and slipped parallel. The face-to-face configuration, where the two rings are exactly superimposed, results to be ~ 4 kJ/mol higher in energy. These data should be combined with the certainly existing (and presumably considerable) dipole–dipole interaction between the S=O group of MPS and the N=C(H) fragment of EBBA, in order to develop sensible considerations about the energetic of possible stable geometries of MPS-EBBA dimers. Let us suppose the rigid “core” $\text{—OC}_6\text{H}_4\text{CHNC}_6\text{H}_4\text{—}$ of the EBBA molecule laying in a plane. This is presumably its equilibrium geometry. It can interact with an MPS molecule via the aforementioned dipole–dipole interaction that bring the two relevant dipoles in antiparallel configuration. In addition, there is also the predominantly dispersive interaction between the two phenyl rings, one belonging to MPS and the other to EBBA. Figure 7 graphically illustrates these considerations. The possible twist exerted by the liquid-crystal solvent on the equilibrium dihedral angle φ_{\min} of MPS may be induced by the balancing between

dipole–dipole interaction (more favored when φ_{\min} is close to zero, as the two molecular plane are closer) and the phenyl–phenyl interaction, advantaged in a T-shaped arrangement.

Finally, strictly speaking and for sake of completeness, the possibility that the stable conformation $\varphi_{\min} \approx 40^\circ$ of MPS in EBBA found by AP-LXNMR is a mathematical artifact (a “false minimum” produced by the AP approach) cannot be categorically excluded (although, as said above, this method proved many times in the past to be very reliable¹¹). In order to corroborate or discard the hypotheses presented above, additional experiments and calculations, e.g., by using the dispersion corrected density functional theory (DFT-*dc*) methods developed in ref.⁴³ are planned for a future study.⁴⁴

7. Conclusions

In this work, a comprehensive approach (including theoretical calculations, MW and LXNMR experiments and computer simulations) to the study of conformational distribution of MPS in different phases of matter has been carried out. In essence, the results confirm the tendency of the molecule to favor conformations (dictated by intramolecular interactions) where the stabilization is basically due to the conjugation energy. Nevertheless, in solution (where the complexity of the problem becomes much greater) there are more or less marked (also “method-dependent”) evidence of effects due to the used solvent. One case in particular (the EBBA-induced significant twist of S=O of MPS with respect to its ring plane, as described by the AP-LXNMR interpretation of the data) is intriguing because it seems to elude a fully satisfying rationalization. Alternatively, sometimes unexpected (and apparently unexplainable) results can represent useful clues for better (and more deeply) understanding phenomena (provided, of course, the methodological strictness of the study). Unless this “anomalous” conformational result is classified as merely a mathematical artifact (a “false minimum”) produced by the AP approach and (hastily?) discarded, it could represent an interesting evidence of specific solute–solvent interactions. In order to shed more light on this particular aspect of the problem (and, in general, to continue this line of research) additional experiments and calculations (by DFT-*dc* methods⁴³) are currently in progress on differently substituted MPS-type molecules.⁴⁴

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Supporting Information Available: Table SI-1, reporting MW experimental transition frequencies of methyl phenyl sulfoxide (MPS). In the second section SI-2, all the technical details and parameters of the Molecular Dynamics (MD) simulations are given. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) *Internal Rotation in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: London, 1974.

(2) Chemoselectivity could be cited as a “chemical example” of this dependence. It is well known that chemical reactions can occur only when the “reactive sites” of molecules are available for effective interactions leading to the products. For flexible reactants, the availability of the reactive sites could be conformation-dependent: as a consequence, (a) the chemical nature, and (b) the absolute and relative quantities of the products of the reaction become “functions” of the reactant conformational equilibrium. In summary, the conformational equilibrium of flexible reactants can affect the chemoselectivity of a reaction.

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(4) Three basic strategies exist for the quantum chemical modeling of molecular interactions in solution.⁵ The first involves discrete models, in which both solvent and solute molecules are explicitly treated allowing for specific solute–solvent interactions. The second approach is based on continuum models. In these strategies, the solvent is represented as a continuum dielectric medium that interacts with the solute. The most popular are the self-consistent reaction-field methods.^{6,7} The third strategy, which brings the advantages of the two aforementioned methods together, is called combined discrete/continuum model. Thus, this model considers both the electronic effects associated to specific solute–solvent interactions and the electric polarization of the bulk solvent.^{8,9}

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