Empirical electrostatic description of organic molecules with formally charged groups

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Many potential objects for molecular design such as ionic liquids, proteins, oligosaccharides, nucleic acids contain formally charged groups. For description of such structures electrostatic interactions, which are usually described as point charges coulomb interaction, play an important role. However most standard methods of charge distribution prediction are well studied and tuned for neutral molecules. When structures containing formally charged groups are considered, accurate description of charge distribution is often not pursued, supposing that group formal charges play leading role. But the question arises regarding the relevance of such approach and which distortions of results in numerical experiments it may cause.

To test the hypothesis of significance of accurate accounting of charge distribution for structures with formally charged groups, molecular dynamics simulations of 1,3-dimethylimidazolium chloride ionic liquid were performed. Simulations contained 4096 ionic pairs and were carried out at 423 and 500K during 5 ns. These calculations were performed with different atomic charges: AM1-BCC, MK-ESP, RESP, Mulliken and Gasteiger. The predicted properties of ionic liquids differ substantially for different charge distributions, especially such dynamics properties as self diffusion coefficients and structural properties as radial distribution functions.

Methods for calculating charge distribution can be divided into non-empirical, semi-empirical and empirical. The latter are more convenient for wide use in molecular modeling because they are fast and have ability to adjust the accuracy of calculation depending on the task and in some cases are topologically symmetrical. In this work for describing structures with formally charged groups a scheme based on dynamical electronegativity relaxation (DENR) [1] is used, as in addition to the advantages listed above it also takes into account inductive effect.

For verifying the adequacy of scheme preliminary parameter optimization was carried out on a structure set obtained by the following way. First, the patterns for structure generation were derived, including specification of most frequently occurring in organic molecules both formally charged and neutral groups and the ways they may be connected. Second, complete generation of a set the structures based on the above patterns was conducted. Third, the set was clustered to give a compact and diverse set of 500 structures, divided into training (450) and test (50) sets. Calculated charges were examined by ability to reproduce reference molecular electrostatic potential computed quantum chemically at HF/6-31G* level. The results were compared with AM1-BCC, Gasteiger, EEM, MMFF94, Lowdin, Mulliken, MK-ESP, RESP schemes. Even in case of rough optimization DENR charges have average RMSD-values comparable to that for existing empirical schemes.

Thus, the significance of accurate accounting charge distribution for structures with formally charged groups was pointed out. Current DENR scheme may be used for such calculations as fast and precise tool to improve electrostatic description of these structures.

[1] D.A. Shulga, A.A. Oliferenko, S.A. Pisarev, V.A. Palyulin, N.S. Zefirov, *SAR QSAR ENVIRON RES*, **2008**, *19*, 153-165.