

Exploring the influence of fluorine substitution on tuning the hydrogen bonding properties using theoretical and spectroscopic methods

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Introduction

Fluorine is the most electronegative element occurring in nature. Introduction of a fluorine atom may influence a number of physico-chemical properties of molecules, i.e.: electrical charges of atoms, acid character of neighboring functional groups, basicity of linear and cyclic amines, pK_a perturbation, conformational changes, bioavailability, toxicity, modulation of lipophilicity and metabolic stability [1-2]. More and more medications possess this element in its structure, as it can affect the bioavailability and activity [3]. Since the 1950s, over 150 fluorine-containing drugs have been released to the market which now make up approx. 20% of all pharmaceuticals, with even higher records for agrochemicals (up to 30%) [4].

Hydrogen bond, one of the best known molecular interaction, affects different properties of compounds, i.e.: increases solubility, boiling temperature, conductivity. The presence of the hydrogen bonds in the sample can be observed using FT-IR spectroscopy. The most important changes in the spectra refer to: band intensities, half-width and the shift of the bands toward lower wavenumbers. To the best of our knowledge no systematic study was performed to evaluate the influence of fluorine substitution on tuning the strength of hydrogen bond.

Methodology

The electrostatic surface potential (ESP) and atomic charge distribution for a series of benzene derivatives with different hydrogen bond donor/acceptor (HBD/A) substituents (-OH, -NH₂, -CHO, -OCH₃, -SCH₃ and -NO₂, Fig. 1) were calculated using DFT/B97-1 method and cc-pVTZ-pp++ basis set. Next, the influence of fluorination on the strength of the hydrogen bond was investigated for a series of aniline–aniline, aniline–CH₃OH and aniline–CH₃OD using FT-IR spectroscopy (spectra were recorded using Thermo Scientific Nicolet™ iS™5 FT-IR Spectrometer equipped with single-reflection ATR plate). The spectra of aniline in gas phase were collected from the NIST database (National Institute of Standards and Technology).

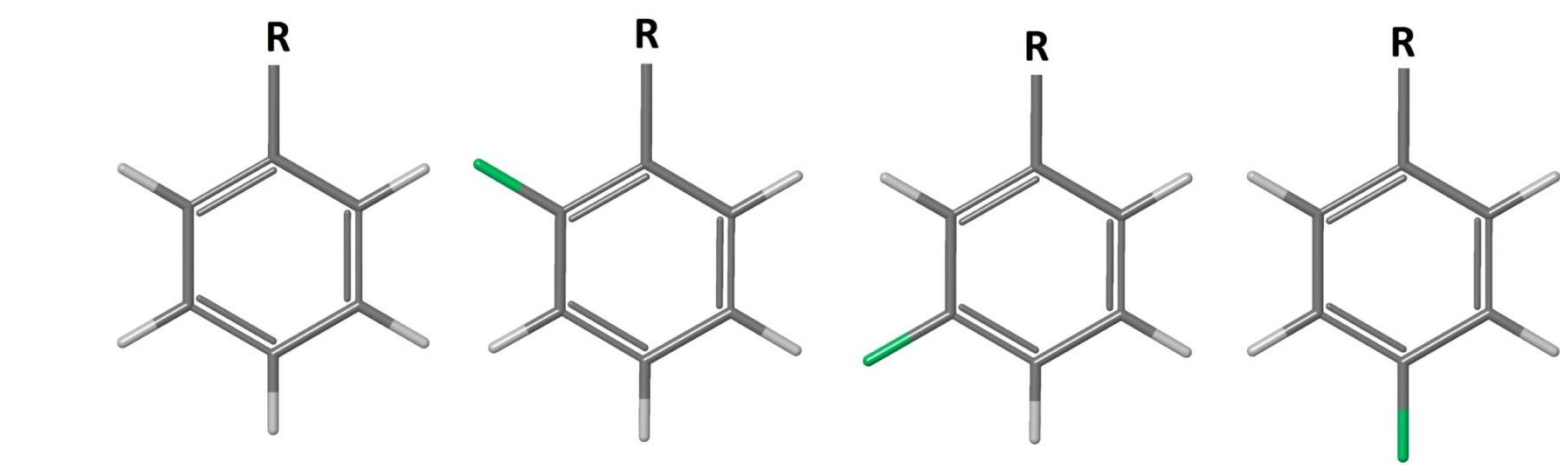


Fig. 1. The models used in ESP calculations, where R = -OH, -NH₂, -CHO, -OCH₃, -SCH₃, -NO₂.

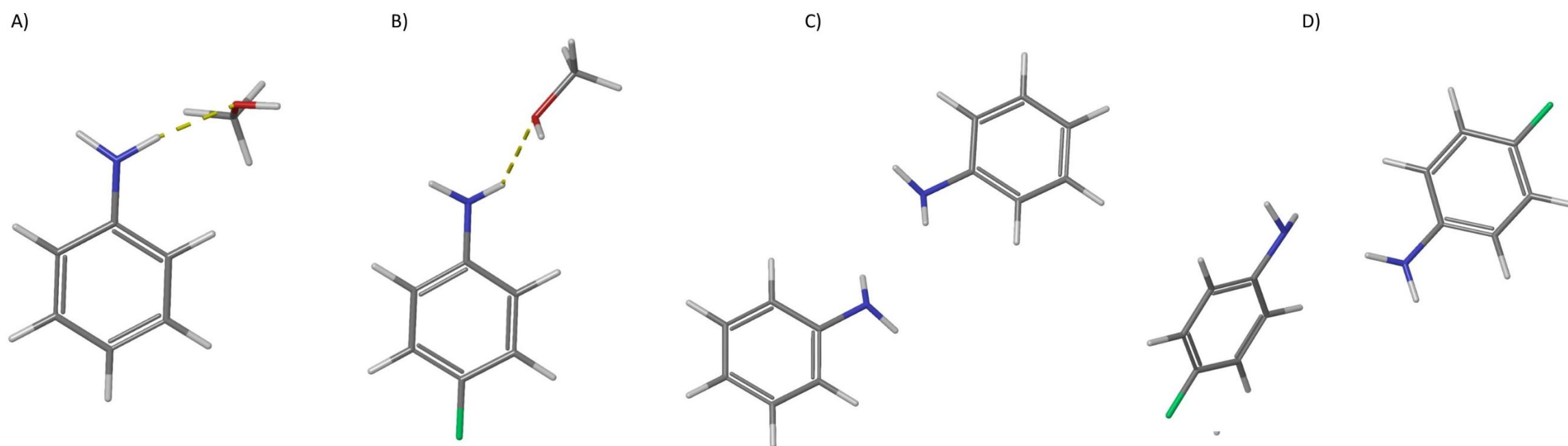
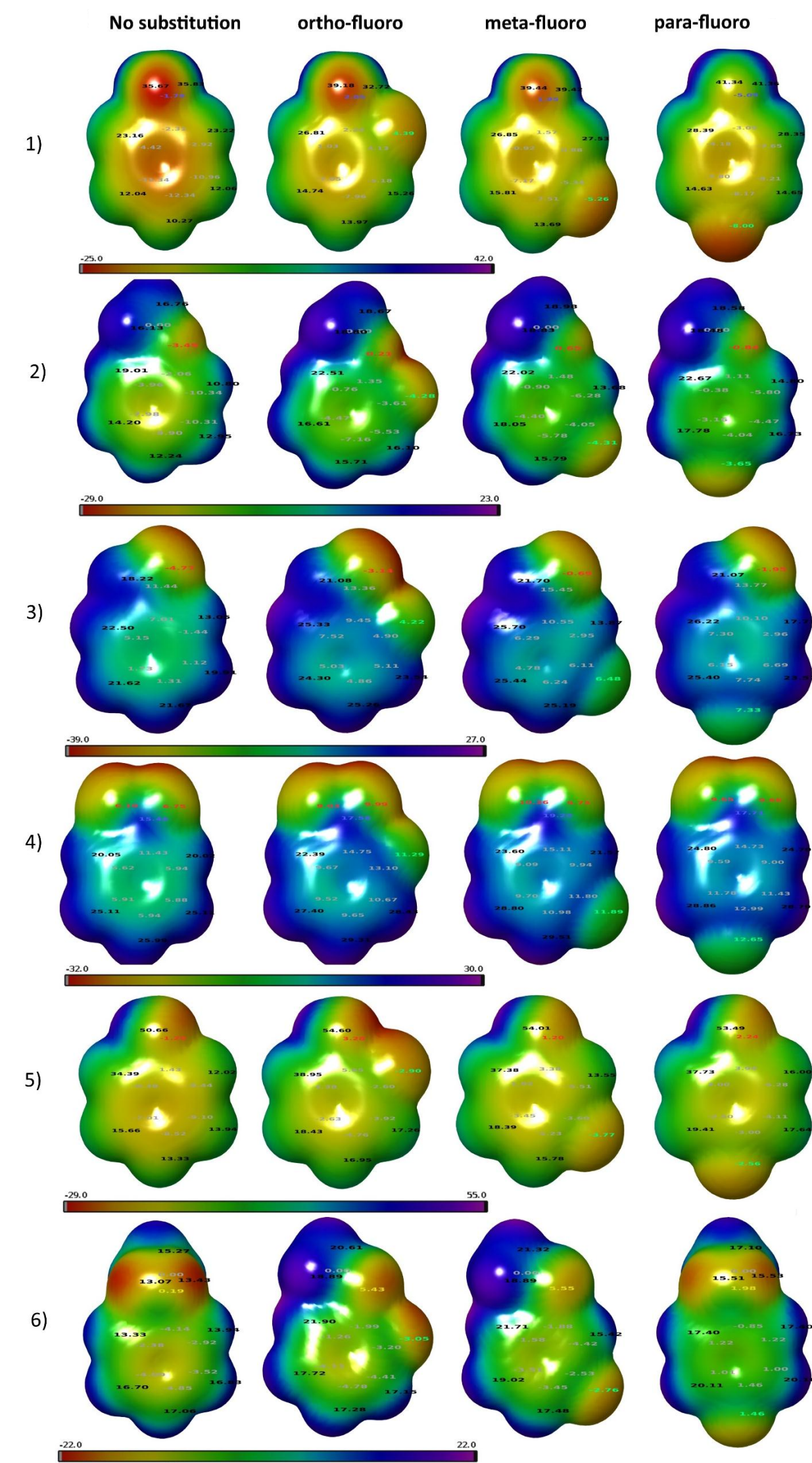


Fig. 2. The models used as input to the calculation of hydrogen bonding energy e.g.: A) unsubstituted aniline b) p-fluoroaniline c) unsubstituted dimer d) p-fluoroaniline dimer.

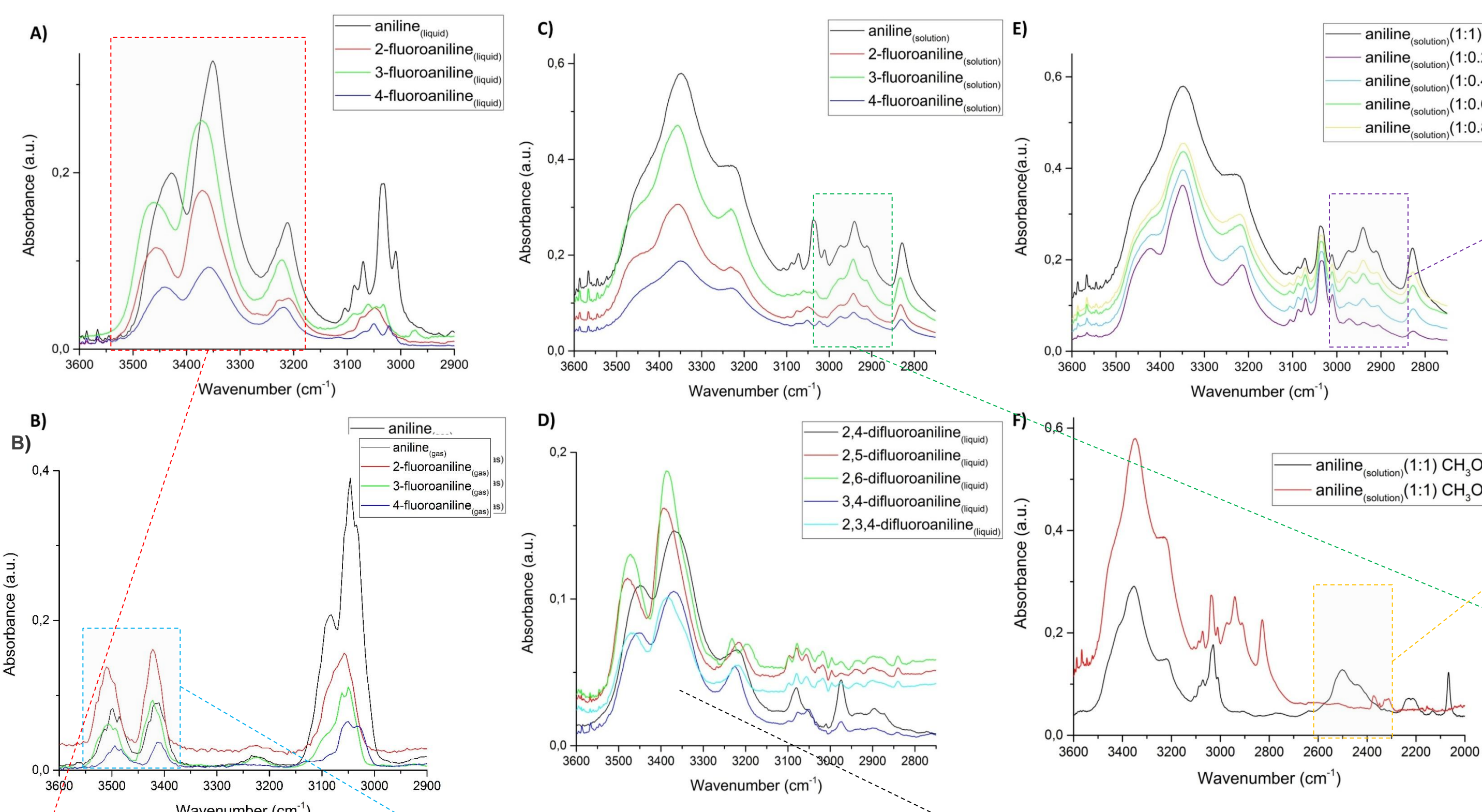
Results and Conclusions

Fig. 3. Molecular electrostatic potential surface of model compounds: 1) aniline, 2) anisole, 3) benzaldehyde, 4) nitrobenzene, 5) phenol, 6) thioanisole, calculated using B97-1/cc-pVTZ-pp++.



Bands at wavelengths 3450 cm⁻¹ and 3550 cm⁻¹ originate from the N-H stretching vibrations (symmetric and antisymmetric, respectively). The intensity showed strict dependence on the fluorine substitution in aniline ring.

Fig. 4. Comparison of the FT-IR spectra of aniline derivatives: A) liquid aniline derivatives, B) gas phase aniline derivatives, C) aniline derivatives in CH₃OH solution, D) polysubstituted aniline derivatives in CH₃OH solution E) various molar ratios of aniline : CH₃OH in F) aniline in solution of CH₃OH and CH₃OD.



The band intensity demonstrates dependence from the amount of CH₃OH.

The band shifted in the direction of the lower frequency after replacing the solvent - which is directly connected with the intermolecular hydrogen bond of aniline-CH₃OH(D).

Appears after mixing aniline with CH₃OH.

Tab. 2. Changes in the frequency of bands derived from the symmetric and antisymmetric vibration of N-H in aniline depending on the position of substitution by fluorine.

| Compounds | Aniline | | | | | | | | |
|--------------------------------------|-------------------|------|------|------|------|------|------|------|---------|
| | Fluorine position | | | | | | | | |
| | no substitution | 2 | 3 | 4 | 2, 4 | 2, 5 | 2, 6 | 3, 4 | 2, 3, 4 |
| V _{asy} [cm ⁻¹] | 3429 | 3455 | 3464 | 3441 | 3450 | 3483 | 3470 | 3451 | 3470 |
| V _{sym} [cm ⁻¹] | 3351 | 3370 | 3372 | 3359 | 3368 | 3394 | 3387 | 3370 | 3387 |

Tab. 3. The calculated geometrical parameter (distance and angle) and energy of hydrogen bonds for aniline derivatives.

| Interaction | Fluorine position | Distance [Å] (C-N...H-N) | Angle (H...N-C) | Energy [kcal/mol] |
|------------------------------|-------------------|-----------------------------|--------------------|----------------------|
| aniline - aniline | no substitution | 2.56 | 149.20 | 1.32 |
| | ortho | 2.22 | 116.50 | 2.11 |
| | meta | 2.71 | 95.70 | 5.55 |
| | para | 2.20 | 108.90 | 0.64 |
| Interaction | Fluorine position | Distance [Å] (C-N...O-H) | Angle (O...H-N) | Energy [kcal/mol] |
| aniline - CH ₃ OH | no substitution | 2.26 | 154.20 | -3.20 |
| | ortho | 2.29 | 154.40 | -3.43 |
| | meta | 2.19 | 158.40 | -4.17 |
| | para | 2.34 | 147.40 | -4.39 |

Tab. 1. The calculated values of atomic charges.

| Compound | Element | Position fluorine | | | |
|--------------|---------|-------------------|-------|-------|-------|
| | | no substitution | ortho | meta | para |
| aniline | f | - | -0.20 | -0.23 | -0.23 |
| | n | -0.72 | -0.67 | -0.71 | -1.06 |
| | h | 0.30 | 0.31 | 0.31 | 0.42 |
| anisole | f | - | -0.19 | -0.23 | -0.22 |
| | o | -0.36 | -0.29 | -0.34 | -0.35 |
| benzaldehyde | f | - | -0.19 | -0.21 | -0.21 |
| | o | -0.43 | -0.42 | -0.43 | -0.44 |
| | h | 0.13 | 0.13 | 0.12 | 0.18 |
| nitrobenzene | f | - | -0.15 | -0.22 | -0.20 |
| | n | 0.59 | 0.63 | 0.63 | 0.64 |
| | o | -0.39 | -0.40 | -0.39 | -0.40 |
| | o | -0.39 | -0.37 | -0.39 | -0.40 |
| phenol | f | - | -0.19 | -0.22 | -0.22 |
| | o | -0.56 | -0.51 | -0.54 | -0.55 |
| | h | 0.39 | 0.39 | 0.39 | 0.39 |
| thioanisole | f | - | -0.19 | -0.22 | -0.24 |
| | s | -0.26 | -0.12 | -0.18 | -0.21 |

- The results confirmed the impact of fluorine on the acidity of the functional groups.
- Substitution of fluorine might induce change in the geometry of molecules, as well as the position of the electron lone pairs.
- Based on the FT-IR spectra and quantum computations the influence of substitution of fluorine and its position in the ring on the strength of hydrogen bonds is visible.
- The results can be used in rational drug design and modification of leading structures to improve the activity and pharmacokinetic and pharmacodynamics properties.

References

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Acknowledgments

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