may enable MINDO parameters to be determined for elements in cases where thermochemical data are lacking.

References and Notes

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Proton Affinity and the Frontier Orbital Concept. Predictions and Pitfalls

Sir:

Application of the frontier orbital concept[1] to the problem of proton attack was implicit in the work of Hieber[2] in which he considered the proton in metal hydrides to be "buried" in the metal electron density. Pitzer[3] rationalized the structure of diborane by considering its formation as resulting from a double proton attack on the π orbital of the hypothetical $B_2H_4^{2-}$ to give the bridged structure.

In this communication we wish to predict the site of proton attack on CH_3X (X = OH, Cl, Br, and I), NF_3, HOF, and $Fe(CO)_5$ by making use of the fundamental relationship between the first ionization potential (IP) of a molecule and the proton affinity (PA).

For an electron donor B the following thermochemical cycle is valid

$$BH^+ \rightarrow B + H^+ \quad \Delta H = PA(B) \tag{1}$$

$$BH^+ \rightarrow B^+ + H \quad \Delta H = D(B^+\text{-}H) \tag{2}$$

$$PA(B) = IP(H) - IP(B) + D(B^+\text{-}H) \tag{3}$$

where IP(H) = 13.598 eV and IP(B) is the first IP of B. The PA may arbitrarily be divided into two hypothetical steps. In the first one, the proton attacks the highest occupied molecular orbital (HOMO) and one electron is transferred from B to H^+. It is this orbital which is ionized in the IP(B) term of eq 3. If no bond were to be formed we would obtain PA(B) = IP(H) − IP(B). In the second step, the separated atoms B^+ and H unite to form BH^+ with a bond strength $D(B^+\text{-}H)$. In this simple analysis, the final position of proton attachment will correspond to the initial site of attack. Subtle electronic energy effects may cause proton migration, however, particularly if there is a large amount of charge rearrangement in B^+ compared to B.

According to Fukui's first postulate,[1] the initial point of attack by an electrophile (in this case the proton) will occur at the position of highest electron density in the HOMO. The localization of the HOMO may be determined by a judicious interpretation of ultraviolet photoelectron spectroscopy (UPS) data. For instance, the UPS of the following molecules has been obtained: $CH_3\textit{O}H$,[4] $CH_3\textit{Cl}$,[5] $CH_3\textit{Br}$,[5] $CH_3\textit{I}$,[5] $\textit{N}F_3$,[6] $H\textit{O}F$,[7] and $\textit{Fe}(CO)_5$.[8] In each case, the first band in the UPS corresponds to electron ejection from an orbital largely localized on the atom which is in italic. This is the position for which proton attack is predicted. Consideration of the symmetry properties of the HOMO allows one to predict the direction of attack, but this information is usually not directly available from UPS. However, utilizing simple MO concepts we would predict, for example, that proton attack on CH_3Cl would occur along a line perpendicular to the C–Cl axis. Likewise, attack on HOF would occur along a line perpendicular to the plane of the molecule.

For CH_3OH and HOF, these predicted results agree with the results of ab initio calculations[9] regarding the position of proton attachment. For CH_3X (X = Cl, Br, I) the result is what one would expect intuitively, namely, attack at the lone pair on the halogen. For $Fe(CO)_5$[10] and NF_3[11] the prediction is in agreement with experimental results, albeit the studies on $Fe(CO)_5$ were carried out in solution whereas our prediction strictly holds only in the gas phase.

There are two molecules for which predictions are not so straightforward. The first is CH_3F where a cursory examination of the photoelectron spectrum would assign the first band as arising predominantly from the CH_3 group since it occurs near the first IP of CH_4. However, the adiabatic (and vertical) IP of CH_3F is *less* than that for CH_4.[12] This is contrary to what one would expect on the basis of inductive effects but can be rationalized by a considerable mesomeric effect[13] of fluorine with the CH_3 group. Further evidence for the strong mixing of CH_3 and F orbitals in the 1e and 2e molecular orbitals is provided by the fact that the UPS exhibits no sharp band due to the fluorine lone pairs in the region of 15.8 eV, such as is observed in HF.[14] We conclude that in CH_3F there is substantial delocalization of the HOMO and hence no prediction can be made regarding the position of proton attack.

The ab initio calculation[12] on CH_3F indicates that the HOMO (2e), although containing a sizeable C–H bonding component, is considerably C–F antibonding. This is a result of delocalization. Calculations utilizing the semiempirical CNDO/2 and INDO molecular orbital methods[15] also indicate that the HOMO is nearly equally divided between the CH_3 and F moieties, just as in the isoelectronic F_2 molecule. The structure of protonated CH_3F is not known, but ab initio calculations[9] indicate that it has a structure similar to that of the isoelectronic CH_3OH molecule.

A second example which illustrates the cautions which must be observed in this application of the frontier orbital concept is provided by ferrocene. The first two peaks in the UPS have been assigned to $^2E_{2g}$ and $^2A_{1g}$ ionic states, corresponding to electron ejection out of orbitals predominantly of Fe 3d character.[16] However, the molecular ground state calculation indicates the HOMO's to be ligand π nonbonding, e_{1g} and e_{1u}.[17] In such a case, when the order of one-electron orbital energies is different from the order of corresponding ionic states in the UPS, a breakdown in Koopmans' theorem is indicated.[17] Consequently, the concept of HOMO is meaningless and no prediction as to the position of proton attack can be made. Experimentally, ferrocene has been shown to protonate both at the iron atom and at the ring.[18]

Finally, we wish to show the utility of the frontier orbital concept in predicting the structure of products resulting from electrophilic attack in a more general system. Such an example is provided by the reaction[19] (in solution) of "Cl^+" with ClF to product $ClClF^+$; that is, the "Cl^+" attacks the chlorine atom and not the fluorine atom. The HOMO in ClF is of π character mainly localized on chlorine.[20] We can therefore also rationalize the fact that $ClClF^+$ is a bent molecule. We conclude that this reaction and those of proton attack discussed above are frontier-controlled and not charge controlled.[21]

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Synthesis of the Tritetracontapeptide Corresponding to the Entire Amino Acid Sequence of Gastric Inhibitory Polypeptide[1]

Sir:

We wish to report the synthesis of a tritetracontapeptide corresponding to the entire amino acid sequence of porcine gastric inhibitory polypeptide (GIP), the structure of which was determined by Brown and Dryburgh[2,3] in 1971. To date only partial syntheses of GIP have been described.[4-6]

In our present synthesis (Figure 1), amino acid derivatives bearing protecting groups removable by hydrogen fluoride[7] were employed. The α-amino function of intermediates was protected by the TFA labile Z(OMe) group.[8] Anisole containing 2% ethanedithiol[9] rather than mercaptoethanol was employed to minimize destruction of the Trp residue during the various TFA deblocking steps. No brown color was produced under these conditions. The Trp content of intermediates was estimated in 3 *N* Tos-OH hydrolysates.[10]

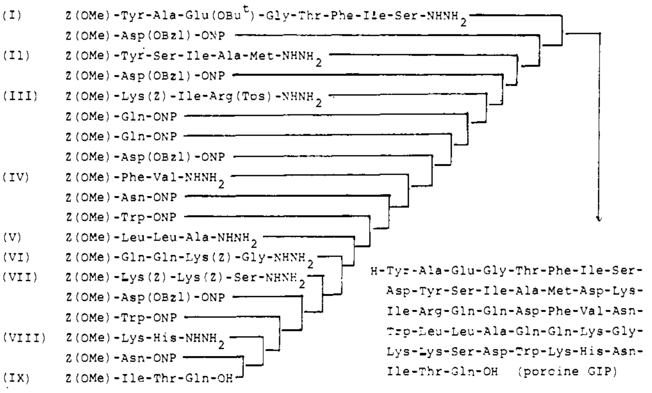

Figure 1. Synthetic route to GIP.

Nine relatively small peptide fragments served as the building blocks for construction of the entire amino acid sequence of GIP. Of these Z(OMe)-Phe-Val-$NHNH_2$ (IV) is a known compound.[11] This strategy was adopted for the reason that these acylating agents could be readily removed by washing or precipitation following each coupling step.

The *N*-terminal octapeptide hydrazide, Z(OMe)-Tyr-Ala-Glu(O-*t*-Bu)-Gly-Thr-Phe-Ile-Ser-$NHNH_2$ (I, mp 249-255°; $[\alpha]^{25}D$ −6.7° in DMSO; Anal. Calcd for $C_{54}H_{76}N_{10}O_{16}$: C, 57.84; H, 6.83; N, 12.49. Found: C, 57.62; H, 7.08; N, 12.48), was obtained by treatment of the corresponding methyl ester with hydrazine. The ester resulted from the DCC plus HOBT condensation[12] of Z(OMe)-Tyr-Ala-Glu(O-*t*-Bu)-Gly-OH and H-Thr-Phe-Ile-Ser-OMe. Z(OMe)-Tyr-Ser-Ile-Ala-Met-$NHNH_2$ (II, mp 247-251°; $[\alpha]^{25}D$ −2.0° in DMSO; Anal. Calcd for $C_{35}H_{51}N_7O_{10}S$: C, 55.17; H, 6.74; N, 12.87. Found: C, 54.89; H, 6.73; N, 12.93) was prepared by the azide condensation[13] of Z(OMe)-Tyr-Ser-$NHNH_2$ and H-Ile-Ala-Met-OMe followed by treatment of the resulting protected pentapeptide ester with hydrazine hydrate. Next, Z(OMe)-Lys(Z)-Ile-Arg(Tos)-$NHNH_2$ (III, mp 177-181°; $[\alpha]^{26}D$ −7.4° in DMF; Anal. Calcd for $C_{42}H_{59}N_9O_{10}S$: C, 57.18; H, 6.74; N, 14.29. Found: C, 57.17; H, 6.76; N, 14.24) was synthesized by the stepwise elongation method starting with H-Arg(Tos)-OMe. The 5-chloro-8-quinolyl ester procedure[14] served to introduce Z(OMe)-Lys(Z)-OH.

Z(OMe)-Leu-Leu-Ala-$NHNH_2$ (V, mp 170-173°; $[\alpha]^{25}D$ −32.2° in DMF; Anal. Calcd for $C_{24}H_{39}N_5O_6$: C, 58.39; H, 7.96; N, 14.18. Found: C, 58.09; H, 7.90; N, 14.21), Z(OMe)-Gln-Gln-Lys(Z)-Gly-$NHNH_2$ (VI, mp 225-229°; $[\alpha]^{25}D$ −43.0° in DMSO; Anal. Calcd for $C_{35}H_{49}N_9O_{11}$: C, 54.46; H, 6.39; N, 16.33. Found: C, 54.25; H, 6.31; N, 16.16), and Z(OMe)-Lys(Z)-Lys(Z)-Ser-$NHNH_2$ (VII, mp 198-202°; $[\alpha]^{25}D$ −8.2° in DMF; Anal. Calcd for $C_{40}H_{53}N_7O_{11}$: C, 59.46; H, 6.61; N, 12.14. Found: C, 59.16; H, 6.69; N, 12.14) were assembled in a stepwise manner by the active ester procedure. Again the 5-chloro-8-quinolyl ester method was employed for the introduction of Z(OMe)-Lys(Z)-OH. Z(OMe)-Lys(Z)-His-$NHNH_2$ (VIII, mp 180-182°; $[\alpha]^{25}D$ −8.3° in DMF; Anal. Calcd for $C_{29}H_{37}N_7O_7$: C, 58.47; H, 6.26; N, 16.46. Found: C, 58.41; H, 6.15; N, 16.62) and Z(OMe)-Ile-Thr-$NHNH_2$ were prepared by the DCC condensation of the respective amino acid derivatives followed by exposure of the resulting esters to hydrazine hydrate.

The crude protected dipeptide ester, Z(OMe)-Lys(Z)-His-OMe, was exposed to methanol-acetic acid to remove the contaminating dicyclohexylamidino derivative.[15]

The hydrazide was then condensed with the triethylammonium salt of Gln via the azide procedure to give Z(OMe)-Ile-Thr-Gln-OH (IX, mp 181-184°; $[\alpha]^{24}D$ +7.7° in DMF;