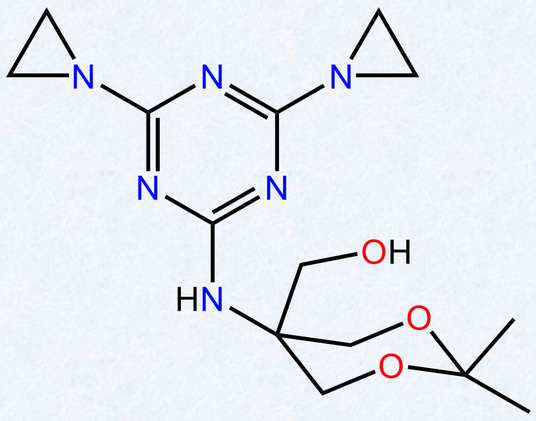
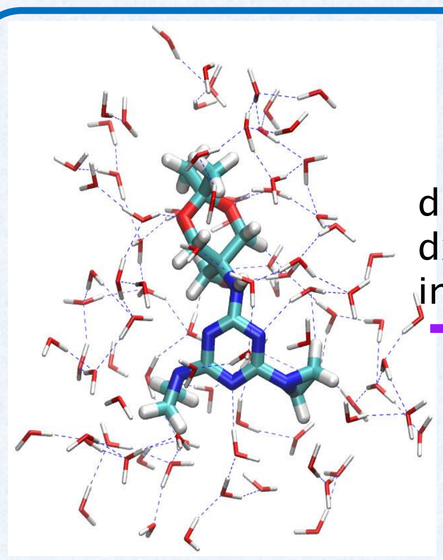
THE MOLECULAR DYNAMICS STUDY OF A DIOXADET DRUG PROPERTIES IN WATER

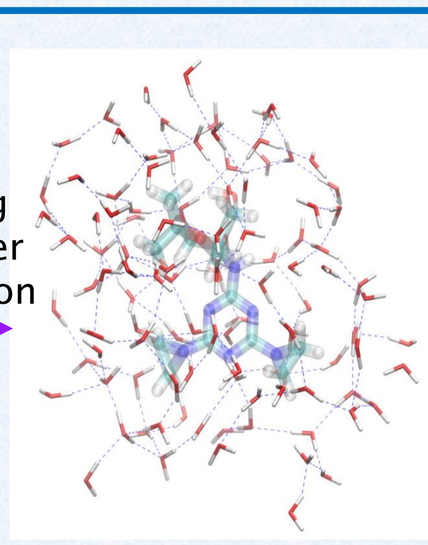
Dioxadet is an effective antitumor drug. Its mechanism of action is alkylation of proteins, DNA, and amino acids. It was developed at the N.N. Petrov NMRC of Oncology in St. Petersburg. It passed phase II clinical trials and was approved for production and use in clinical practice. It has less toxicity and fewer side effects than cisplatin. The main purpose of this study is to evaluate the physicochemical properties of dioxadet in water.



Molecular dynamics methods and the Gromacs software package were used for the calculations. Parametrization was performed using online services and the software package AmberTools.



disabling dxt-water interaction

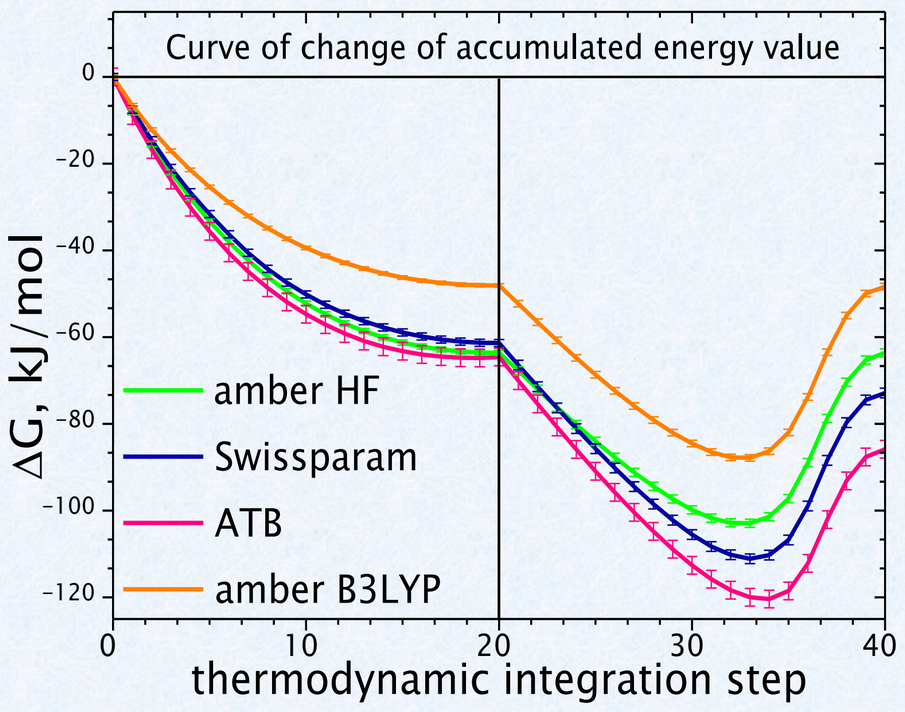


$$\Delta G_{HF} = (-63{,}6 \pm 0{,}9)\ \frac{kJ}{mol}$$

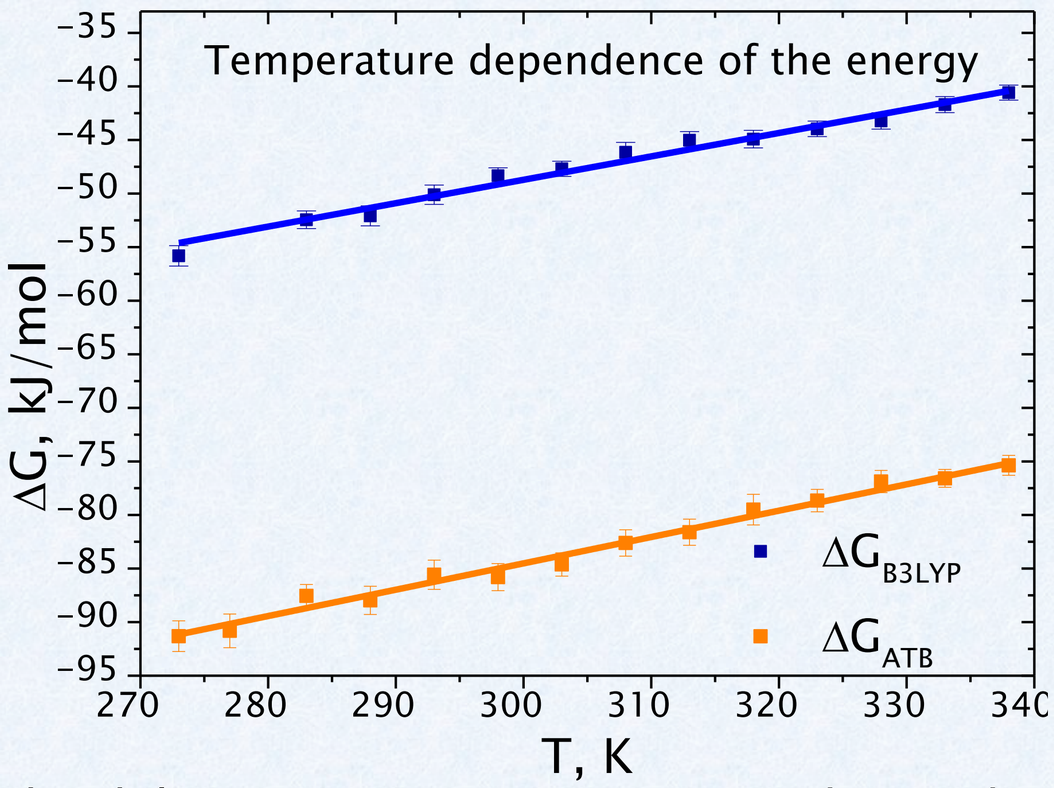
$$\Delta G_{B3LYP} = (-48{,}3 \pm 0{,}8)\ \frac{kJ}{mol}$$

$$\Delta G_{atb} = (-85{,}8 \pm 2{,}0)\ \frac{kJ}{mol}$$

$$\Delta G_{swiss} = (-72{,}9 \pm 1{,}1)\ \frac{kJ}{mol}$$



The energy is estimated between the states in which water interacts with a molecule and freely passes through. The resulting energy is the energy of solvation of the gas in water.
Qualitative analysis is not affected by the difference in models.



Hydrophilicity criteria:
$\Delta S < 0, \Delta H < 0$

Approximated according to the equation:
$\Delta G = \Delta H - T\Delta S$

In this case there is no temperature dependence of enthalpy and entropy, so the obtained values are considered qualitatively. The negative enthalpy is explained by the formation of new interactions - Coulomb, van der Waals, hydrogen bonds; the negative entropy is explained by the decrease in the chaotic motion or orientation of the solvent molecules and/or the dioxadet itself.

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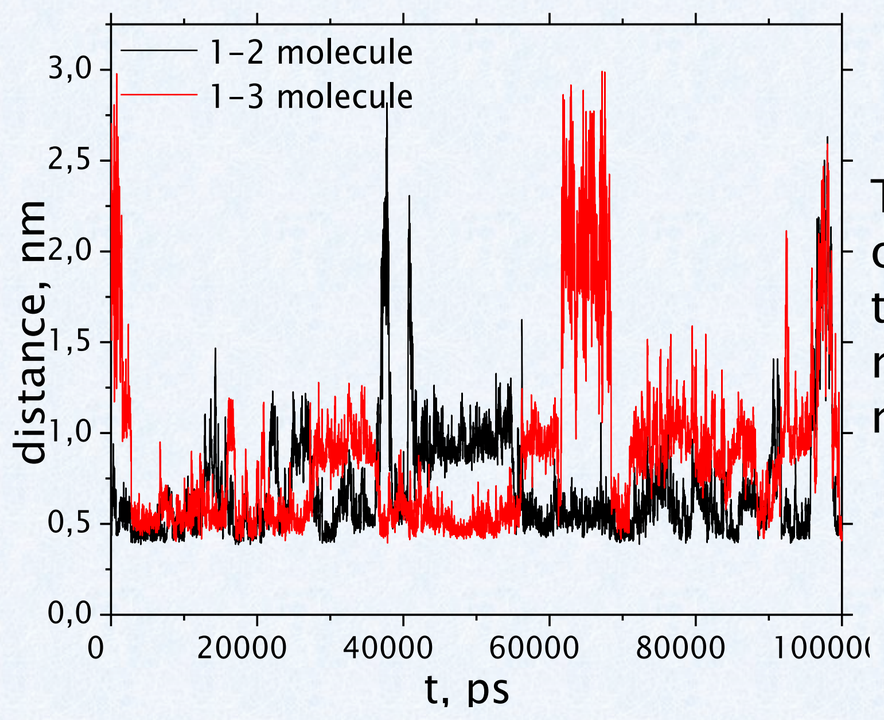
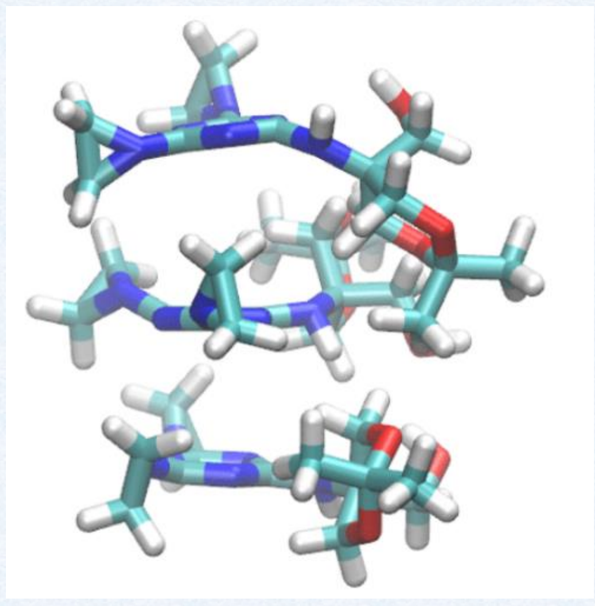
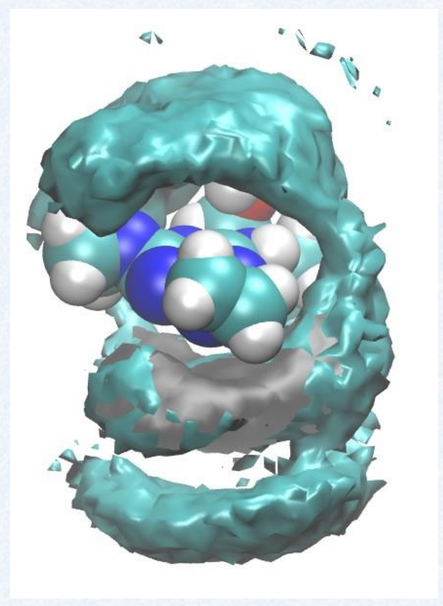


Time dependence of the distance to the center of mass of dioxadet molecules.



An example of the order of molecules in water.



Spatial distribution for the ATB-model.

Dioxadet molecules associate. Sometimes molecules are arranged in stacks. The behavior of the molecules is explained by the presence of relatively large charges on the atoms in the aromatic ring, in other words, by electrostatic interactions.