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Is the Fukui Function a Right Descriptor of Hard−Hard Interactions?

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To verify whether the maximum or the minimum Fukui function site is better for protonation reactions or an altogether different local reactivity descriptor, viz., the charge is necessary, we calculate the Fukui functions (using a finite-difference approximation as well as a frozen-core approximation) and charges (Mulliken, Hirshfeld, and natural population analysis schemes) of several hydroxylamine derivatives, their sulfur-containing variants, and amino acids using B3LYP/6-311G(d,p) technique. While the Fukui functions provide the wrong selectivity criterion for hard−hard interactions, the charges are found to be more reliable, vindicating Klopman's idea. It is transparent from the present results that the hard−hard interactions are better explained in terms of charges, whereas the Fukui functions can properly account for soft−soft interactions known to be frontier-controlled.

I. Introduction

The Fukui function has been used in several works as a natural descriptor of site selectivity.[1−8] Within the Li−Evans[9] reactivity and selectivity rules, for soft−soft interactions, the preferred reactive site in a molecule should have the highest value of the Fukui function, whereas the hard−hard interactions are supposed to be described through the minimum value of this local index. This criterion often correctly characterizes the reactivity in molecules with only one reactive site.[5−8] However, for polyfunctional systems where more than one site can be attacked, the Fukui function seems to fail predicting the selectivity of hard−hard interactions. Since hard−hard interactions are charge controlled and soft−soft interactions are frontier controlled,[10] the Fukui function is not expected to describe well the hard−hard interactions.[11] In this paper, we would like to verify the prognosis that hard−hard reactions are better described by charges than the Fukui functions.

We study a family of hydroxylamines where both nitrogen and oxygen atoms are active sites for a protonation reaction in addition to some of those compounds where oxygen is substituted by sulfur. We also consider some aliphatic amino acids possessing a similar reactivity pattern. The general reaction can be illustrated with hydroxylamine molecule as

$$\mathrm{NH_2OH} + \mathrm{H^+} \rightarrow \mathrm{NH_3{}^+\,OH} \qquad \text{(i)}$$

$$\mathrm{NH_2OH} + \mathrm{H^+} \rightarrow \mathrm{NH_2OH_2{}^+} \qquad \text{(ii)}$$

Experimental data show[12−14] that process i is more favorable than process ii, and sulfur being softer than oxygen would be less preferable than nitrogen for protonation. We compare the Fukui functions of different sites calculated by using the finite difference approximation as well as the frontier orbital scheme. For the charge calculation we compare three different population analysis schemes, viz., Mulliken population (MPA), Hirshfeld population (HPA),[15] and natural population (NPA) in order to have a better insight.

The formal definition of Fukui function within density functional theory (DFT) is given by

$$f(r) = \left(\frac{\delta\mu}{\delta\upsilon(r)}\right)_N = \left(\frac{\partial\rho(r)}{\partial N}\right)_{\upsilon(r)} \qquad (1)$$

Owing to the discontinuity of the $\rho(r)$ vs N curve, we have three possible derivatives as follows:

$$f^{\alpha}(r) = \left(\frac{\partial\rho(r)}{\partial N}\right)^{\alpha}_{\upsilon(r)} \qquad (2)$$

where the superscript $\alpha = \pm$ or 0, allows us to have three different types of Fukui functions: f_k^- for electrophilic attack, f_k^+ for nucleophilic attack and f_k^0, which measures the radical reactivity. Because in this work we are studying protonation reactions, only f_k^- will be useful to analyze.

This quantity can be condensed to a single value for each atom in a molecule. It can be done using two approximations: The first one is the Mulliken population based approach to the frozen-core approximation to the Fukui function as follows:[16]

$$f_k^- \approx |\phi_{\mathrm{HOMO}}|^2 = \sum_{\upsilon \in k}^{AO} |C_{\upsilon\mathrm{HOMO}}|^2 + \sum_{\mu \neq \upsilon}^{AO} |C_{\mu\mathrm{HOMO}} C_{\upsilon\mathrm{HOMO}}| S_{\mu\nu} \qquad (3)$$

and the other definition is[17]

$$f_k^- = [q_k(N) - q_k(N-1)] \qquad (4)$$

using a Hirschfeld population analysis to the finite difference approximation to eq 2.

II. Results and Discussion

Figure 1 depicts the optimized structures for hydroxylamines and their sulfur-containing variants, and Figure 2 shows the

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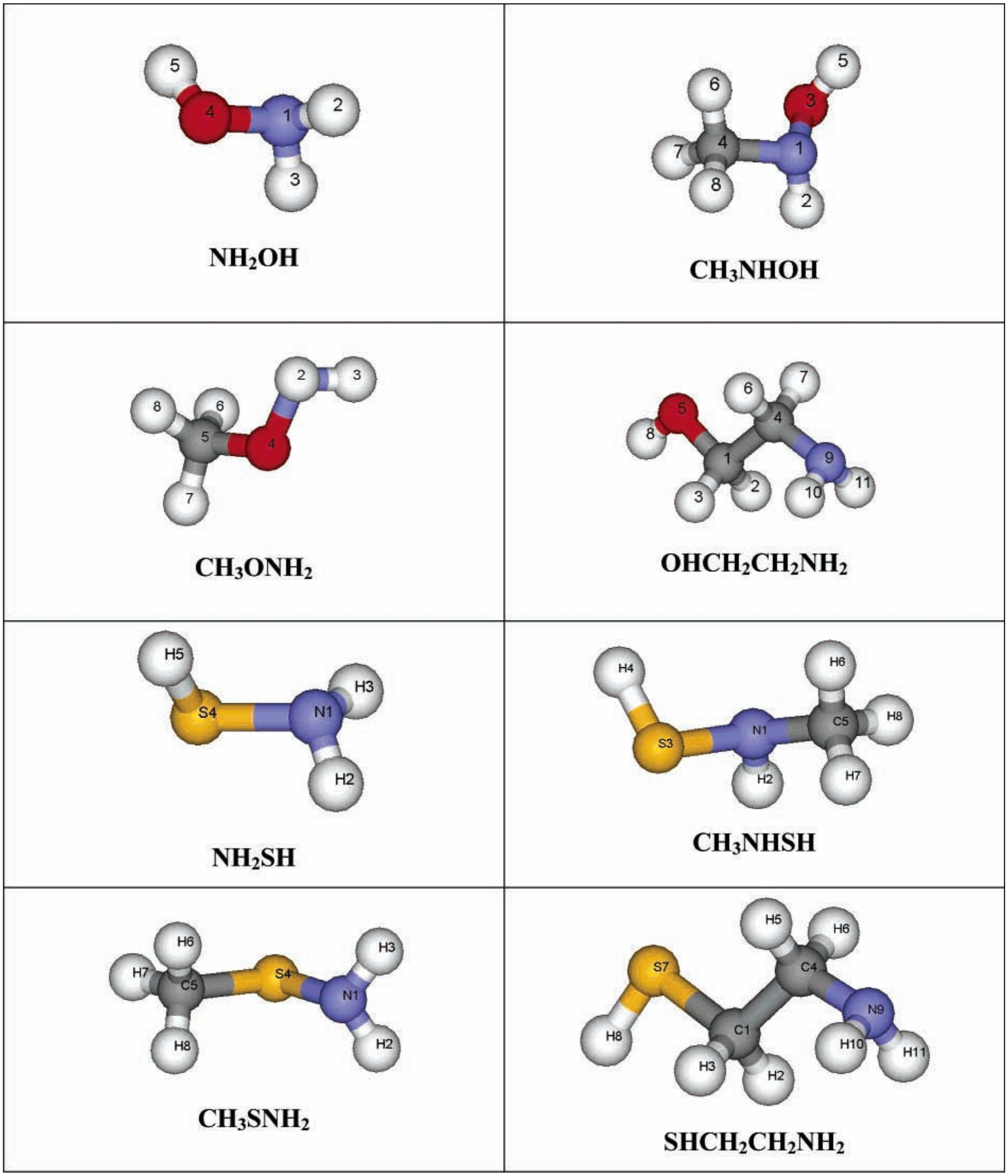

Figure 1. Optimized structures of hydroxylamines and their corresponding sulfur-substituted molecules.

optimized structures of amino acids studied in this work. These optimizations have been done at B3LYP/6-311G(d,p) level of theory with Gaussian98 program.[18] The Mulliken charge analysis was performed using the Gaussian output, and the Stock−Holder charge analysis has been done with the DMOL program.[19] The results are summarized in Tables 1−12. All quantities are expressed in atomic units. Fukui functions were calculated using the two different approximations explained above, eq 3 for f_k^-(I) and eq 4 for f_k^-(II) in the tables. In most of the cases, the highest value of the Fukui function is on a nitrogen atom, no matter the approximations that are being used, whereas the oxygen shows a lower value of this index. On the basis of only this result, we could conclude that the oxygen atom (and *not* the nitrogen atom) is the most susceptible site to be attacked by a proton; vide the Li−Evans rule.[7] The experimental evidence[12−14] for those systems counters this inference since the protonation takes place on the nitrogen atom for all the molecules.

The charge analysis presents more variations. For NH_2OH and CH_3NHOH, the charges cannot predict the protonation sites properly due to inherent drawback of the charge partitioning schemes. As suggested by a reviewer, we have also done the MPA via an SCF/3-21G calculation using a geometry obtained from a large basis set to obtain an identical trend in most cases. To make sure that these systems refer to “hard−hard” and not “hard−soft” reactions, we present the global hardness values in Table 5 and we see that these two systems are actually hard. Natural and Hirshfeld populations provide correct behavior for

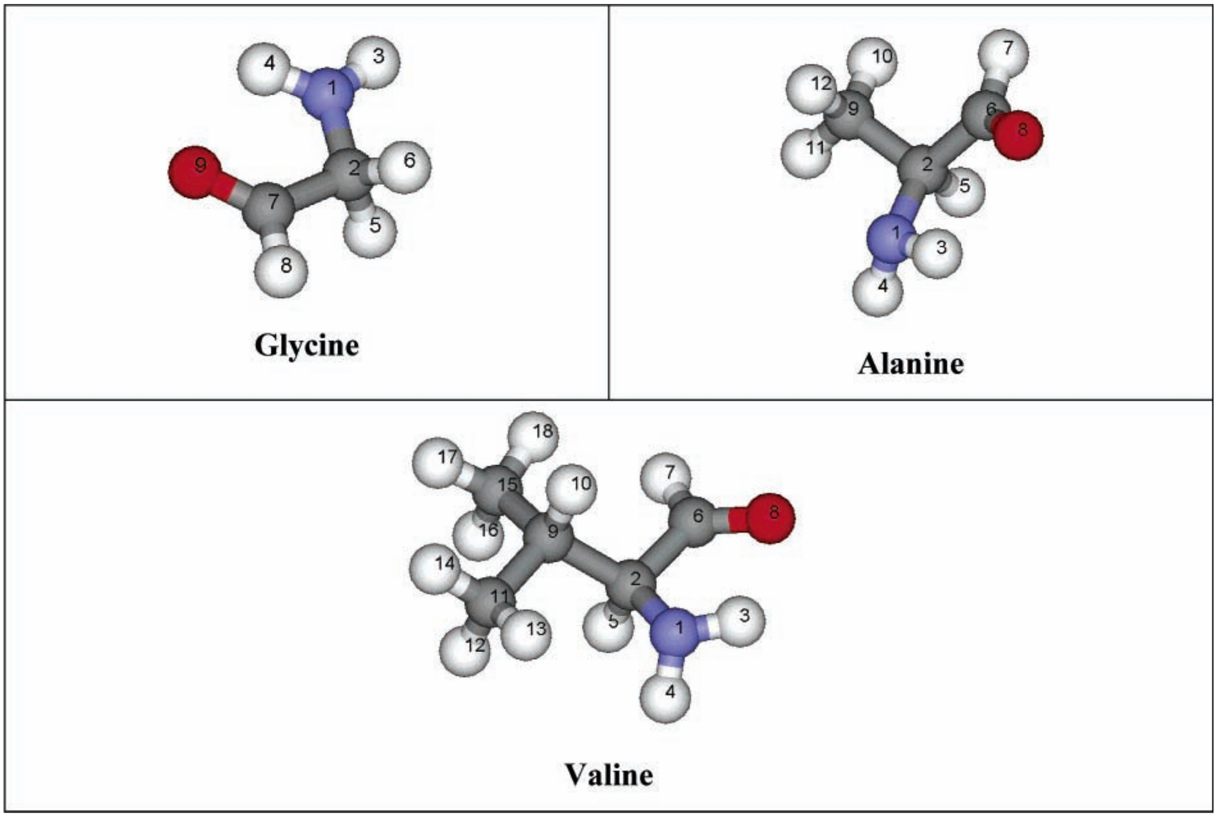

Figure 2. Optimized structures of aliphatic amino acids.

TABLE 1: Fukui Function and Charge Analysis Results for NH_2OH

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.7399	0.4038	−0.3076	−0.1679	−0.5084
H 2	0.0192	0.1235	0.2120	0.1004	0.3220
H 3	0.0192	0.1235	0.2120	0.1004	0.3220
O 4	0.1913	0.2415	−0.3820	−0.1918	−0.5843
H 5	0.0305	0.1076	0.2656	0.1587	0.4487

TABLE 2: Fukui Function and Charge Analysis Results for NH_2OCH_3

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.7052	0.2521	−0.2990	−0.1546	−0.5112
H 2	0.0177	0.0964	0.2116	0.1036	0.3270
H 3	0.0182	0.0964	0.2116	0.1036	0.3270
O 4	0.2085	0.2322	−0.3414	−0.1307	−0.4351
C 5	0.0313	0.0942	−0.0643	−0.0229	−0.1889
H 6	0.0082	0.0830	0.0890	0.0294	0.1545
H 7	0.0022	0.0625	0.1036	0.0421	0.1723
H 8	0.0088	0.0830	0.0890	0.0294	0.1545

TABLE 3: Fukui Function and Charge Analysis Results for CH_3NHOH

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.6896	0.3077	−0.2566	−0.1133	−0.3436
H 2	0.0230	0.0952	0.2071	0.1023	0.3248
O 3	0.1393	0.1889	−0.3681	−0.1815	−0.5966
C 4	0.0398	0.0884	−0.1581	−0.0614	−0.3708
H 5	0.0206	0.0842	0.2644	0.1606	0.4519
H 6	0.0180	0.0667	0.1089	0.0331	0.1813
H 7	0.0673	0.1073	0.0987	0.0205	0.1671
H 8	0.0023	0.0618	0.1036	0.0393	0.1860

TABLE 4: Fukui Function and Charge Analysis Results for $OHCH_2CH_2NH_2$

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
C 1	0.0782	0.0762	−0.0105	−0.0017	−0.0194
H 2	0.0061	0.0701	0.0739	0.0199	0.1392
H 3	0.0061	0.0701	0.0739	0.0199	0.1392
C 4	0.0456	0.0531	−0.1301	−0.0172	−0.1796
O 5	0.0101	0.1819	−0.4017	−0.2243	−0.7345
H 6	0.0135	0.0533	0.1208	0.0356	0.1816
H 7	0.0137	0.0533	0.1208	0.0356	0.1816
H 8	0.0060	0.0662	0.2378	0.1561	0.4491
N 9	0.7911	0.2332	−0.4520	−0.2272	−0.8277
H 10	0.0148	0.0712	0.1836	0.1000	0.3352
H 11	0.0148	0.0712	0.1836	0.1000	0.3352

TABLE 5: Global Hardness of Hydroxylamines, Sulfur-Substituted Molecules, and Aliphatic Aminoacids

molecule	η
NH_2OH	0.1511
NH_2OCH_3	0.1503
CH_3NHOH	0.1429
$OHCH_2CH_2NH_2$	0.1379
NH_2SH	0.1215
NH_2SCH_3	0.1192
CH_3NHSH	0.1204
$SHCH_2CH_2NH_2$	0.1256
glycine	0.0979
alanine	0.1054
valine	0.1039

NH_2OCH_3 accounting for the protonation properly. The results for $OHCH_2CH_2NH_2$ (Table 4) reveal that all charge analysis schemes correctly describe the protonation site, albeit with a very close charge values in N and O sites for $OHCH_2CH_2NH_2$, using HPA. For two electrostatically similar sites, the reaction may be considered a "frontier-controlled" one as a "tie-breaker". It may be noted that the HPA is known[20] to provide "too small" charges owing to the maximum transferability of the corresponding atoms-in-a-molecule.

To test the proposition[21] that the maximum Fukui function site is the best for hard−hard interactions, although it is counter to the Li−Evans criterion[9] of minimum Fukui function as demonstrated by many researchers,[8] we calculate the Fukui

TABLE 6: Fukui Function and Charge Analysis Results for NH_2SH

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.0186	0.2073	−0.6046	−0.2204	−0.9320
H 2	0.0151	0.0821	0.2415	0.1064	0.3566
H 3	0.0151	0.0821	0.2415	0.1064	0.3566
S 4	0.9466	0.5186	0.0442	−0.0250	0.1213
H 5	0.0047	0.1101	0.0775	0.0325	0.0976

TABLE 7: Fukui Function and Charge Analysis Results for NH_2SCH_3

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.0149	0.1614	−0.6017	−0.2193	−0.9562
H 2	0.0131	0.0708	0.2381	0.1048	0.3604
H 3	0.0131	0.0708	0.2381	0.1048	0.3604
S 4	0.8874	0.4372	0.1284	0.0096	0.3236
C 5	0.0216	0.0816	−0.4159	−0.1122	−0.6950
H 6	0.0249	0.0625	0.1402	0.0351	0.1993
H 7	0.0001	0.0533	0.1325	0.0418	0.2083
H 8	0.0249	0.0533	0.1402	0.0418	0.1993

TABLE 8: Fukui Function and Charge Analysis Results for CH_3NHSH

site	f_k^- (I)	f_k^- (II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
N 1	0.0661	0.1731	−0.5507	−0.1636	−0.7618
H 2	0.0906	0.0686	0.2370	0.1035	0.3569
S 3	0.7175	0.4189	0.0508	−0.0147	0.1160
H 4	0.0705	0.0941	0.0764	0.0333	−0.3504
C 5	0.0061	0.0676	−0.1591	−0.0601	0.1016
H 6	0.0119	0.0479	0.1278	0.0365	0.1877
H 7	0.0319	0.0733	0.1055	0.0237	0.1626
H 8	0.0055	0.0565	0.1122	0.0417	0.1873

TABLE 9: Fukui Function and Charge Analysis Results for $SHCH_2CH_2NH_2$

site	f_k^- (I)	f_k^- (II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$	q_{natural}
C 1	0.0229	0.0507	−0.3735	−0.0698	−0.4802
H 2	0.0239	0.0443	0.1391	0.0305	0.1886
H 3	0.0239	0.0443	0.1391	0.0305	0.1886
C 4	0.0002	0.0365	−0.1174	−0.0201	−0.1774
H 5	0.0014	0.0345	0.1324	0.0355	0.1852
H 6	0.0014	0.0345	0.1324	0.0355	0.1852
S 7	0.9215	0.3771	−0.0514	−0.0647	−0.0667
H 8	0.0048	0.0717	0.0683	0.0389	0.1187
N 9	0.0004	0.1894	−0.4445	−0.2191	−0.8182
H 10	0.0001	0.0585	0.1877	0.1013	0.3381
H 11	0.0001	0.0585	0.1877	0.1013	0.3381

TABLE 10: Fukui Function and Charge Analysis Results for Glycine

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$
N 1	0.8368	0.2406	−0.5396	−0.2255
C 2	0.0293	0.0807	−0.0511	−0.0174
H 3	0.0081	0.0831	0.2144	0.1125
H 4	0.0079	0.0743	0.2275	0.0974
H 5	0.0516	0.0773	0.1107	0.0389
H 6	0.0516	0.0773	0.1107	0.0389
C 7	0.0075	0.0877	0.1398	0.1299
H 8	0.0001	0.0894	0.0768	0.0369
O 9	0.0072	0.1896	−0.2891	−0.2111

TABLE 11: Fukui Function and Charge Analysis Results for Alanine

site	f_k^- (I)	f_k^- (II)	$q_{Mulliken}$	$q_{Hirshfeld}$
N 1	0.8080	0.2068	−0.4500	−0.2220
C 2	0.0397	0.0614	−0.1214	0.0162
H 3	0.0136	0.0638	0.2032	0.0898
H 4	0.0141	0.0729	0.1927	0.1055
H 5	0.0599	0.0700	0.1194	0.0361
C 6	0.0048	0.0840	0.1900	0.1321
H 7	0.0009	0.0867	0.0767	0.0368
O 8	0.0119	0.1915	−0.2845	−0.2052
C 9	0.0281	0.0453	−0.2583	−0.0992
H 10	0.0081	0.0409	0.0985	0.0339
H 11	0.0006	0.0421	0.1122	0.0397
H 12	0.0103	0.0345	0.1214	0.0370

TABLE 12: Fukui Function and Charge Analysis Results for Valine

site	f_k^-(I)	f_k^-(II)	q_{Mulliken}	$q_{\text{Hirshfeld}}$
N 1	0.7644	0.1789	−0.4500	−0.2169
C 2	0.0469	0.0506	−0.1076	0.0147
H 3	0.0145	0.0573	0.2052	0.0850
H 4	0.0116	0.0622	0.2000	0.1065
H 5	0.0331	0.0532	0.1211	0.0372
C 6	0.0147	0.0716	0.1982	0.1313
H 7	0.0074	0.0692	0.0868	0.0396
O 8	0.0143	0.1650	−0.2905	−0.2048
C 9	0.0534	0.0295	−0.1699	−0.0144
H 10	0.0078	0.0300	0.1217	0.0317
H 11	0.0086	0.0335	−0.2762	−0.1019
H 12	0.0016	0.0280	0.0906	0.0280
H 13	0.0079	0.0193	0.1244	0.0303
H 14	0.0006	0.0384	0.1062	0.0352
C 15	0.0078	0.0276	−0.2798	−0.1006
H 16	0.0006	0.0231	0.1015	0.0310
H 17	0.0044	0.0385	0.1137	0.0378
H 18	0.0005	0.0243	0.1046	0.0306

function and charges for NH_2SH, NH_2SCH_3, CH_3NHSH and $SHCH_2CH_2NH_2$ as well and present the results in Tables 6−9. We see that the maximum Fukui function site is on sulfur and not on nitrogen, violating the proposition of Fuentealba et al.[21] It also highlights the useless attempt of explaining hard−hard interactions using Fukui functions (some times minimum and at other times maximum) against Klopman's idea. It may, however, be noted that the charges can always explain the proper protonation site of these systems.

The results for the three amino acids (glycine, alanine and valine) are presented in Tables 10−12. It is heartening to note that for all of them, with both the charge analysis schemes (MPA and HPA), the protonation is properly described, and the Fukui functions are not the proper descriptors. Therefore, considering the intrinsic inadequacies associated with various population analysis schemes, it may be considered that the charges are more powerful descriptors of hard−hard interactions than the Fukui functions.

III. Conclusions

Diametrically opposite criteria of maximum and minimum Fukui functions have been prescribed in analyzing hard−hard interactions in recent years. It has been a common belief that the frontier-controlled soft−soft reactions are better explained by the relative values of the condensed Fukui functions at various atomic sites of the molecule, whereas the hard−hard interactions are better described by the corresponding charges because of the electrostatic nature of these interactions. To demonstrate this, DFT/6-311G(d,p) calculations of the Fukui functions and Mulliken, Hirschfeld and natural charges of various hydroxylamine derivatives, corresponding sulfur-substituted molecules, and amino acids are performed. It is discernible that the Fukui functions are poor descriptors of the preferred site of protonation reaction. Charges are shown to be better descriptors. This clearly points out that the hard−hard interactions are charge controlled and hence charge is the proper descriptor whereas the Fukui function is the ideal descriptor for the frontier controlled soft−soft interactions.

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