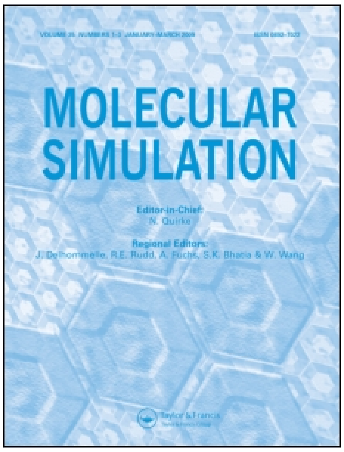

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Conformation of Ortho-fluoro-substituted Biphenyls in CCl_4 Solution: Molecular Dynamics Simulation

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CONFORMATION OF *ORTHO*-FLUORO-SUBSTITUTED BIPHENYLS IN CCl_4 SOLUTION: MOLECULAR DYNAMICS SIMULATION

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The molecular dynamics simulation of 2,2′-difluorobiphenyl, 2,6-difluorobiphenyl and 2,6,2′,6′-tetrafluorobiphenyl was performed in the CCl_4 solution, in order to reproduce the solvent influence on the conformation of these molecules. Parameters necessary for the description of the intrinsic rotational potential were obtained from *ab initio* calculations. The solvent influence was assumed to be van der Waals solute–solvent interaction, described by the GROMOS96 force field. The solvent tended to decrease a dihedral angle and a volume of the solute molecule. The correlation between the solvent effect energy and the molecular volume was observed, including earlier results obtained for biphenyl.

Keywords: Biphenyl; Rotational potential; MD simulation; Solvent influence

I. INTRODUCTION

Biphenyl derivatives are model molecules for investigating the dynamics of internal rotation in aromatic side-chains in proteins. This motion is of a prime importance for the functions of certain enzymes [1, 2]. Biphenyl is also related to polyparaphenylene (PPP), one of the most investigated examples of a conducting polymer, and the rotation around the single bond in biphenyl is an important factor, determining the conduction mechanism of PPP and similar compounds [3]. Halogeno derivatives of biphenyl are biologically active and this activity is related to their conformation [4].

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In our recent papers [5–6], we investigated the solvent influence on the conformation of the biphenyl molecule in CCl_4 solution. Molecular dynamics simulations based on GROMOS96 force field parameters and on *ab initio* rotational potentials were performed for biphenyl and 3,5,3′,5′-tetrafluorobiphenyl. It was found, that the *meta* substitution did not cause significant changes in conformational properties in solution [6].

Conformational behaviour of biphenyl has been studied for years [7–30]. The value of the rotational angle is determined by the intrinsic potential for internal rotation, and the effect of environment. The former can be rationalized as the electron delocalization effect, which tends to keep the molecule planar, and the sterical repulsion between the *ortho* carbon and hydrogen atoms, acting in the opposite direction. These opposite forces are of the same order of magnitude, and the equilibrium conformation strongly depends on the surrounding molecules. It was shown, that in the solid state the planar conformation was the most favorable one [7–12], whereas in liquid or solution the twisted ones, characterized by the torsional angle in between 0 (solid) and 45 (gas phase) [13–23]. As the *ortho* atoms are the most important factor determining steric effects, conformations of *ortho* substituted biphenyls are of special interest. There are not many experimental results concerning the conformation of these derivatives, except for electron diffraction data [31]. On this basis, the torsional angle in 2,2′-difluorobiphenyl was believed to be equal to 60 deg, and in perfluorobiphenyl 70 deg. Of special interest was the finding for 2,2′-difluorobiphenyl, which revealed the existence of the *cis* conformer only, although there was no reason found, excluding the possibility of the *trans* structure. For all the derivatives investigated, it became clear that *ortho* substituents increased the sterical repulsion, which favored the perpendicular conformation, and the mean angle was shifted from 45 deg in the biphenyl case to higher values in the *ortho* substituted cases.

In the present study, we undertook the molecular dynamics simulation of *ortho-fluoro*-substituted biphenyls in the CCl_4 solution. Apart from searching the mean conformation in solution, we investigated the modifications, caused by the solvent, on the internal rotational potential, determined by *ab initio* estimations.

II. *AB INITIO* CALCULATIONS OF THE ROTATIONAL POTENTIALS

The torsional potential of 2,2′-difluorobiphenyl, 2,6-difluorobiphenyl and 2,6,2′,6′-tetrafluorobiphenyl was estimated computationally by Cioslowski and Mixon [32] (RHF/6-31G**). The authors have located the energetic minima and maxima (transition states). Their results are collected in Table I.

For 2,2′-difluorobiphenyl, the optimized dihedral angle was the one involving carbon atoms attached to hydrogens. To adopt such data for our molecular dynamics purposes, as we did in [5, 6], we expanded the potential in the Fourier series:

$$V = \sum_{k=1}^{n} V_k[1 + \cos(k\varphi)] \tag{1}$$

The values of V_k are collected in Table II. The term for $k = 0$ can be omitted, since it is a constant, and we are interested in relative energy differences between conformers. Because of the different type of symmetry, we needed more non-zero terms to parametrize the potential of 2,2′-difluorobiphenyl. The curves are plotted in the Figure 2. The *ab initio* HF/6-31G** calculations supported the experimental ED results, but they did not explain the absence of the *trans* form of 2,2′-difluorobiphenyl.

TABLE I The torsional potential of 2,2′-difluorobiphenyl, 2,6-difluorobiphenyl and 2,6,2′,6′-tetrafluorobiphenyl [32]

Molecule	*Angle (deg)*	*Rel. energy (kJ/mol)*	*Rotamer*
2,2′- difluorobiphenyl	0.0	53.17*	*cis*
	54.7	0.00**	gauche
	92.2	4.64*	perpendicular
	128.7	1.00**	anti-clinal
	180.0	25.37*	*trans*
2,6-difluorobiphenyl	0.0	27.17*	planar
	53.4	0.00**	gauche
	90.0	3.01*	perpendicular
2,6,2′,6′-tetrafluorobiphenyl	0.0	131.46*	planar
	59.2	0.00**	gauche
	90.0	3.85*	perpendicular

* Energetic maxima.
** Energetic minima.

TABLE II Fourier expansion parameters for the potentials on dihedral angle (in kJ/mol)

Molecule	V_1	V_2	V_3	V_4	V_5	V_6
2,2′-difluorobiphenyl	7.229	15.449	5.029	10.034	1.640	1.848
2,6-difluorobiphenyl	–	10.780	–	7.079	–	1.300
2,6,2′,6′-tetrafluorobiphenyl	–	58.009	–	29.621	–	5.798

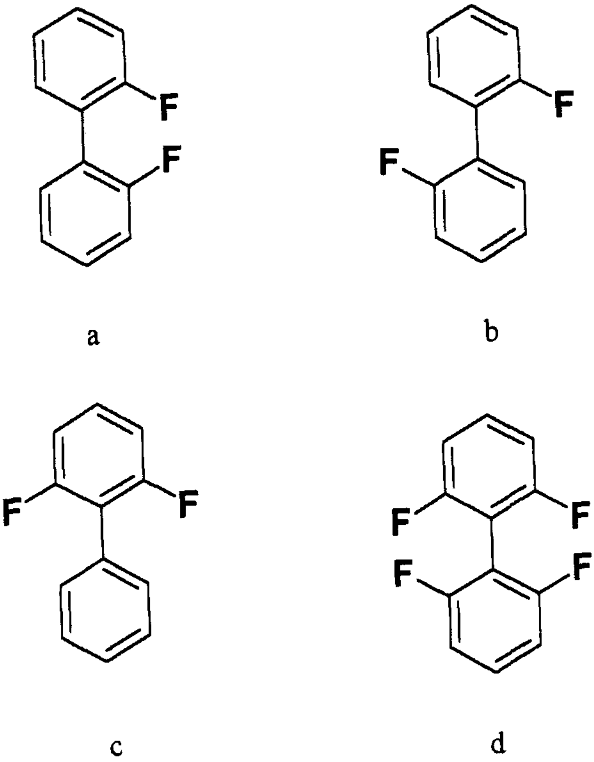


FIGURE 1 Structures of: (a) *cis*-2,2′-difluorobiphenyl, (b) *trans*-2,2′-difluorobiphenyl, (c) 2,6-difluorobiphenyl, (d) 2,6,2′,6′-tetrafluorobiphenyl.

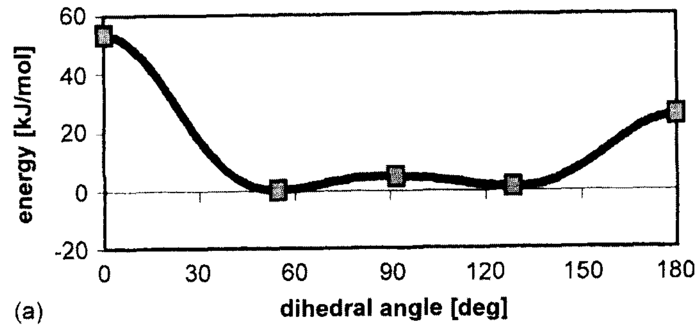


FIGURE 2 Fitted *ab initio* RHF/6-31G** potentials for: (a) 2,2′-difluorobiphenyl, (b) 2,6-difluorobiphenyl, (c) 2,6,2′,6′-tetrafluorobiphenyl [32].

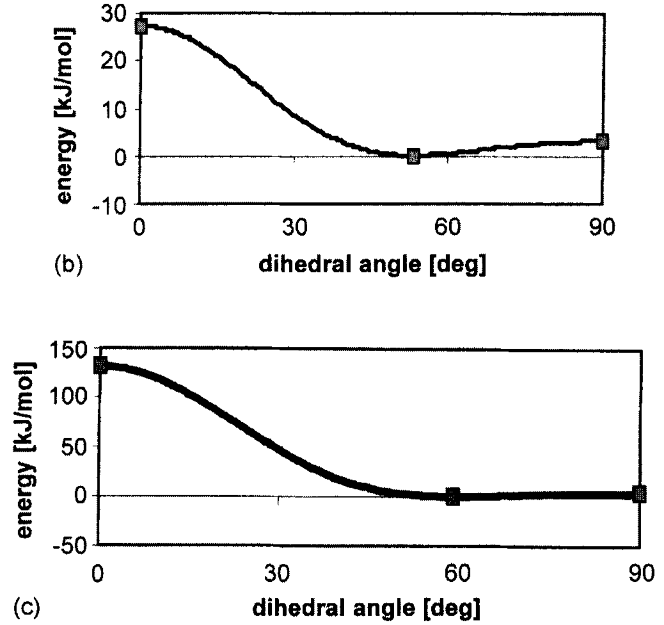


FIGURE 2 (Continued).

III. MOLECULAR DYNAMICS SIMULATION

We performed Molecular Dynamics simulation of 2,2′-difluorobiphenyl, 2,6-difluorobiphenyl and 2,6,2′,6′-tetrafluorobiphenyl in the carbon tetrachloride solution. The suite of molecular simulation programs GROMOS96 was used [33]. One molecule of a solute was embedded into solvent consisting of 205 CCl_4 molecules, in a cubic box with an edge of 3.2 nm. Such box dimensions correspond to a density of 1.6 g/cm^3, characteristic for carbon tetrachloride at the temperature of simulation of 300 K. The simulation was performed at constant volume, with a weak coupling to the temperature bath at 300 K, using Berendsen's thermostat [34] with the coupling constant of 50 fs. After a careful equilibration, a production run of 500 ps followed, with applied step of 0.5 fs.

The rotational potential of biphenyl derivatives was explicitly introduced from *ab initio* determinations in the form provided by Eq. (1), with coefficients listed in Table II. The covalent bond, covalent bond-angle and improper dihedral-angle forces were described by GROMOS96 force field

TABLE III Van der Waals 6 – 12 parameters of the non-bonded interactions in the modelled system [33]

Atom	$C_{12}^{1/2}(kJmol^{-1}nm^6)^{1/2}$	$C_6^{1/2}(10^{-6}kJmol^{-1}nm^{12})^{1/2}$
C	0.04838	1.837
H	0.0092	0.123
F	0.03432	0.8722
$C(CCl_4)$	0.051292	2.7568
$Cl(CCl_4)$	0.087201	3.5732

parameters [33]. The interactions involving fluorine atoms were additionally based on the UFF (Universal Force Field) parametrization [35].

For pairs of atoms of two different molecules, including the solute molecule, the non-bonded potential was of the 6 – 12 form. The values of the parameters for all the atom types used in the simulation are listed in Table III.

The non-bonded interactions were evaluated by the twin-range method [33], with a short-range cut-off radius of 1.2 nm and the long-range one of 1.4 nm. The long-distance interactions between atoms outside the inner cut-off sphere were updated every 10 time-steps.

As in [6], in order to analyze the effect of the solvent on the conformation of a solute molecule, we performed simulations with no torsional potential given explicitly. That model was expected to provide information about the solvent influence on conformations of the biphenyl derivatives, with no assumption of any particular internal interaction.

For each run, the trajectory was saved every 200 steps, giving rise to 5000 samples, from which the probability density was calculated. No special sampling technique, like umbrella sampling [36], or thermodynamic integration [37], was applied in the high-energy region, since we were interested in the mean conformation, and not in the determining of energy barriers in solution.

IV. RESULTS AND DISCUSSION

Figure 3 shows data obtained directly from molecular dynamics simulation, together with distribution functions *in vacuo* at 300 K, obtained as a result of neglecting the entropy effect and treating the *ab initio* energy [32] as the potential of mean force. The values of $\theta_{\max}$ and $\langle\theta\rangle$, which is the weighted average value of the torsional angle, calculated upon the whole range $<0, 90>$ degrees ($<90, 180>$ deg for *trans*-2,2′-difluorobiphenyl), that can be compared with experimental results, are collected in Table IV.

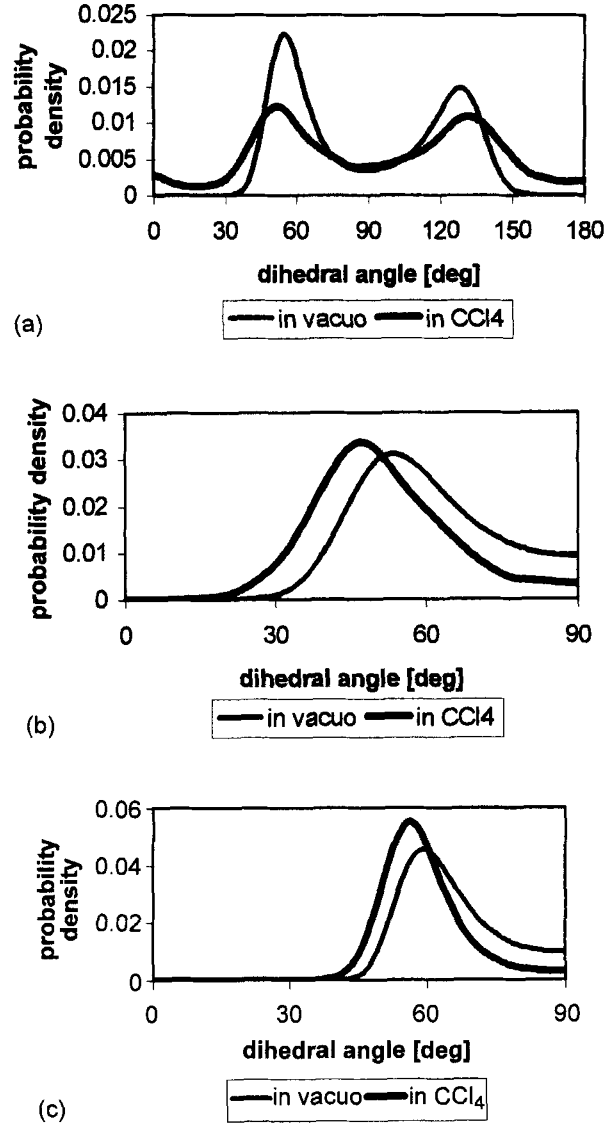


FIGURE 3 Simulation results at 300 K for (a) 2,2′-difluorobiphenyl, (b) 2,6-difluorobiphenyl, (c) 2,6,2′,6′-tetrafluorobiphenyl.

For all the *ortho* derivatives investigated, the positions of the maximum in solution are shifted in the direction of the planar conformation. This is in accordance with results obtained for biphenyl [6]. For both *cis* and *trans* forms of 2,2′-difluorobiphenyl, as well as 2,6,2′,6′-tetrafluorobiphenyl, the

TABLE IV Values of $\langle\theta\rangle$ and θ_{max} at 300 K (in deg)

Molecule	$\langle\theta\rangle$ *in vacuo*	$\langle\theta\rangle$ *in solution*	θ_{max} *in vacuo*	θ_{max} *in solution*
2,2′-difluorobiphenyl *cis*	60.0	53.0	54.5	52.0
2,2′-difluorobiphenyl *trans*	122.5	130.0	128.5	131.5
2,6-difluorobiphenyl	60.0	51.0	53.5	47.0
2,6,2′,6′-tetrafluorobiphenyl	65.0	59.0	59.0	56.0

maxima are shifted about 2.5–3 deg, but because of the observed increased occupation of forms characterized by the dihedral angle less than 30 deg and more than 150 deg, the mean values differ from those obtained for the *vacuo* case even more: 6–7.5 deg. The same qualitative dependence is observed for 2,6-difluorobiphenyl, but in this case the decrements, caused by solvent, take higher values of 6.5 deg for the position of the maximum, and 9 deg for the mean value. The corresponding values for the unsubstituted biphenyl were reported 1.5–2.0 deg for θ_{max}, and 3.5–4.5 deg, depending on the potential parameterization used, for $\langle\theta\rangle$ [6].

The mean value of the central dihedral angle in biphenyl derivatives in solution is a result of intramolecular forces, moderated by the solvent influence always in the direction of the planar form. In order to determine quantitatively the energy influence on the solute molecule from the surrounding solvent molecules, we applied the method, introduced in [6]. We performed the model simulation of the investigated derivatives with no inner torsional potential imposed. The normalized distribution functions obtained from the simulations, according to this technique, are presented in the Figure 4.

Since in this case the sampling is believed to be adequate for all the dihedral angles (no high energy barriers, for which special techniques like umbrella sampling should be used), we can directly calculate the potential of mean force:

$$W(\theta) = -RT\ln[P(\theta)/P_{max}]$$

We assume that $W(\theta_{max}) = \theta$. The results are presented in Figure 5.

Comparing energy scales in Figures 1 and 4 one can notice, that the relative solvent influence on the internal rotational potential is strongest in the case of the 2,6-difluorobiphenyl. This results in the above mentioned decrement of almost 10 deg of the value of the mean dihedral angle. The other derivatives are less affected, as well as biphenyl [6]. Such an energy influence can be related to changes of the molecular volume, calculated for various conformations [6].

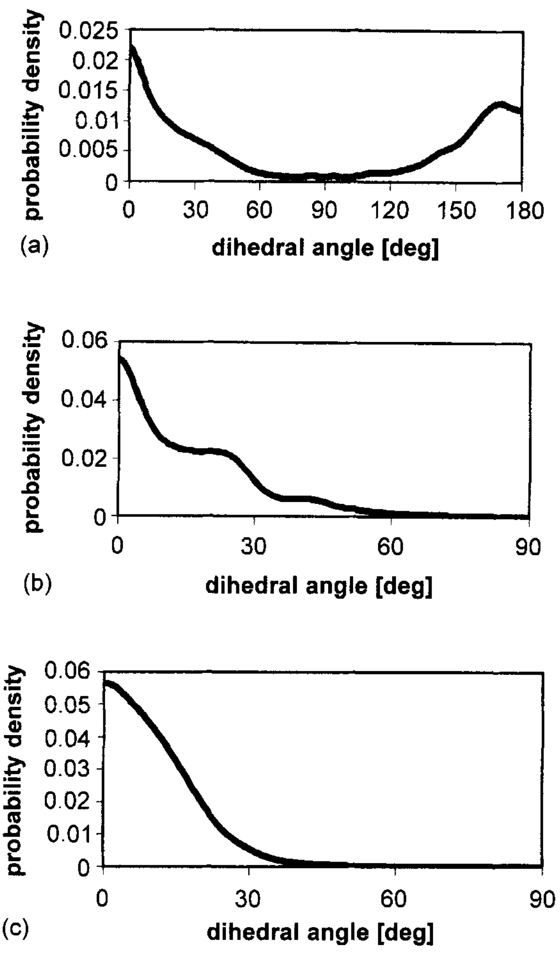


FIGURE 4 Simulation results in the case of no inner rotational potential imposed: (a) 2,2′-difluorobiphenyl, (b) 2,6-difluorobiphenyl, (c) 2,6,2′,6′-tetrafluorobiphenyl.

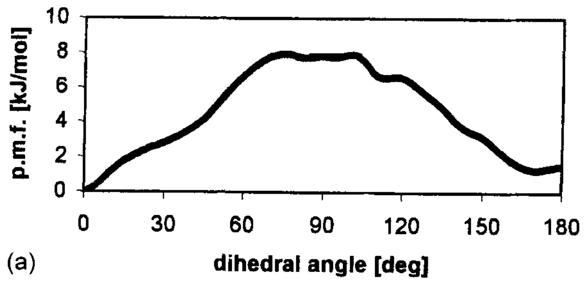
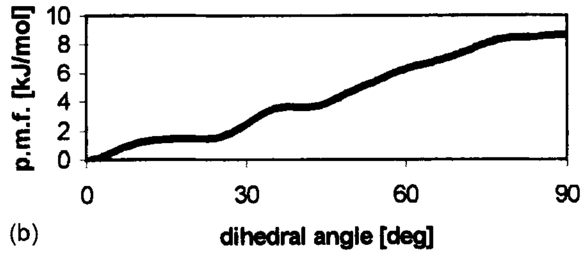


FIGURE 5 Potential of mean force (p.m.f) in the case of no inner rotational potential imposed. (a) 2,2′-difluorobiphenyl, (b) 2,6-difluorobiphenyl, (c) 2,6,2′,6′-tetrafluorobiphenyl.



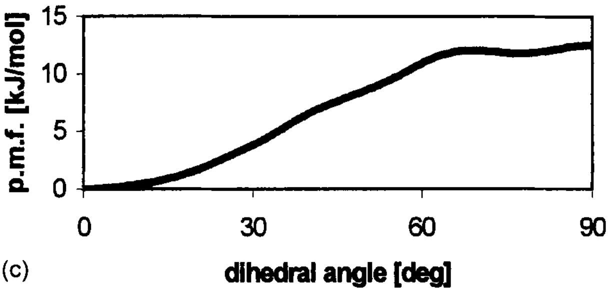


FIGURE 5 (Continued).

The applied procedure of computing the molecular volume was as follows [6]: the molecule of interest was built of overlapping van der Waals spheres. The van der Waals radii used for calculations were based on GROMOS96 force-field parameters, and were equal to 1.35 (hydrogen), 1.9 (carbon) and 1.65 (fluorine) Å. The dihedral angle between the rings was changed from 0 to 90 deg, with an interval of 10 deg. The molecule was embedded into a rectangular box, and ten intersections of the box with a regular rectangular grid consisting of 25^3 points were performed, giving rise to 156250 probe points in total. The molecular volume was then calculated as a ratio of the number of probe points inside at least one sphere, to the total number of points, and multiplied by the volume of the box.

In order to explain the shape of the curves (Fig. 6), we conclude, that the changes in our modelled molecular volume are due to the overlapping of the van der Waals spheres, mainly those of the *ortho* substituents. The least value of the volume is therefore observed for a planar conformation, and it increases with the dihedral angle up to the perpendicular form.

Comparing Figures 5 and 6, one can identify a correlation between the solvent effect energy, and the respective change in the molecular volume. The correlation is presented in Figure 7. For the sake of simplicity, both

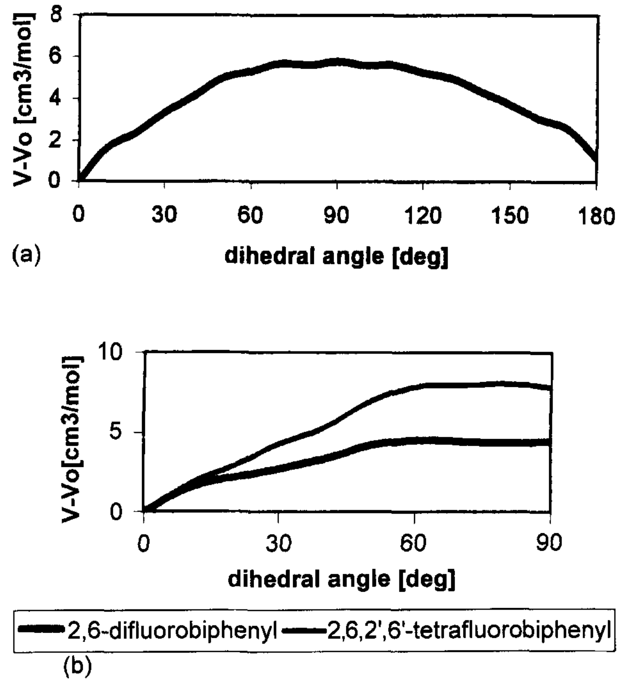


FIGURE 6 Increment of the molecular volume: (a) 2,2′-difluorobiphenyl, (b) 2,6-difluorobiphenyl and 2,6,2′,6′-tetrafluorobiphenyl.

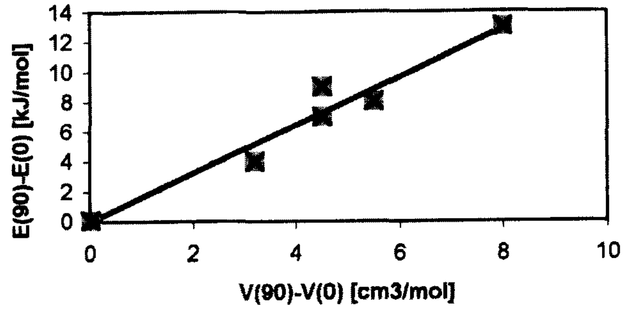


FIGURE 7 Correlation between the increment of molecular volume and the solvent effect energy for a transition from the planar to the perpendicular form for *ortho* fluoro-derivatives of biphenyl.

cis and *trans* forms of 2,2′-difluorobiphenyl were assumed to change its dihedral angle in the range between 0 (planar form) and 90 (perpendicular form) degrees.

Assuming that in an equilibrium state the entropy changes are negligible, for all the derivatives the following formula is valid:

$$\Delta E_{0\to 90} = p_{\text{mean}} \Delta V_{0\to 90}$$

The value of mean pressure, p_{mean}, averaged for all the derivatives investigated, is about 16 kbar (compare with the discussion in [23]), and is the value characterising the group of solutes and the solvent. The work that has to be done against the solvent, in order to increase the volume and hence the dihedral angle between phenyl rigs, can be described as the work of the cavity creation in the solvent.

V. CONCLUSIONS

As in the case of the biphenyl molecule [5, 6], the modelled solvent influence on the biphenyl *ortho* fluoro derivatives conformation results in a flattening of the solute molecule. The energetic effect, corresponding to solute–solvent interaction, is not very large, comparing with the intrinsic rotational barriers. That effect is related to the change of the molecular volume – the energy is needed to increase the volume and the dihedral angle. The straight proportional correlation between the volume change and the energy of the solvent effect is true for the group of investigated molecules to a good approximation. Further investigations, concerning the *ortho*-chloro-biphenyl derivatives, are in progress.

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