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COMMENTS

Comment on the Paper "On the Limits of Highest-Occupied Molecular Orbital Driven Reactions: The Frontier Effective-for-Reaction Molecular Orbital Concept"

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In a recent paper, da Silva et al.[1] argued that Fukui's concept of frontier orbitals[2] was obsolete and unsatisfactory. To corroborate this statement, they consider the acidity of carboxylic acids, phenols, and alcohols. For this purpose, the orbital energies of the highest occupied molecular orbitals (HOMOs) and some specific molecular orbitals lower than HOMOs are compared with the experimental pK_a values. It turned out (not surprisingly!) that the latter gave better correlations with the measured data. Da Silva et al.[1] found it necessary to baptize these specific MOs as frontier effective-for-reaction MOs (FERMOs), claiming that it is a new concept. This is not true, as expounded in the present comment.

A suitable vehicle in exploring acidity is provided by a triadic (trichotomy) analysis. Let us consider the proton abstraction as a reverse protonation of the conjugate base anion A^-. Then, the thermodynamic cycle yields the following triadic formula:[3]

$$\mathrm{APA}(\mathrm{A}^-)_\alpha = -\mathrm{IE}(\mathrm{A}^-)^{\mathrm{Koop}}_{\alpha,n} + E(\mathrm{ei})^{(n)}_{\alpha,\mathrm{rex}} + (\mathrm{BAE})^{\bullet}_{\alpha} + 313.6\ \mathrm{kcal/mol} \quad (1)$$

Here, APA stands for the absolute proton affinity, α is the site of protonation, and 313.6 kcal/mol is the electron affinity of the proton. Further, $-\mathrm{IE}(\mathrm{A}^-)^{\mathrm{Koop}}_{\alpha,n}$ denotes the *n*th ionization energy of the anion calculated in Koopmans' approximation.[4] The second and third terms represent the relaxation and bond association energies, respectively. The sum of $-\mathrm{IE}(\mathrm{A}^-)^{\mathrm{Koop}}_{\alpha,n}$ and $E(\mathrm{ei})^{(n)}_{\alpha,\mathrm{rex}}$ gives the first adiabatic ionization energy of the anion, $-\mathrm{IE}(\mathrm{A}^-)^{\mathrm{ad}}_{1}$, as required by the thermodynamic cycle. However, the inclusion of Koopmans' term is pivotal, because it has a high interpretative value. The trichotomy components in eq 1 correspond to the final, intermediate, and initial state effects in the deprotonation process, respectively. The *n*th MO, which hosts the electron to be ejected, is the molecular orbital most closely related to the protonated center undergoing the largest change in the protonation process. This is FERMO in the terminology of da Silva et al.,[1] but we would prefer the term principal MO. This could be the HOMO, but it is usually not the case. For example, in azoles, the principal MOs are HOMO−2 orbitals without exception.[5] They describe the σ-electron density of the nitrogen lone pair(s), while the higher two occupied orbitals correspond to the π-density within the five-membered ring. The latter are not suitable, because protonation of the anion takes place in the molecular plane. Triadic analysis of the amplified acidity in higher azoles with a larger number of nitrogens leads to the conclusion that enhancement is a consequence of a combined effect of the principal MO stabilization and the increased relaxation of the electron density. Let us focus on the acidity of the carboxylic acids, which in the words of da Silva et al.[1] did not receive proper attention before their work. The fact of the matter is that triadic analyses of carboxylic acids do exist.[3,6] In acetic acid anions, $X{-}COO^-$ ($X = H, CH_3, F, CF_3$), the principal MOs are HOMO−1. The methyl group decreases acidity relative to the parent HCOOH compound due to an increase in the relaxation energy. This example provides a nice illustration of the fact that the one-particle MO picture is insufficient and that a complete triadic analysis of acidity is necessary, if its understanding is our goal.[3] The electronegative F and CF_3 substituents strongly stabilize the principal MOs, thus leading to a considerably higher acidity. However, even in these two cases, the quantitative agreement can be achieved only if all three trichotomy contributions are taken into account. Similarly, in the para-substituted benzoic acids,[6] encompassing a large variety of substituents, the amplified acidity is primarily a result of the stabilization of the principal HOMO−3 orbitals. A combined effect of the relaxation and bond association energies is small but not negligible. For example, the contribution to the acidity of the relaxation energy for the *p*-NO_2 substituent is 6 kcal/mol higher relative to the parent benzoic acid.

Let us briefly comment on the acidity of a large family of para-substituted phenols.[7] Let us focus on the superacidifying substituents SO_2CF_3, $S(O)({=}NSO_2CF_3)CF_3$, and $C(CN){=}C(CN)_2$ only. The principal MOs for the former two moieties are HOMO−2, whereas in the last one it is HOMO−3. Undoubtedly, considerable increase in the acidity of para-substituted phenols relative to the parent phenol induced by these superacidifiers arises due to the stabilization of the principal MOs. However, the relaxation energy contributions to the relative APA values are 3.8, −14.5, and 26.9 kcal/mol for SO_2CF_3, $S(O)({=}NSO_2CF_3)CF_3$, and $C(CN){=}C(CN)_2$ substituents, respectively, while the bond association energy effect yields 9.0, 32.3, and −1.4 kcal/mol in the same order. Obviously, these numbers cannot be disregarded if a good description of the trend of changes in acidity is desired. On the other hand, the electron-donating substituents such as OH, NH_2, and CH_3 reduce the acidity of the parent phenol. In these cases, the contributions to the change in acidity arising from the orbital energy of the principal MOs are negligible, whereas the contributions of the relaxation and bond association energies are decisive.

The inadequacy of the single-electron MO model can also be illustrated by the proton affinity of imino bases, since the same triadic formula mutatis mutandis holds for the protonation of neutral bases.[8,9] Consider formamidine and guanidine. Their principal MOs are HOMO−1 orbitals, which possess the same orbital energies. According to the one-electron MO picture, they should have the same APA values. However, triadic analysis

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shows that guanidine is more basic and that its APA is higher by 8.7 kcal/mol. The main contribution comes from the increased relaxation effect.

It follows that FERMOs “introduced” by da Silva et al.[1] have their predecessor and that the single-electron MO picture is not satisfactory in rationalizing (de)protonation processes. Instead, it is an important ingredient of the triadic analysis.

References and Notes

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