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Control over the Hydrogen-Bond Docking Site in Anisole by Ring Methylation

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***Abstract:** The supramolecular docking of methanol to anisole may occur via an OH···O hydrogen bond or via an OH···π contact. The subtle balance between these two structures can be varied in supersonic jets by one order of magnitude through single to triple methylation of the aromatic ring and introduction of a single tert-butyl substituent, as evidenced by infrared spectroscopy. This steep variation makes it possible to assess the accuracy of relative quantum-chemical energy predictions on a kJ mol^{-1} level, promising insights into inductive, mesomeric, and dispersive effects. The zero-point-corrected B3LYP-D3/aVTZ level is shown to provide an accurate relative description of the two very different hydrogen bonds, similar to a wavefunction-based protocol including CCSD(T) corrections applied to the same structures. M06-2X alone systematically overestimates the stability of π coordination.*

The reactivity of aromatic molecules can be adjusted systematically by ring substitution due to their delocalized π cloud. Solvation, as a subtle and reversible form of reactivity, should reflect thermodynamic aspects of this control. However, the effects are usually too weak at room temperature and too additive to be observed in bulk solution. Low-temperature microsolvation,[1] in contrast, can reveal even delicate preferences for one or the other solvent docking site. A prerequisite is the easy exchange between the solvation sites, that is, the absence of major isomerization barriers.[2]

The well-studied anisole molecule[1,3–6] may be viewed as an electron-rich benzene derivative or as an electron-depleted ether. The underlying mesomeric effect makes the two hydrogen-bond docking sites, namely the oxygen (O) and the π cloud, similarly attractive.[7] For methanol as a solvent, docking at the oxygen site is preferred by slightly more than 1 kJ mol^{-1}. This is concluded from the relative abundance of the two isomers in a supersonic jet expansion and supported by high-level quantum chemical calculations.[8] Because the two docking sites are also close together in space, their interconversion is facile even at low temperatures. This makes anisole a promising test system for the ability of quantum chemical methods to predict the relative energy of the two types of hydrogen bonding—soft and delocalized to the π cloud vs. directed to the oxygen. Because of this difference in directionality, zero-point energy effects are important, but it has been argued that the harmonic approximation is largely sufficient for this purpose[8] and this is further elaborated in the present work.

We have undertaken a systematic study of the methylation of anisole to change the π cloud attractivity relative to the oxygen site for the docking of methanol. A number of effects are expected to come into play. The +I effect of the methyl group and the +M effect of the methoxy group may interact differently in *ortho*/*para* (*o*/*p*) and *meta* (*m*) position. Furthermore, *o* substitution partially shields the methoxy site, double *o* substitution even twists it out of resonance with the ring, thus returning some of its intrinsic electron density. Dispersion interactions make the ring site more attractive, steric interactions may prevent the best access to any of the docking sites. At this point, we put aside attempts to qualitatively predict the relative importance and interplay of these effects. An adequate quantum chemical description must capture all of them and thus predict the net effect in a reliable and systematic way. Once this is the case, one may try to disentangle the individual contributions by analysis of the theoretical results. Therefore, the goal of the present contribution is to provide a reliable experimental data set and to compare it to quantum-chemical total energy predictions (obtained from the Gaussian09[9] and Turbomole[10,11] packages) using augmented correlation-consistent basis sets, as indicated. Similar methods were applied successfully to the anisole dimer.[6] When D3 dispersion corrections are applied to density functionals,[12] Becke-Johnson damping is typically implied[13] (see, however, anharmonic calculations in the Supporting Information (SI)). B3LYP-D3 results are compiled in Tables S1 and S2 in SI. As an example for a density functional with integrated mid-range dispersion contributions, we have chosen M06-2X[14] (Table S3 in SI). There are different π docking geometries for methanol in the structure optimizations, with the CO bonds of anisole (with C_{aryl}) and methanol more antiparallel or more perpendicular to each other (Table S2 in SI). Results for the more stable one in a given anisole species are reported, assuming that the π structures interconvert in the supersonic jet.

Experimentally, the anisole derivatives are mixed at room temperature with methanol and a large excess of He in the gas phase. All compounds (methanol (Roth, ≥99.9%), anisole (Fluka, >99%), all methylanisoles and 3,5-dimethylanisole (Alfa-Aesar, 99%), 2,*n*-dimethylanisoles (Sigma, 97–98%), 2,3,5-trimethylanisole (TCI, >97%), and helium (Linde, 99.996%)) are used as purchased. The gas mixture is pulsed into vacuum through a 600 mm slit, forming an adiabatic expansion zone in which the molecules are cooled by He

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collisions and aggregated by molecular collisions. This zone is probed by a synchronized, interferometrically modulated IR beam, and the absorption due to OH stretching fundamental excitation is probed by a sensitive detector.[15] By controlling the expansion pressure and concentration of the molecular species, one can identify OH stretching signals due to 1:1 complexes, which are characteristically downshifted from that of monomeric methanol (3686 cm^{-1}). Figure 1 shows a few examples of the spectra obtained (see Figure S6 in SI for the complete set). OH⋯O coordination exhibits larger shifts than OH⋯π coordination for this class of molecules (see Figure S7 in SI for a correlation between experiment and theory). The fraction of OH⋯π coordination x_π can be quantified with an estimated error of 0.1 by comparison to predicted infrared band strengths (Table S4 in SI, see Figure S8 for a detailed error analysis). In the case of band splittings or accidental band overlap, the error may also be larger, but no evidence for two or more coexisting π-bonded complexes was found in the spectra. When x_π is plotted as a function of the predicted energy advantage of OH⋯π coordination for a range of anisole derivatives (Figures 2 and 3), a sigmoidal curve is expected, which switches from 0 when OH⋯O is more attractive to 1 when OH⋯π wins. $x_\pi \approx 0.5$ is anticipated when the two docking sites are energetically equivalent. The steepness of this sigmoidal curve depends on a number of experimental constraints. Although the molecular complexes generated in the supersonic jet expansion are translationally and rotationally very cold ($T_r < 20$ K), their conformational temperature T_c will be somewhat higher, because hydrogen bond switching involves a barrier and complexes cooled below this barrier will tend to be frozen in their current conformation. Anisole appears to be a favorable system in terms of this interconversion barrier because the alcohol molecule only has to move a short distance along a conjugated π system. This justifies a lower limit for T_c of about 30 K in favorable cases. If the barrier is higher due to steric hindrance, the conformational temperature will be higher (up to ca. 100 K[16]) and some methanol molecules may get trapped in a less favorable docking site independent of its energy. A reasonable estimate for the fraction of kinetically trapped methanol molecules is 20 % (vide infra). This defines a sigmoidal zone for x_π abundance enclosed by a 30 K thermodynamic Boltzmann distribution and a 100 K kinetically modified Boltzmann distribution, which is shown by shading in the following figures. The most sensitive testing case for theory is the inflection region at $x_\pi \approx 0.5$, where the docking sites are isoenergetic. In the graphical representation, this is the region where the two shaded zones meet, not implying that the experimental error of the method vanishes. By plotting the experimentally observed π fractions as a function of predicted energy difference $\Delta E_0 = E_0^{\mathrm{O}} - E_0^{\pi}$ (filled symbols) and by uniformly shifting them to maximize overlap of the data points with the shaded zone (empty symbols), one obtains approximate average errors of the predicted energy difference. Shifts smaller than 0.5 kJ mol^{-1} are not considered robust in terms of the experimental accuracy and the harmonic approximation used in the zero-point energy evaluation and are thus not applied. We emphasize that the harmonic zero-point energy contribution to the energy difference is on the order of 1 kJ mol^{-1} (Table S1 in SI) and therefore included, whereas the anharmonic corrections presumably contribute an order of magnitude less[8] (Table S5 in SI).

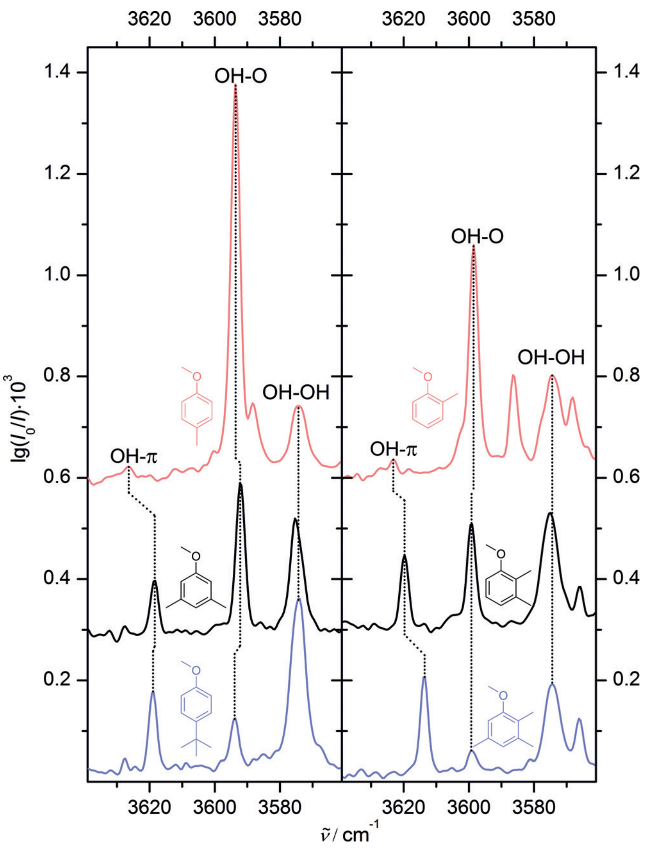

Figure 1. Six representative OH-stretching jet FTIR spectra for methanol docking on substituted anisoles with an OH-O (top), mixed (middle), and OH-π preference (bottom). Also marked is the methanol dimer signal (OH-OH); slight variations are due to spectral overlap. Not labeled are minor contributions from mixed trimers. Left column: anisole derivatives without *o* substitution, right column: with *o* substitution and slightly higher OH-O stretching wavenumber due to reduced accessibility.

Figure 2a shows the plot obtained for anisoles without *ortho*-substitution for the B3LYP-D3/aVTZ approach (see Figure S10 in SI for a comparison to similar results obtained with a wavefunction-based protocol[8] using the same optimized structures). The spectroscopic data points follow the shaded area best if the energy difference is uniformly shifted by merely 0.8 kJ mol^{-1} towards OH⋯O docking (empty circles). This suggests that B3LYP-D3/aVTZ provides a quite balanced description of the two different types of hydrogen bonding. Single methylation of anisole in *m* or *p* position has little effect on the clear OH⋯O binding preference. In the *m* case, there is positional isomerism (see Table S3 in SI), but this has no influence on the plot. Double *m* methylation raises the π fraction to almost 40 % and therefore provides a critical test for theory. It is tempting to invoke the *o*/*p* directing effect of methyl groups[17] for the enhanced π preference, but we concentrate on the net quantum chemical effect at this stage. A *tert*-butyl group in *p* position switches the preference to OH⋯π, in agreement with

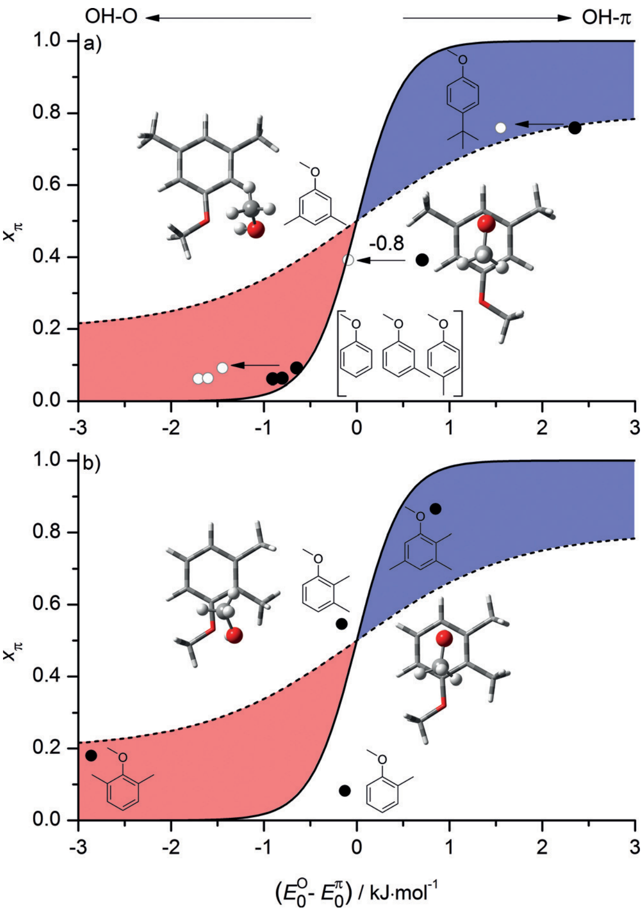

Figure 2. Experimental fraction x_π of methanol docking to the π system rather than to the oxygen of anisoles with varying ring-methylation patterns as a function of the predicted zero-point-corrected energy difference between the best O and π docking sites at the B3LYP-D3/aVTZ level. a) No methyl groups in the *o* positions ensures good accessibility of the O atom; theoretical values (filled circles) uniformly shifted by 0.8 kJ mol^{-1} towards O docking preference (empty circles) achieve a better match with the experimental findings. b) Methylation including the *o* position; only unshifted theoretical values shown.

the theoretical predictions. All this suggests that quantum chemical docking preferences can be adequately assessed by observing relative conformational abundances in supersonic jet spectra.

Figure 2b shows the situation for *o*-substituted anisoles, where the oxygen atom is less accessible due to the neighboring methyl group and where the methanol molecule therefore tends to dock in a more perpendicular way relative to the anisole plane. No systematic correction can be deduced from the experimental data, and the energy scale is thus plotted without shift. An interesting case is the left-most structure with double *o* methylation, where the steric demand forces the ether substituent out of plane, attenuating its π conjugation and thus raising the O acceptor potential. The preferred π face is now opposite to the O face, further introducing kinetic hindrance and explaining the detection of some π docking. As the energy barrier between O and π coordination is increased due to interruption of the conjugation and symmetry breaking between the two π faces, one observes trapping of the minority species despite its energetic disadvantage. However, the results are still consistent with a conformational temperature as low as 100 K and 20% kinetic trapping, as indicated by the dashed border of the shaded zone. This confirms the assumptions made above concerning the maximum extent of kinetic trapping. Singly *o*-methylated anisole shows a clear O preference in the experimental spectrum, although this is only predicted by a tiny margin at the theoretical level. Additional *m* methylation is predicted to have almost no energetic effect, but experimentally there is a nearly perfect 1:1 mixture of O and π coordination. Double *m* methylation switches to π preference in the experimental spectra, which is confirmed by theory. The pattern is thus somewhat more irregular but the overall agreement is still satisfactory.

The performance degrades when the popular M06-2X functional is consistently used for geometry optimization, electronic energy, zero-point energy and IR cross section. M06-2X/aVTZ should minimize basis set convergence issues reported for Minnesota functionals.[18] A systematic theoretical bias towards the π binding site is revealed by the spectroscopic data. As Figure 3a summarizes, the required shift for *o*-unsubstituted anisoles amounts to 4 kJ mol^{-1} or 20% of the total interaction. No O-docking would be predicted at all for the investigated compounds although this is the dominant structural motif observed. The discrepancy decreases by about a factor of 2 when M06-2X energies are evaluated with B3LYP-D3-optimized structures (Figure S9 in SI). MP2/aVQZ performance is similarly poor when combined in a protocol with B3LYP-D3 structures and vibrational properties[8] (Figure S10 in SI). In analogy to Figure 2, the match improves for *o*-substituted anisoles (Figure 3b). Here, the required corrective M06-2X/aVTZ shifts are only slightly larger than 1 kJ mol^{-1} and the steep transition with increasing methylation is described quite well. Given the poor performance for *o*-unsubstituted anisoles, this is revealed as a fortuitous error cancellation, similar to but exceeding that shown in Figure 2b.

Our spectroscopic method of determining the docking preference of methanol to anisole at low temperature in a kind of intermolecular balance experiment is thus found to reveal the following features of competitive docking and their theoretical description:

i) Changes in predicted docking preference by less than 1 kJ mol^{-1} have qualitative experimental consequences. The method is sensitive.
ii) Dramatic failures such as for M06-2X are exemplified. The method can discriminate poor from good or fortuitously matching quantum chemical approaches.
iii) Fortuitous error compensation is revealed by studying different substitution classes. Only methods which pass the test for different classes can be expected to provide a systematic description of hydrogen-bond docking preferences.
iv) Among the density functionals, M06-2X performs unsatisfactorily, whereas B3LYP-D3 passes all currently available tests. Our experimental findings are in line with earlier theoretical assessments of density functionals.[19,20] Among the wave-function-based methods, inclusion of higher-order electron correlation corrections appears to

be essential, similar to the case of π stacking,[6,21,22] but a consistent CCSD(T) treatment would be desirable to secure this statement.

After the demonstration of an intermolecular balance tool for assessing hydrogen-bond docking in anisole, the chemical substitution pattern must be extended to further exclude fortuitous performance. Furthermore, a systematic decomposition of the bonding contributions into electrostatic, polarization, and dispersion forces is indicated[23,24] and will be the subject of future investigations. Confirmation of the present relative binding energies by absolute binding energy methods[6,25] would be attractive. Our method is complementary to NMR-based intramolecular balances in solution.[26] It avoids any compensation effects by the macroscopic solvent environment and is therefore located closer to accurate theoretical modeling and farther from practical application. Considering the difficulties in dissolving lignin for biofuel production and the omnipresence of aromatic ether structures and hydroxyl groups in this biopolymer, the insights from the present work may still contribute a little to solvent design in this important technological challenge.[27]

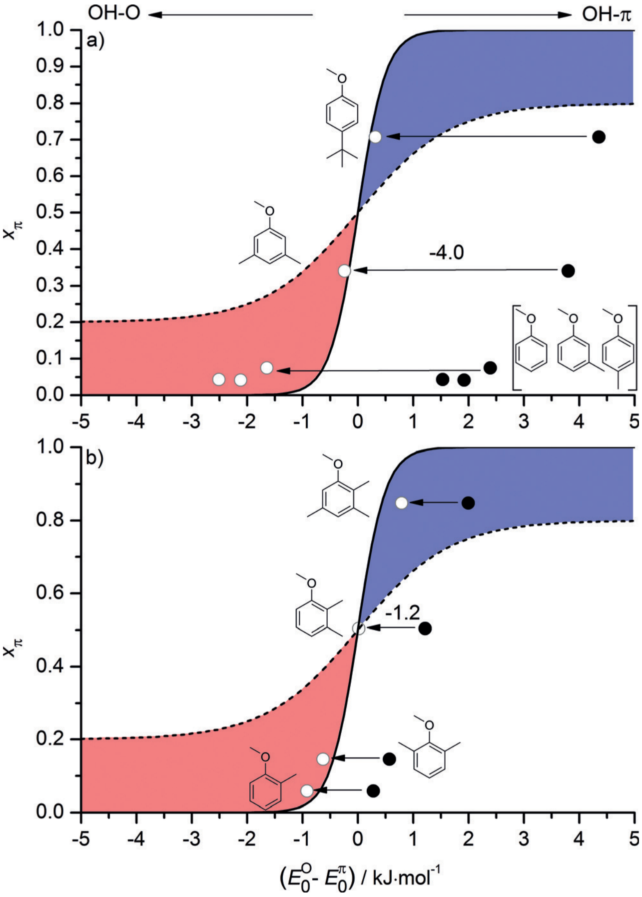

Figure 3. In analogy to Figure 2, but for consistent M06-2X/aVTZ predictions (circles). The deviations from experiment are significantly larger (filled symbols), in particular for anisoles without *o*-methyl groups, again biasing towards π coordination. Shifts by 4.0 (1.2) kJ mol^{-1} towards O coordination (empty symbols) are needed to achieve satisfactory overlap with the shaded zone for anisoles without (with) *o* substitution. Note the extended energy scale.

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