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COMMENTS

Comment on "Assessing the Efficacy of Nonsteroidal Anti-Inflammatory Drugs Through the Quantum Computation of Molecular Ionization Energies"

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Shakman and Mazziotti[1] have calculated the ionization energies (IE) of 12 salicylic acids and 15 phenols and examined the statistical correlations between these IE and the efficacy of these 27 molecules, acting as anti-inflammatory agents. To calculate these IE, the authors employed the Hartree−Fock method and density functional theory (DFT), using the B3LYP and PBEPBE functionals with and without Koopmans' theorem.[2] Our aim is to complement the report of Shakman and Mazziotti[1] by comparing their statistical correlations with those obtained via a computation of ionization energies by semiempirical AM1[3] and ab initio molecular HF calculations.[4] The anti-inflammatory efficacy of the tested molecules, including the salicylic acid and phenol derivatives studied by Shakman and Mazziotti,[1] as well as benzoic acid derivatives, determined earlier,[5] is expressed as their pIC_{50}, which is the logarithm of the reciprocal of IC_{50}, the 50% inhibitory concentration of the prostaglandin production in mouse macrophages. The quantum mechanical methods used to determine IE have to be related to correlation coefficicients *R* observed between the IE of the tested molecules and their biological potency. Our aim is to verify if less demanding semiempirical methods, more adapted to large molecules, are able to provide statistical correlations as satisfactory as density functional theories or ab initio molecular orbital calculations applied to the same set of molecules.

The correlation coefficients *R* obtained by Shakman and Mazziotti[1] for the 27 molecules, which they selected, are 0.66 and 0.56 for the Hartree−Fock method and in a range between 0.69 and 0.72 for the density-functional methods. For the same 27 molecules, using a semiempirical AM1 method carried out with the Hyperchem 4 program, we obtain a linear correlation expression:

$$\begin{gathered}\mathrm{pIC}_{50} = 2.89E(\mathrm{HOMO}) + 31\\ n = 27 \qquad R = 0.83\end{gathered} \tag{1}$$

The corresponding *E*(HOMO) and pIC_{50} values of eq 1 are reported in a Table S1, available in the Supporting Information.

Ab initio calculations by Mehler and Gerhards[4] for 34 salicylic acid, benzoic acid, and phenol derivatives yield the regression expression:[4]

$$\begin{gathered}\mathrm{pIC}_{50} = 0.077E(\mathrm{HOMO}) + 21.64\\ n = 34 \qquad R = 0.84\end{gathered} \tag{2}$$

Using a semiempirical AM1 method carried out with the Hyperchem 4 program for 32 molecules out of the 34 molecules studied by Mehler and Gerhards,[4] we obtain the regression

$$\begin{gathered}\mathrm{pIC}_{50} = 2.66E(\mathrm{HOMO}) + 28.90\\ n = 32 \qquad R = 0.86\end{gathered} \tag{3}$$

The two molecules discarded are two benzoic acids with 3,5-dihydroxy and 4-*n*-propyl substituents. This series of 32 molecules includes the 27 molecules selected by Shakman and Mazziotti.[1]

For the same 32 molecules, the ab initio method used by Mehler and Gerhards[4] yields

$$\begin{gathered}\mathrm{pIC}_{50} = 0.076E(\mathrm{HOMO}) + 21.504\\ n = 32 \qquad R = 0.82\end{gathered} \tag{4}$$

Table S2 reporting the AM1 and ab initio E(HOMO) values of these 32 molecules is available in the Supporting Information.

Comparing the different statistical correlation coefficients reported above, it is possible to conclude, at least for the molecules studied here, that the correlation coefficients, $R =$ 0.83 and 0.86, obtained by simple semiempirical quantum mechanical method AM1 can be successfully compared with those obtained by more sophisticated and more demanding methods such as B3LYP and PBEPBE density-functional[1] or ab initio HF[4] computations.

It is interesting to notice that all calculations using *E*(HOMO) values yield data describing vertical ionization potentials, i.e., calculations where the molecular geometries of both molecules and cations are identical. In the DFT particular case, the *E*(HOMO) are those generated by the Kohn and Sham[6] noninteracting electron model. Consequently, the DFT computations give *E*(HOMO) values lower than the exact ones by a deviation ΔE. It has been found that this ΔE is an almost constant quantity if the correct electronic structure of the cation is taken into account, by minimizing the energy.[7] In such conditions, the linear expressions obtained from *E*(HOMO) computed by DFT correspond effectively to genuine vertical ionizations. In contrast, those obtained by optimizing also the geometries of the ions, as done by Shakman and Mazziotti,[1] describe adiabatic ionizations. This distinction betweeen vertical

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and adiabatic ionizations, important in gas processes, is usually neglected for chemical and biochemical phenomena in condensed phases.

The better quality of the semiempirical method with respect to the DFT ones, exhibited by the linear correlation coefficients reported above, is consistent with a remark by Parr and Yang[8] stating that the semiempirical methods may be considered as some kinds of simplified but well parametrized DFT approaches.

Editor's Note. The Author of the original work reviewed this Comment and is in agreement with the content.

Supporting Information Available: Table S1 giving *E*(HOMO) and pIC_{50} values of eq 1and Table S2 giving M1 and ab initio *E*(HOMO) values. Diagrams related to linear regressions (1), (3), and (4). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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