Theoretical study of the rotational barrier height of the anisole molecule for different solvents and partition coefficients solvent/water

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The height of the rotational barrier of anisole molecule (methoxybenzene) has been studied for 20 different environments, including vacuum, using the continuum reaction field method in connection with a quantum-chemical calculation. The energy of the isolated molecule was calculated by the PCILO method. Before the anisole molecule energy calculation in particular solvents, two models of anisole and phenol hybridization were tested *in vacuo* and the influence of the hybridization on their conformation was investigated. It has been found that the resulting conformations do not depend on the type of oxygen atom hybridization used. However, the O atom hybridization influences the energy shift of the whole conformational map. It has also been found that the way of including solvent effect used gives the right trend of the partition coefficients of anisole, despite the fact that the values of the partition coefficients systematically differ from those resulting from the experiment. However, the way of including solvent effect has failed to predict the height of the rotational barrier in various environments.

Используя метод непрерывного реакционного поля в сочетании с квантовохимическими расчетами, исследованы высоты барьеров внутреннего вращения молекулы анизола (метоксибензола) в 20 различных средах, включая вакуум. Энергия изолированной молекулы была рассчитана методом PCILO. Перед проведением расчетов внутренней энергии молекулы анизола в отдельных растворителях были испытаны две модели анизольной и фенольной гибридизации в вакууме и было исследовано влияние гибридизации на их конформацию. Обнаружено, что конечная конформация не зависит от типа используемой гибридизации атома кислорода. Однако, гибридизация атома O влияет на энергетический сдвиг всей конформационной карты. Также было найдено, что способ учета эффекта растворителя дает верное представление о коэффициентах распределения анизола, хотя и рассчитанные величины коэффициентов распределения постоянно отличались от экспериментально установленных. Способ учета эффекта растворителя не помог, однако, предсказать высоту барьера внутреннего вращения в различных средах.

The PCILO [1—4] method using the formalism of localized orbitals, needs as input information the "binding" model of the studied system in which the σ and π bonds are defined, as well as the hybridization of lone pairs. In case that there exists the possibility to define a few different "binding" models for the studied system, the result obtained by PCILO will depend on particular model. In such a case, two possibilities can be distinguished: one of the structures is strongly preferred and we can further work only with this structure, or several structures are from energetical point of view approximately equivalent and all of them contribute to the final wave function.

To determine the type of hybridization of lone pairs, in contrast to determination of the "binding" model, the intuition is used more frequently. In case of uncertainty, different types of hybridization can be used, while a minimum of the energy is the criterion of the best model. In the presented work the latter procedure was used for the anisole and phenol molecule, the oxygen atom of which can be with sp^3 or sp^2 hybridization.

Molecules of anisole and phenol, respectively, have been studied *ab initio* in [5] and as the models of adrenergic drugs in paper [6] by *Petrongollo* and *Tomasi*. In the last paper the main attention was paid to the property of the electrostatic potential generated by the molecule. The studied molecules are interesting not only as the models of adrenergic drugs but also as the fragments of local anesthetics of carbamate type [7, 8].

Results and discussion

The standard bond lengths and bond angles [9] have been used in our calculation. Both systems have been forced to rotate about the oxygen—phenol axis with step of 15° and in case of anisole the methyl group has been rotated with step of 15°, too. The other degrees of freedom have been neither changed nor optimized. The calculations for anisole interaction with particular solvents have been performed for all rotations mentioned above.

The oxygen atom of the phenol —OH group and —OCH_3 group of the anisole can be in sp^3 hybrid state, forming two σ bonds and bearing two lone pairs similarly as sp^3 AO's. This atom can be in sp^2 hybrid state as well, forming also two σ bonds, while one of its lone pairs forms sp^2 AO and the second one forms pure p-orbital.

Table 1 presents the calculated stable conformations of the anisole and phenol molecules for both, sp^2 and sp^3 hybridization of O atom. It is evident from the results that in the case of phenol molecule, the geometry with OH group in the plane of benzene ring with sp^3 hybridization of O atom is much stable. For anisole molecule the most stable conformation was found for geometry in which the bond O—CH_3 forms the angle of 60° with benzene ring and the hybridization of O atom

Table 1

Total energies and stable conformations of anisole and phenol

Substance	Hybridization of oxygen AO's			
	sp^2		sp^3	
	E/(kJ/mol)	φ/°	E/(kJ/mol)	φ/°
Anisole	−195387.71	60	−195318.46	60
Phenol	−172413.46	0	−172432.60	0

E — the total energy;
φ — the angle between O—C (O—H) bond and the benzene ring.

is sp^2. The final, most stable conformation for both of the studied molecules, however, does not depend on the type of O atom hybridization. In both cases the most stable hybridization of oxygen atom orbitals is that which enables joining both lone pairs in the interaction with π system of benzene ring. Yet this result is in contradiction with an intuitive expectation of pure p-orbital on the phenol oxygen atom and the energy effect of the interaction with two hybrid atom orbitals is probably greater than that of the interaction with one p-orbital. The resulting conformations both of phenol and anisole are in agreement with the results in [5], where the phenol hydrogen atom is in the plane of benzene ring and oxygen—methyl bond in anisole makes the angle of 90° with the plane of benzene ring. Our result is in qualitative agreement with this paper because only two positions of methyl group (parallel with benzene ring plane and perpendicular with it) have been taken into consideration in the cited paper. Nonplanar structure of anisole agrees with experimental findings of *Aroney* and coworkers [10], too.

The rotation barrier O-phenyl for phenol was calculated to be 8.37 kJ mol^{-1} and for anisole 6.30 kJ mol^{-1}. The experimental value for phenol is 13.64 kJ mol^{-1} and that for anisole 15.10 kJ mol^{-1} [11, 12] (both for gas phase; for anisole in liquid phase it is 25.31 kJ mol^{-1} [13]). The calculated conformational map for anisole (*in vacuo*) is shown in Fig. 1.

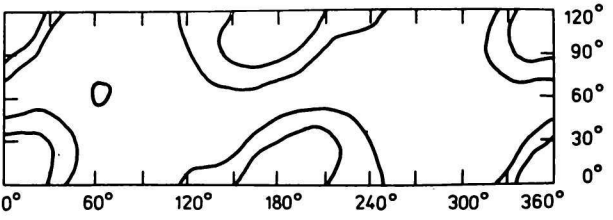

Fig. 1. Conformational map of anisole *in vacuo*.
(The maps for other environments are the same, except for a constant shift.)

The influence of the environment on the conformation and the height of rotation barrier of anisole molecule was also investigated. The environment effect was calculated by the method based on *Sinanoglu* [14] and *Beveridge et al.* [15] procedure modified and successfully used by *Tvaroška et al.* [16, 17]. The most stable position of anisole —CH_3 group was obtained the same for all solvents as for the vacuum.

Table 2 presents the total energies for the most stable anisole conformers in particular solvents, the energy differences between the *in vacuo* and particular solvent conformer as well as the values of the height of the energy barrier for rotation about oxygen—phenyl axis. From the table it is obvious that anisole interacts most strongly with pyridine. Surprising is the fact that the calculated value of the height of the rotation barrier just slightly depends on the environment and it is nearly equal to the *in vacuo* value, in contrast to experimental fact where the height of the rotation barrier is two-times greater in liquid than in gas phase [13].

Table 2

Total energies and rotational barrier heights of anisole in particular environments

Environment	Total energy	Difference from vacuum	Height of the barrier
	kJ mol^{-1}	kJ mol^{-1}	kJ mol^{-1}
Vacuum	−195387.708	0.000	6.30
n-Hexane	−195515.653	127.945	7.07
Cyclohexane	−195513.826	126.118	7.05
1,4-Dioxan	−195524.040	136.332	7.23
CCl_4	−195521.031	133.331	7.08
Benzene	−195516.552	128.844	7.05
CS_2	−195525.846	138.138	7.08
t-Butylamine	−195478.386	90.678	6.86
$CHCl_3$	−195528.195	140.487	7.42
Fluorobenzene	−195526.562	138.854	7.27
Tetrahydrofuran	−195518.820	131.112	7.31
Pyridine	−195528.709	141.001	7.48
Isoamyl alcohol	−195480.374	92.666	6.93
Isobutyl alcohol	−195505.073	117.365	6.20
Acetone	−195510.407	122.699	7.35
Ethanol	−195511.282	123.574	7.40
Methanol	−195508.299	120.591	7.55
Acetonitrile	−195509.524	121.816	6.95
Dimethyl sulfoxide	−195507.850	120.142	7.33
Water	−195494.552	106.844	7.90

From the parameter list in Table 2 the partition coefficients (solvent/water) for the solvents with known experimental data were calculated. In Table 3 are the

Table 3

Experimental and calculated values of logarithm of partition coefficient for anisole

Solvent	log (*P*) (experimental)	log (*P*) (calculated)
n-Hexane	2.1	3.73
Cyclohexane	2.3	3.41
$CHCl_3$	3.12	5.95

logarithms of calculated and experimental values [18] of partition coefficients at 295 K. For the calculation of partition coefficients the following relation was used

$$\log \frac{a_s}{a(H_2O)} = \frac{\Delta G(H_2O) - \Delta G_s}{2.303\ RT} \qquad (1)$$

where $\Delta G(H_2O)$ and ΔG_s are the values from Table 2, R is the gas constant, and T is the particular temperature.

The use of E^i_{tot} values from Table 2 instead of ΔG is justifiable because of the fact that E^i_{tot} for i-th solvent involves some entropy terms which are connected with cavity forming and solute—solvent interactions. The terms connected with ΔS of pure substance are cancelled in eqn (*1*).

As seen from Table 3, the calculated values of partition coefficients correlate with the trend of experimental data but the deviation is considerably large. In case of the larger set of experimentally known partition coefficients it would be possible to draw and test the linear dependence between the calculated and experimental partition coefficients, which could lead eventually to the prediction.

The used method for the solvent effect calculation [16, 17] is a continuum one and does not take into account specific interactions between the solvent and the solute. Using this method, the good results can be expected only at the absence of specific interactions or in the case when particular specific interaction is conformationally independent, *i.e.* it is just a constant contribution, shifting the total energy of each conformer by the same value. For the studied anisole molecule it can be expected that possible specific interactions are conformationally independent. The systematic deviation between the calculated and experimental partition coefficients can be explained by the fact that in the case of interaction with water, specific interaction which decreases the value $\Delta G(H_2O)$ is not included. In this case the numerator in the expression (*1*) (right-hand side) is greater than it should be, from which follows the systematic overestimation of calculated partition coefficient.

Failing of the method used for rotation barrier calculation is another question to explain. The rotation barrier heights resulting from the calculation differ only slightly from the height barrier in vacuum while the experimental values are more than twice of those in gas phase. This disagreement may be accounted for by the fact that the method considering the environment as continuum does not involve specific interactions with solvent. These effects can only be involved by the supermolecule model. The continual model regards a molecule as if in vacuum in which the force field generated by the environment acts. The fact that condensed phase is thought is not taken into consideration in another way.

In both the rotation barrier height calculation and partition coefficients calculation other effects may be present, *i.e.* the electron density distribution from the PCILO wave function need not be correct. However, experience of other authors [16, 17] does not ascribe to this effect too much importance. It might seem a certain effect must be taken into consideration by the use of supermolecule model which, in combination with continuum model, could remove some of the drawbacks mentioned above.

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