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

Katherine B. Shakman and David A. Mazziotti*

Department of Chemistry and The James Franck Institute, The University of Chicago, Chicago, Illinois 60637

Received: March 31, 2007; In Final Form: May 25, 2007

The clinical efficacy of nonsteroidal anti-inflammatory drugs has been related to ionization energies [Mehler and Gerhards, *Int. J. Quantum Chem*. **1989**, *25*, 205]. In this paper we employ modern quantum-chemical calculations to re-examine the statistical correlation between clinical efficacy and ionization energies. Ionization energies are computed by density functional theory, with and without Koopman's theorem, for a series of salicylic acids and phenols whose activities, or efficacy, are known. Using a regression analysis, we show that improving the treatment of electron correlation beyond previous studies enhances the statistical correlation between clinical activities and ionization energies.

I. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin (acetylsalicylic acid) and Ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid), are some of the most common drugs in use in the United States today. They are employed to treat headaches, cramps, pain, and swelling from athletic injuries and sickness, and even heart disease. The use of these "miracle drugs," however, will not always yield miraculous results. In recent years, many newly developed, highly popular NSAIDS, such as Vioxx, have been taken off the market due to the discovery of dangerous side effects even though they also have beneficial effects such as decreased gastrointestinal bleeding.[1] Unfortunately, the process of screening potential drugs for anti-inflammatory activities in the laboratory is a protracted and potentially costly one. An important approach to alleviating the costs in time and effort is the development of a simple computational diagnostic for screening activity. Therefore, in the present paper, we build upon previous investigations[2−5] through the use of quantum-mechanical methods that include electron correlation to analyze molecules for their effectiveness as anti-inflammatory drugs.

A key step in the activity of an NSAID is its oxidation to reduce the cyclooxygenase (COX) enzyme by (i) electron or (ii) hydrogen transfer. Independent of the mechanism for oxidation, however, a drug's ionization energy offers a useful measure of a drug's oxidative potential, and consequently, an NSAID's activity should be correlated to its ionization potential. Previous work, employing either elementary molecular-orbital or empirical methods for the electron correlation, established a link between activities and ionization energies (or potentials).[2−5] In the present paper, we build upon previous work by treating the electron correlation with the more sophisticated density functional theory, implemented in the Gaussian[6] package. Total energy calculations were performed on 27 molecules, 15 phenols, and 12 salicylic acids, and their anions with Hartree−Fock and density-functional (B3LYP and PBEPBE functionals) methods in a 6-31G basis set. Ionization energies were computed by two approaches: (i) Koopman's Theorem,[7] which observes that the absolute value of the energy of the highest occupied molecular orbital (HOMO) is approximately equal to the ionization energy, and (ii) the difference (ΔE) between the total energy of the molecule and the total energy of its corresponding anion, i.e., the energy difference due to removing an electron (a direct measure of the ionization energy). To facilitate comparison with earlier work of Mehler and Gerhards,[2−4] we use a common set of molecules and pharmacological data.

II. Theory

We investigated modern methods of computing ionization energy (IE) because of the strong relationship between a molecule's IE and its ability to reduce a target molecule. The reduction may occur by (i) electron or (ii) hydrogen transfer.[8] In the first case, the anti-inflammatory agent loses an electron in an ionization process while in the second, the hydrogen atom transfers from the anti-inflammatory molecule in a process that, while not ionization, is also an oxidation. A detailed study of either of these mechanisms would require consideration of the cyclooxygenase enzyme, zero-point energies, and solvent effects. Independent of the specific mechanism, however, the ionization potential of the molecule provides a potentially useful quantum-mechanical diagnostic for its oxidative potential. The goal of the present work is to characterize with modern electronic structure methods the statistical correlation between molecular ionization energies and pharmacological activities.

The ionization energy, or IE, of a molecule is the difference in total energy between the neutral molecule and the molecule after an electron has been removed. In what we call the ΔE method, we compute the IE directly as

$$\mathrm{IE} = E_\mathrm{r} - E_\mathrm{m}$$

where E_r is the total energy of the radical and E_m is the total energy of the neutral molecule. In Koopman's method, we approximate the IE by Koopman's theorem,[7] which states that

$$\mathrm{IE} \approx |E_\mathrm{HOMO}|$$

* Corresponding author. E-mail: damazz@uchicago.edu. Phone: 773-834-1762. Fax: 773-834-5250.

10.1021/jp0725331 CCC: $37.00
Published on Web 07/04/2007

TABLE 1: For Each Salicylic Acid and Phenol, We Report the Absolute Energy $|E_{HOMO}|$ of the HOMO Orbital (Koopman's IE), the Ionization Energy (IE), and the Pharmacological Activity (pIC50)[a]

		$\|E_{HOMO}\|$[a]			IE[b]		
R group[c]	HF	B3LYP	PBEPBE	HF	B3LYP	PBEPBE	pIC50[d]
			Salicylic Acids				
H	0.33041	0.23597	0.20376	0.27393	0.30628	0.30122	3.33
3-OH	0.50754	0.22411	0.19025	0.26743	0.29223	0.28523	4.43
4-OH	0.49986	0.23668	0.20336	0.27555	0.30318	0.29573	3.02
5-OH	0.50098	0.21776	0.18422	0.26308	0.28464	0.27744	4.61
3-F	0.51274	0.24267	0.20820	0.28658	0.31225	0.30455	3.82
5-F	0.51129	0.24026	0.20575	0.28511	0.30960	0.30161	3.82
3-Cl	0.47320	0.24444	0.21123	0.28494	0.31012	0.30228	3.89
4-Cl	0.47211	0.25098	0.19883	0.28761	0.31759	0.31048	3.31
5-Cl	0.46449	0.24330	0.21010	0.28500	0.30845	0.30023	4.06
3-IPR	0.44962	0.23053	0.19870	0.26382	0.29394	0.28785	3.92
4-IPR	0.45623	0.23231	0.19920	0.26776	0.29777	0.29106	3.29
5-IPR	0.45839	0.22708	0.19570	0.26508	0.29613	0.28960	4.12
			Phenols				
H	0.31712	0.22319	0.19052	0.26477	0.29944	0.29573	3.54
2-OH	0.31091	0.21275	0.17857	0.25818	0.28581	0.27976	5.34
3-OH	0.31979	0.22121	0.18704	0.26362	0.29391	0.28692	5.15
2-CH3	0.31034	0.21794	0.18555	0.25745	0.29029	0.28581	5.16
3-CH3	0.31300	0.21943	0.18664	0.25845	0.29267	0.28783	4.74
4-CH3	0.30628	0.21469	0.18259	0.25588	0.28622	0.28142	5.26
2-ETH	0.30911	0.21695	0.18461	0.25537	0.28775	0.28282	5.88
3-ETH	0.31326	0.21942	0.18652	0.25809	0.29150	0.28689	5.26
4-ETH	0.30621	0.21519	0.18329	0.25640	0.28541	0.27979	5.61
2-F	0.33197	0.23214	0.19711	0.27979	0.30721	0.30064	3.57
3-F	0.33552	0.23650	0.20195	0.28171	0.31197	0.30559	4.05
4-F	0.32871	0.22832	0.19310	0.27720	0.30321	0.29618	3.98
2-Cl	0.33158	0.23508	0.20149	0.27801	0.30569	0.29896	4.62
3-Cl	0.33567	0.23941	0.20579	0.27956	0.31060	0.30394	4.61
4-Cl	0.32956	0.23258	0.19883	0.27729	0.30235	0.27729	4.86

[a] Energies are reported in atomic units. [b] Energies are computed by the Hartree−Fock (HF) method and two density-functional theories, B3LYP and PBEPBE, in the 6-31G basis set. [c] ETH, ethyl; IPR, isopropyl. [d] Ref 2.

where $|E_{HOMO}|$ is the absolute value of the energy of the highest occupied molecular orbital (or HOMO) of the molecule. Koopman's theorem only requires calculation of the molecule's molecular orbitals. Molecular and radical energies and orbitals are computed by both the Hartree−Fock method and density functional theory. In contrast to previous work,[2−5] we (i) compute the IEs, not only by Koopman's theorem but also by the energy differences between the neutral molecules and their radicals, and (ii) include electron correlation in the calculation of the IEs through density functional theory. It should be noted that, while the ΔE method is the more direct method of determining ionization energy, there are still some approximations inherent in the calculations, because each level of theory (HF, B3LYP, PBEPBE) in a finite basis set is an approximation to the many-electron Schrödinger equation. Furthermore, while we are building on past results by employing more sophisticated theory, we must recognize, however, that though we expect our calculations to be more accurate, improved accuracy does not necessarily imply that our results will demonstrate a greater correlation with activity (potency).

III. Results

Energy calculations were performed for 27 molecules and their radical ions by the Hartree−Fock (HF) method and two density-functional theories, using the B3LYP and PBEPBE functionals, in Pople's[9] 6-31G basis set. In all cases the molecular geometries of *both* molecules and ions were optimized with the B3LYP functional. The results were not observed to be sensitive to the type of density functional employed in the geometry optimization. Radicals are treated by unrestricted Hartree−Fock and density functional methods. Table 1 shows absolute energy $|E_{HOMO}|$ of the HOMO orbital (Koopman's IE), the directly computed ionization energy (IE), and the pharmacological activity (pIC50) where the activity pIC50 is defined as the negative logarithm of 50% of the concentration that inhibits the release of 12-*O*-teradecanol-phorbol-13-acetate-induced prostaglandin E_2 from mouse macrophages.[10] In comparison to the IEs from density functional theory with B3LYP and PBEPBE, the Hartree−Fock method underestimates the IE due to the lack of electron correlation. In contrast, when the IE is approximated as $|E_{HOMO}|$ by Koopman's theorem, the Hartree−Fock method overestimates the IE because $|E_{HOMO}|$ does not account for the lowering of the ion's energy that occurs when the molecule's orbitals are re-optimized for the ion.[7] Interestingly, the $|E_{HOMO}|$ from B3LYP or PBEPBE is generally below the IE from B3LYP or PBEPBE. The statistical correlations of IE and $|E_{HOMO}|$ with activity are studied by regression analysis in Figures 1 and 2, respectively.

Figure 1 displays the linear regression of the IE and the activity pIC50 where the IE is computed from (a) HF, (b) B3LYP, and (c) PBEPBE. Values of the correlation coefficient R indicate significant statistical correlation between IE and activity for all three of the electronic structure methods. The correlation coefficients R from HF, B3LYP, and PBEPBE, 0.6633, 0.6896, and 0.6954, can be interpreted to mean that roughly 50% ($R^2 \times 100\%$) of the variation in activity (pIC50) can be attributed to the ionization energy. Figure 2 displays information similar to Figure 1 with the ionization energy measured by $|E_{HOMO}|$. Here coefficients R of 0.5642, 0.7253, and 0.6932 from HF, B3LYP, and PBEPBE are obtained. For the B3LYP density functional method, we observe, there is slightly greater correlation of activity with $|E_{HOMO}|$ than the directly computed IE. Importantly, for both Koopman's ionization energy ($|E_{HOMO}|$) and the direct IE, the R values from the

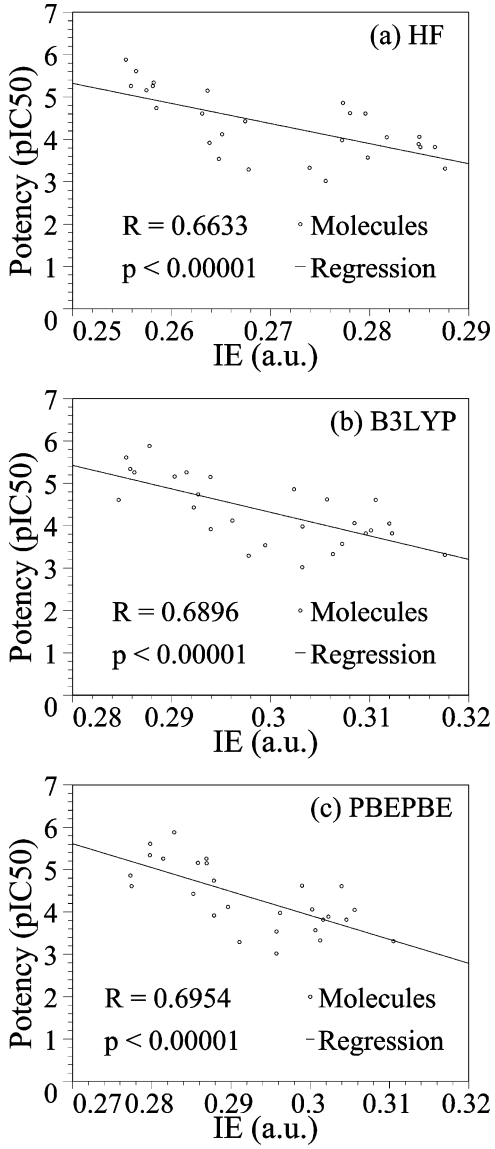

Figure 1. Figure displays the linear regression of the IE and the activity pIC50 where the IE is computed from (a) HF, (b) B3LYP, and (c) PBEPBE. Values of the correlation coefficient *R* indicate significant statistical correlation between IE and activity for all three of the electronic structure methods.

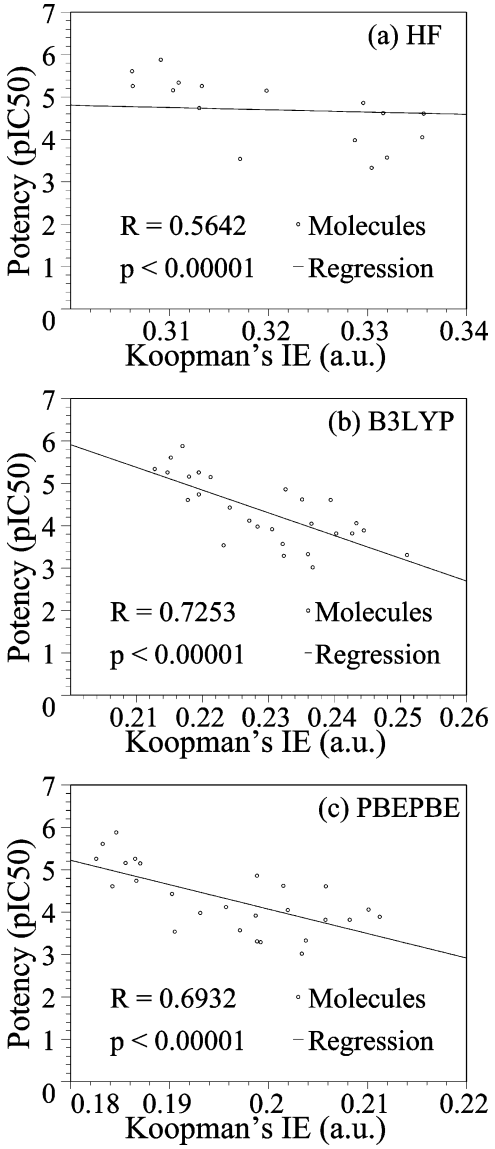

Figure 2. Figure displays the linear regression of the IE, measured by $|E_{HOMO}|$, and the activity pIC50 where the IE is computed from (a) HF, (b) B3LYP, and (c) PBEPBE. Values of the correlation coefficient *R* indicate significant statistical correlation between $|E_{HOMO}|$ and activity for all three of the electronic structure methods.

density functional methods in b and c are larger than the *R* value from the Hartree−Fock method, which indicates that electron correlation has a significant role in anti-inflammatory predictive capability. The statistical significance of the observed correlation between IE and activity is supported by the computed p-values of the linear regressions, which are all less than 0.00001.

IV. Discussion and Conclusions

Ionization energies (IEs), calculated by density functional theory as well as Hartree−Fock, show a significant correlation with the activities of a series of nonsteroidal anti-inflammatory drugs (NSAIDS). Inclusion of electron correlation through density functional theory substantially enhanced the statistical correlation between the IEs and the activities, especially when the IEs were estimated by Koopman's theorem. Previous studies,[2−4] performed before the development of modern density functional theory, examined the relation between IEs and activities by a simpler molecular orbital theory in a minimal basis set while a more recent study[5] computes IEs of larger NSAIDS by an empirical theory. The present work shows that (i) a significant statistical correlation between IE and activity persists when more accurate electronic structure methods, namely density functional theories, are employed, and (ii) the inclusion of electron correlation by the density functionals (B3LYP or PBEPBE) improves upon the statistical correlation obtained by the Hartree−Fock method. The correlation coefficients reveal that IEs account for roughly 50% of the observe activity, and hence, the IEs, which provide a general measure of the molecule's oxidative potential, are a strong chemical indicator for assessing pharmacological activity of NSAIDS. Although the present approach does not consider details of the oxidation or the structure of the cyclooxygenase enzyme, the ability of the ionization energy to predict anti-inflammatory activity without substantial complexity or computational cost is an important, practical advantage. In future work, it would be interesting to employ IEs from adding electron correlation to the Hartree−Fock method by ab initio or reduced-density-matrix methods.[7,11] Calculation of IEs by Koopman's theorem has also been used to assess the efficacy of antioxidants for

treating cancer;[12] in fact, there is evidence that NSAIDS may be especially effective anticarcinogens.[13] Screening molecules for oxidative potential is also important in the design of therapeutic drugs for sickle-cell anemia.[14] The predictive ability of the present quantum-mechanical approach for analyzing the efficacy of NSAIDS can potentially be improved by combining IEs with other indicators in a multidimensional statistical model.[15,16]

Acknowledgment. D.A.M. acknowledges the NSF CAREER, the ACS Petroleum Research Fund, the David and Lucile Packard Foundation, and the Alfred P. Sloan Foundation, and K.S. acknowledges the Camille and Henry Dreyfus Foundation Special Grant Program in the Chemical Sciences.

References and Notes

(1) Solomon, S. D.; McMurray, J. J.; Pfeffer, M. A.; Wittes, J.; Fowler, R.; Finn, P. et al. *N. Engl. J. Med.* **2005**, *352*, 1071.

(2) Mehler, E. L.; Gerhards, J. *Int. J. Quantum Chem.* **1989**, *35*, 205.

(3) Mehler, E. L.; Gerhards, J. *Mol. Pharmacol.* **1985**, *31*, 284.

(4) Mehler, E. L.; Gerhards, J. *Int. Am. Chem. Soc.* **1985**, *107*, 5856.

(5) Zoete V.; Bailly F.; Maglia F.; Rougee M; Bensasson *Free Radical Biol. Med.* **1999**, *26*, 1261.

(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(7) Szabo A.; Ostlund N. S. *Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory*; Dover: New York, 1996.

(8) Wang, L.; Song, Y.; Zhang, X.; Liu, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3241.

(9) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(10) Habicht, J.; Brune, K. *J. Pharm. Pharmacol.* **1983**, *35*, 718.

(11) Mazziotti, D. A. *Acc. Chem. Res.* **2006**, *39*, 207.

(12) Zoete, V.; Rougee, M.; Dinkova-Kostova, A. T.; Talalay, P.; Bensasson, R. V. *Free Radical Biol.* **2004**, *36*, 1418.

(13) Subbaramiaiah, K.; Dannenberg, D. J. *Trends Pharmacol. Sci.* **2003**, *24*, 96.

(14) Rohrman, B. A.; Mazziotti, D. A. *J. Phys. Chem. B* **2005**, *109*, 13392.

(15) Kauffman, G. W.; Jurs, P. C. *Inf. Comput. Sci.* **2001**, *41*, 1553.

(16) Li, G. Y.; Rosenthal, C.; Rabitz, H. *J. Phys. Chem. A* **2001**, *205*, 7765.