

Table III. Derived Heats of Formation (kcal/mol)^a

| molecule | 6-31G* | |
|----------|-------------|----------------------------|
| | SCF (RMP2) | expt |
| 1 | 57.0 (56.6) | 53.5 ^b |
| 2 | 30.0 (29.4) | 30.5 ^b |
| 3 | 3.6 (3.6) | 3.0 ^b |
| 4 | -22.7 | -24.47 ± 0.86 ^c |

^aThe heat of formation of 4, calculated as described in the text, and the heats of formation of 1, 2, and 3 derived from that of 4 and the 6-31G* SCF (RMP2) heats of hydrogenation, Table II. ^bCalculated from the experimental heat of formation of 4 and the experimental heat of hydrogenation, ref 2. ^cReference 19.

difference (2.2) between 4 and adamantane obtained using the molecular mechanics method of Warshel.²⁰ In the present work we have computed the 6-31G* RMP2 isomerization energy of 4 → adamantane to be -11.0 and the zero-point energy difference to be 1.2 using the Boyd molecular mechanics method (0.9 in AM1). Given the differences in the ab initio isomerization energies and the uncertainties in the zero-point energy and experimental heat of formation of adamantane, we revise our earlier estimate of the ΔH_f of hexahydrotriquinacene to -22.7 ± 1.0 . Although this value is in slight disagreement with experiment, it does encompass the values of -23.1, -22.6, and -22.1 obtained with the

(20) (a) Lifson, S.; Warshel, A. *J. Chem. Phys.* **1979**, *49*, 5116. (b) Huler, E.; Sharon, R.; Warshel, A. QCPE Program 247, Indiana University, Bloomington, IN.

group equivalent methods of Wiberg²¹ and Ibrahim et al.,²² and with MM2.⁹

Using -79.7 (-79.3) for the enthalpy change of 1 → 4 and -22.7 for the heat of formation of hexahydrotriquinacene, we predict ΔH_f of triquinacene to be ca. 57.0 (56.6). For comparison, the empirical method of Ibrahim et al.²² (with our 6-31G* SCF energy) gives a ΔH_f of 53.0; its value for the ΔH_f of cyclopentene is too low by 1.4. Using -22.7 and the heats of hydrogenation (Table II), the heats of formation of 2 and 3 are estimated to be 30.0 (29.4) and 3.6 (3.6), respectively. These results are collected in Table III. The respective MM2 energies of 1, 2, 3, and 4 are 59.8, 32.2, 5.3, and -22.1 kcal/mol, in reasonable agreement with the ab initio results.

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Registry No. 1, 6053-74-3; 2, 31678-74-7; 3, 57595-39-8; 4, 17760-91-7; adamantane, 281-23-2; cyclopentane, 287-92-3; cyclopentene, 142-29-0.

(21) (a) Wiberg, K. B. *J. Comput. Chem.* **1984**, *5*, 197. (b) Wiberg, K. B. *J. Org. Chem.* **1985**, *50*, 5285.

(22) Ibrahim, M. R.; Schleyer, P. v. R. *J. Comput. Chem.* **1985**, *6*, 157.

Chemical Hardness and Bond Dissociation Energies

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Abstract: An empirical method is proposed to rank order Lewis acids and bases in terms of their local hardness, $\bar{\eta}$, at their reaction sites. The method uses bond energy differences between two acids (or bases) of different chemical hardness. The assumption is made that in an exchange reaction, $A:B' + A':B = A:B + A':B'$, the most stable pair will match the softest acid with the softest base, and the hardest acid with the hardest base. The relative values of $\bar{\eta}$ obtained in this way for many cations and anions are both consistent and logical for the most part. The few exceptions have simple explanations.

Recently two new chemical concepts have been derived from density functional theory.^{1,2} These are the absolute electronegativity, χ , and the absolute hardness, η . The exact and approximate definitions of these quantities are $\chi = (\partial E / \partial N)_v \approx (I + A) / 2$, and $\eta = -1/2(\partial \chi / \partial N)_v \approx (I - A) / 2$. E is the electronic energy, N the number of electrons, v the potential of the nuclei, I the (vertical) ionization potential, and A the (vertical) electron affinity. The relationships apply to any isolated chemical system, atom, ion, molecule, or radical. A number of values of χ and η have been calculated for various system, using experimental values of I and A .³

χ must be a constant, the same at every point in a chemical system. The hardness, however, allows for local values, $\bar{\eta}$;⁴ η is

the global, or average, value. The softness, σ , is simply the reciprocal of η .

If two chemical systems, X and Y, are brought into contact, electrons will flow from the one of lower χ to that of higher χ until the electronegativities become equalized. An approximate value for ΔN , the number of electrons transferred, is given by

$$\Delta N = (\chi_X - \chi_Y) / 2(\eta_X + \eta_Y) \quad (1)$$

Equation 1 has been found useful for a number of reactions between neutral species.^{3,5} A large value of ΔN gives rise to strong bonds, or to low energy barriers. However, it is far from a complete prescription for bonding.

The concept of chemical hardness was first introduced to describe Lewis acids and bases.⁶ The definitions used were only qualitative, essentially emphasizing polarizability as the major factor. In simple MO theory, the quantity 2η is the energy gap

(1) Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801-3807.

(2) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512-7516.

(3) Pearson, R. G. *Inorg. Chem.* **1988**, *27*, 734-740.

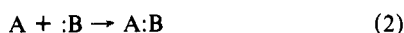
(4) Berkowitz, M.; Ghosh, S. K.; Parr, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 6811-6814. Berkowitz, M.; Parr, R. G. *J. Chem. Phys.* **1988**, *88*, 2554-2557.

(5) Pearson, R. G. *Inorg. Chem.* **1984**, *25*, 4675-4679.

(6) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.

between the HOMO and the LUMO. A small gap characterizes a molecule as having both a small value of $(I - A)$, and also as being highly polarizable. Thus there is consistency between the old and new definitions.

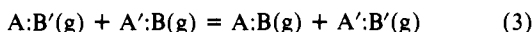
Bond energies were related to hardness through the HSAB principle.⁶ In the general acid–base reaction,



“hard acids will prefer to coordinate to hard bases, and soft acids will prefer soft bases.” The data used to support this state was varied, including heats of reaction, equilibrium constants, rates of reaction, and even the nonexistence of certain compounds. But the underlying reason was always assumed to be the strength of the bond between A and B.

Density functional theory confirms and amplifies the reasons given earlier for the HSAB principle.^{7,8} Soft acids and bases form covalent bonds, which are further stabilized by mutual polarization, including hyperconjugation. Hard acids and bases form ionic bonds. But there is still no simple way to calculate the contribution to the bond energy which results from the correct matching of soft–soft, or hard–hard combinations.

However, the fact that values of η are now assigned for some acids and bases makes it possible to use the HSAB principle to empirically rank order other acids and bases. Consider the exchange reaction



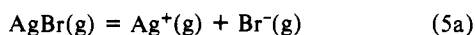
If other bond-determining factors are constant, the reaction will be exothermic, if A' is softer than A, and B' is softer than B. This may be restated as

$$hs + sh = hh + ss \quad 0 > \Delta H \quad (4)$$

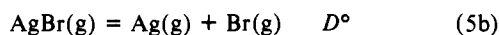
where h and s are read as the harder of the two acids (bases), and the softer of the two bases (acids).

There are obviously many other bond-determining factors such as the electronegativities of A and B, their charges and sizes, the matching of orbital overlaps, and steric repulsions.⁹ It is impossible to keep all of these factors constant, but at least one should only compare acids, or bases, of the same charge. Also, a series of acids, or a series of bases, should only be compared when their mean bond strengths to the reference acids, or bases, are about the same.

The HSAB principle refers to heterolytic bond energies, e.g.,



Because only differences are needed in (3), it is possible to use the more familiar standard homolytic bond dissociation energies, $D^\circ = \Delta H^\circ_{298}$.



A large number of such bond energies are now available. They are usually good to 1–2 kcal/mol.¹⁰

The main objective of this paper is to rank order a number of systems for which I and A values are not likely to be available. These are anions and polyatomic cations. For anions $(I - A)/2$ is no longer a useful approximation to η . For polyatomic cations, it is very difficult to measure the second ionization potential, which is the correct I . Also it is likely that the global value of η is not as meaningful as the local value, $\bar{\eta}$, at the reaction site. Bond energies will be much more dependent on $\bar{\eta}$ than η .

If a molecule, X–Y, is treated as an acid–base complex, it is necessary to identify the constituent acid and base. In principle this depends on the electronegativities of the radicals, X and Y. If $\chi_Y > \chi_X$, then X⁺ is the acid and Y[−] is the base. Table I gives

Table I. Experimental Values (eV) for Radicals

| radical | I^a | A^b | χ | η |
|---|-------------------|-------------------|--------|--------|
| F | 17.42 | 3.40 | 10.41 | 7.01 |
| OH | 13.17 | 1.83 | 7.50 | 5.67 |
| NH ₂ | 11.40 | 0.74 | 6.07 | 5.33 |
| CH ₃ | 9.82 | 0.08 | 4.96 | 4.87 |
| Cl | 13.01 | 3.62 | 8.31 | 4.70 |
| SH | 10.41 | 2.30 | 6.40 | 4.10 |
| PH ₂ | 9.83 | 1.25 | 5.54 | 4.29 |
| SiH ₃ | 8.14 | 1.41 ^c | 4.78 | 3.37 |
| Br | 11.84 | 3.36 | 7.60 | 4.24 |
| SeH | 9.80 ^c | 2.20 | 6.00 | 3.80 |
| I | 10.45 | 3.06 | 6.76 | 3.70 |
| H | 13.59 | 0.74 | 7.17 | 6.42 |
| HO ₂ | 11.53 | 1.19 | 6.36 | 5.17 |
| NO ₂ | >10.10 | 2.30 | >6.20 | >3.90 |
| CN | 14.02 | 3.82 | 8.92 | 5.10 |
| C ₆ H ₅ S | 8.63 | 2.47 | 5.50 | 3.08 |
| C ₆ H ₅ O | 8.85 | 2.35 | 5.60 | 3.25 |
| C ₂ H ₃ | 8.38 | −0.39 | 4.00 | 4.39 |
| <i>i</i> -C ₃ H ₇ | 7.57 | −0.48 | 3.55 | 4.03 |
| <i>t</i> -C ₄ H ₉ | 6.93 | −0.30 | 3.31 | 3.61 |
| C ₆ H ₅ | 8.95 | 0.10 | 5.20 | 4.10 |
| C ₂ H ₃ | 8.95 | 0.74 | 4.85 | 4.10 |
| HCO | 9.90 | 0.17 ^f | 5.04 | 4.88 |
| CH ₃ CO | 8.05 | 0.30 | 4.18 | 3.87 |
| CCl ₃ | 8.78 | 1.90 ^g | 5.35 | 3.45 |
| CF ₃ | 9.25 | >1.10 | >5.18 | <4.08 |
| SiCl ₃ | 7.92 | 2.50 ^g | 5.20 | 2.70 |
| NO | 9.25 | 0.02 | 4.63 | 4.61 |
| Mn(CO) ₅ | 8.44 ^d | 2.00 ^h | 5.20 | 3.20 |

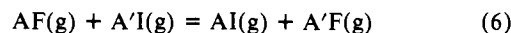
^aReferences 45 and 46. ^bReferences 47 and 48, except as indicated. ^cOrtiz, J. V. *J. Chem. Phys.* **1987**, *87*, 1701–1704. ^dBidinosti, D. R.; McIntyre, N. S., *Chem. Commun.* **1966**, 555–556. ^eNimlos, M. R.; Ellis, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 6522–6529. ^fChandrasekhar, J.; Andrade, J.; Schleyer, P. v. R., *J. Am. Chem. Soc.* **1981**, *103*, 5612–5614. ^gMoc, J.; Latajka, Z.; Ratajszak, H. *Chem. Phys. Lett.* **1986**, *136*, 122–127. ^hBeauchamp, J. L.; Stevens, A. E., private communication.

values of the absolute electronegativities for a large number of monovalent radicals, to help in making assignments.

The values of χ give the relative tendencies to donate or accept an electron when X and Y are at some distance from each other. They may not be a good measure of bond polarity at bonding distances.^{11,19} This is certainly true for the H atom, which is much more likely to be protonic than hydridic because of the superior penetrating power of the former. It is difficult to calculate or measure actual charges on atoms in molecules, particularly for hydrogen.¹² However, we can be fairly sure, from the properties of the alkanes, that H must have an effective electronegativity close to that of CH₃.

Fortunately considerable leeway is found to exist in deciding which part of a molecule is to be called the acid, and which the base. As long as the values of χ_X and χ_Y are not too different, either choice can be made in applying eq 4. Chemical common sense is usually a good guide. Thus CH₃CHO may be considered as either CH₃⁺, HCO[−] or HCO⁺, CH₃[−]. But CH₃OH should not be treated as HO⁺, CH₃[−].

Hardness Values for Cations. To rank order monovalent cations as Lewis acids, we need to select two bases of quite different hardness and apply the HSAB principle to the exchange reaction 3. The fluoride and iodide ions are good choices since they differ greatly in hardness, and a great deal of bond energy data is available.



All that is needed are the homolytic bond energies for each acid. Define the difference

$$\Delta_1 = D^\circ_{\text{AF}} - D^\circ_{\text{AI}} \quad (7)$$

(11) See Mortier, W. J.; Ghosh, S. D.; Shankar, S. *J. Am. Chem. Soc.* **1986**, *108*, 4315–4320.

(12) Francl, M. M.; Hout, R. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 563–570.

(7) Pearson, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8440–8441.

(8) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223–234.

(9) For a useful discussion see: Kutzelnigg, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 272–278.

(10) Eggers, K. W.; Cocks, A. T. *Helv. Chim. Acta* **1973**, *56*, 1516–1552. McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493–522. Huber, K. P.; Herzberg, G. *Constants of Diatomic Molecules*; Van Nostrand Reinhold: New York, 1979.

Table II. Empirical Hardness Parameters for Cationic Lewis Acids

| acid | D°_{AF} , kcal ^a | D°_{Al} , kcal ^a | Δ_1 , kcal |
|--|--------------------------------------|--------------------------------------|-------------------|
| CF ₃ ⁺ | 130 | 54 | 76 |
| SiH ₃ ⁺ | 148 ^b | 72 ^d | 76 |
| CH ₃ CO ⁺ | 120 | 50 | 70 |
| HCO ⁺ | 122 | 52 | 70 |
| H ⁺ | 136 | 71 | 65 |
| C ₆ H ₅ ⁺ | 124 | 64 | 60 |
| C ₂ H ₃ ⁺ | 119 | 63 | 56 |
| <i>t</i> -C ₄ H ₉ ⁺ | 108 | 50 | 58 |
| <i>i</i> -C ₃ H ₇ ⁺ | 107 | 53 | 54 |
| C ₂ H ₅ ⁺ | 107 | 53 | 54 |
| CH ₃ ⁺ | 109 | 56 | 53 |
| C ₃ H ₅ ⁺ | 98 | 44 | 54 |
| <i>c</i> -C ₃ H ₅ ⁺ | 111 | 59 | 52 |
| Li ⁺ | 137 | 82 | 55 |
| Na ⁺ | 123 | 69 | 54 |
| Tl ⁺ | 105 | 64 | 41 |
| CN ⁺ | 112 | 73 | 39 |
| NO ⁺ | 56 ^c | 20 ^c | 36 |
| Cs ⁺ | 118 | 82 | 36 |
| I ⁺ | 67 | 36 | 31 |
| Cu ⁺ | 102 | 75 | 27 |
| Ag ⁺ | 87 | 61 | 23 |
| HO ⁺ | 56 | 52 ^c | -4 |

^aData from ref 10, except as indicated. ^bReference 16. ^cFrom heats of formation: *JANAF Thermochemical Tables*, 3rd ed.; American Chemical Society: Washington, D.C., 1985. ^dEstimated from data on (CH₃)₃SiX and SiH₃X: Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246-252.

The larger Δ_1 is, the harder is the acid, A⁺.

The assumption is that F⁻ is harder than I⁻. This can be verified by looking at Δ_1 values for monatomic cations such as Na⁺, $\eta = 21.1$, and Ag⁺, $\eta = 7.0$, and applying eq 4. Essentially the same method was used earlier to rank order metal ions before values of η were taken as standards.¹³

For the metal ions the known values for η agree well with the order given by Δ_1 , except for Tl⁺. This ion has $\eta = 7.16$ eV, which makes it soft, but $\Delta_1 = 42$ kcal is unexpectedly large. This discrepancy is a result of the nature of the 6s electrons of Tl⁺. These s electrons are not useful for π -bonding stabilization, unlike p and d electrons.

Table II gives the values of Δ_1 for a large number of cations where the data are available. The order is that of decreasing Δ_1 and decreasing hardness. As explained earlier, this is taken to be the order of local hardness, $\bar{\eta}$.

The rank order agrees very well with expectations based on earlier chemical criteria.¹⁴ The spread is quite impressive, about 80 kcal/mol. An extreme example is



The greater stability of the products results not from any novel bonding effects, but from a proper matching of the bonding capabilities of SiH₃⁺ and HO⁺ with those of F⁻ and I⁻.

The large values of $\bar{\eta}$ for CF₃⁺ and SiH₃⁺ presumably arise from large net positive charges on C and Si, compared to that on carbon in CH₃⁺, for example. The same may be said for CH₃CO⁺, but here the substantial dipole moment also plays a role. There is also an orbital component to $\bar{\eta}$, the LUMO being involved for acids, and the HOMO for bases.^{4,15} The LUMOs of CF₃⁺ and CH₃CO⁺ are delocalized over several atoms, while that for CH₃⁺ is not. This makes CF₃⁺ and CH₃CO⁺ harder.

All the acids of Table II pass the test of approximately equal strength, except for NO⁺. Its bonds are all only about half as strong as the others. Equation 4 cannot be used for nitrosyl compounds with any confidence. Also, the small value of Δ_1 is misleading, and NO⁺ is probably harder than indicated. While HO⁺ and CN⁺ are included in the table, the large χ values for

Table III. Empirical Hardness Parameters for Anionic Bases

| base | D°_{HB} , kcal ^a | $D^{\circ}_{CH_3B}$, kcal ^{a,d} | Δ_3 , kcal |
|--|--------------------------------------|---|-------------------|
| F ⁻ | 136 | 109 | 27 |
| Cl ⁻ | 103 | 85 | 19 |
| Br ⁻ | 88 | 70 | 18 |
| I ⁻ | 71 | 56 | 15 |
| OH ⁻ | 119 | 92 | 27 |
| SH ⁻ | 91 | 74 | 17 |
| SeH ⁻ | 79 | 67 | 12 |
| NH ₂ ⁻ | 107 | 85 | 22 |
| PH ₂ ⁻ | 87 ^e | 76 ^f | 11 |
| AsH ₂ ⁻ | 75 ^b | 63 ^f | 12 |
| CH ₃ CO ₂ ⁻ | 106 | 83 | 23 |
| C ₆ H ₅ O ⁻ | 87 | 64 | 23 |
| NO ₂ ⁻ | 102 | 80 | 22 |
| CH ₃ O ⁻ | 104 | 83 | 21 |
| HO ₂ ⁻ | 88 | 69 | 19 |
| ONO ⁻ | 78 ^c | 60 ^c | 18 |
| NO ₂ ⁻ | <78 ^d | 61 ^d | <17 |
| NCS ⁻ | 96 ^d | 77 ^d | 19 |
| C ₆ H ₅ NH ⁻ | 88 | 71 | 17 |
| <i>n</i> -C ₃ H ₇ S ⁻ | 87 | 72 | 15 |
| C ₆ H ₅ S ⁻ | 83 ^o | 69 | 14 |
| CH ₃ ⁻ | 105 | 90 | 17 |
| SiH ₃ ⁻ | 91 | 85 | 6 |
| GeH ₃ ⁻ | 87 | 83 | 4 |
| C ₆ H ₅ CH ₂ ⁻ | 88 | 72 | 16 |
| NCCH ₂ ⁻ | 93 | 81 | 12 |
| CH ₃ COCH ₂ ⁻ | 98 | 86 | 12 |
| C ₃ H ₅ ⁻ | 86 | 74 | 12 |
| C ₆ H ₅ ⁻ | 86 | 74 | 12 |
| C ₆ H ₅ ⁻ | 111 | 100 | 11 |
| C ₂ H ₃ ⁻ | 115 | 105 | 10 |
| HC ₂ ⁻ | 130 | 122 | 8 |
| CH ₃ CO ⁻ | 96 | 91 | 5 |
| CF ₃ ⁻ | 106 | 101 | 5 |
| CN ⁻ | 124 ^g | 122 ^g | 2 |
| NC ⁻ | 110 ^h | 98 ^h | 12 |
| H ⁻ | 104 | 105 | -1 |

^aFrom ref 10, except as indicated. ^bSmyth, R. C.; Brauman, J. I. *J. Chem. Phys.* **1972**, *56*, 4620-4625. ^cO-bonded isomer. ^dN-bonded isomer. ^eHeat of formation of CH₃XH₂ interpolated from (CH₃)₃X and XH₃. ^fHeat of formation interpolated from (CH₃)₄Ge and GeH₄. ^gC-bonded isomer. ^hN-bonded isomer. ⁱSome values from heats of formation. See ref 49 and *JANAF Thermochemical Tables*, 3rd ed.

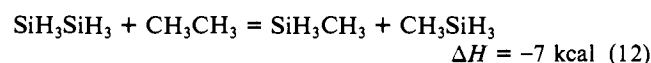
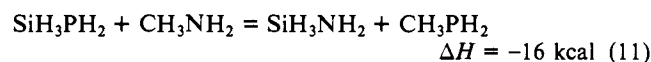
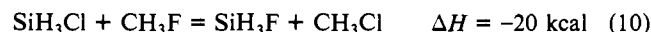
HO and CN (Table I) mean that there will be few cases where they can be considered as the acids.

Other pairs of bases may also be used to rank order Lewis acids. A convenient pair for organic cations is OH⁻ and SH⁻. Define the bond energy difference

$$\Delta_2 = D^{\circ}_{AOH} - D^{\circ}_{ASH} \quad (9)$$

and the values found fall in descending order SiH₃⁺ > CH₃CO⁺ > H⁺ > C₆H₅⁺ > *t*-C₄H₉⁺ > *i*-C₃H₇⁺ > C₂H₅⁺ > CH₃⁺. This is the same order as for Δ_1 . The range of Δ_2 is from 36 kcal for SiH₃⁺ to 18 kcal for CH₃⁺.

Other combinations of bases with a first long row donor and a higher row donor may be used. However, data are scarcer and the sensitivity diminishes in going from the halogens to group 14. Compare the reactions¹⁶



Two reference bases with donor atoms such as P or As, or S and

(13) Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson and Ross: Stroudsburg, Pa, 1973.

(14) No reference given.

(15) Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6223-6227.

(16) Luke, B. T.; Pople, J. A.; Krogh-Jespersen, M.; Apeloig, Y.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1986**, *108*, 260-269. The energies are actually theoretical values from ab initio calculations. However, such calculations are usually reliable for differences in energy as in eq 10 to 12.

Table IV. Relative Hardness Values for Anions Using Acetyl Cation as Reference

| base | $D^\circ_{\text{CH}_3\text{COB}}$, kcal ^a | $D^\circ_{\text{CH}_3\text{B}}$, kcal ^a | Δ_4 , kcal |
|--|---|---|-------------------|
| F ⁻ | 120 | 109 | 11 |
| Cl ⁻ | 84 | 85 | -1 |
| Br ⁻ | 65 | 70 | -5 |
| I ⁻ | 51 | 56 | -5 |
| OH ⁻ | 109 | 92 | 17 |
| SH ⁻ | 74 | 74 | 0 |
| CH ₃ O ⁻ | 98 | 83 | 15 |
| C ₂ H ₅ S ⁻ | 76 | 72 | 4 |
| CH ₃ CO ₂ ⁻ | 84 | 83 | 1 |
| NH ₂ ⁻ | 95 | 85 | 10 |
| C ₆ H ₅ NH ⁻ | 84 | 71 | 13 |
| CH ₃ ⁻ | 85 | 90 | -5 |
| C ₆ H ₅ ⁻ | 95 | 100 | -5 |
| CH ₃ COCH ₂ ⁻ | 75 | 86 | -11 |
| H ⁻ | 89 | 105 | -16 |

^aReferences 10 and 49.

Se, would also not be very discriminating since they do not offer enough in hardness.

Hardness Values for Anions. A convenient choice for ranking anions, and neutral bases, is H⁺ and CH₃⁺. They are acids of comparable strength, though H⁺ is almost always stronger. They are not as much different in hardness as F⁻ and I⁻, but this is compensated for by the large amount of bond energy data available. We define the bond energy difference

$$\Delta_3 = D^\circ_{\text{HB}} - D^\circ_{\text{CH}_3\text{B}} \quad (13)$$

Table III gives the results for a number of common anions.

The larger Δ_3 is, the harder is the base. The results are usually very consistent with prior expectations. For simple anions we find the orders F⁻ > Cl⁻ > Br⁻ > I⁻; OH⁻ > SH⁻ > SeH⁻; NH₂⁻ > PH₂⁻ ~ AsH₂⁻; CH₃⁻ > SiH₃⁻ > GeH₃⁻; F⁻ ~ OH⁻ > NH₂⁻ > CH₃⁻; Cl⁻ > HS⁻; PH₂⁻ > SiH₃⁻; Br⁻ > HSe⁻ > AsH₂⁻ > GeH₃⁻. These are certainly as expected on the basis of polarizability. They are also in the same order as the corresponding radicals (Table I).

This is not accidental since it has been shown to be expected for spherical, uniformly charged ions.³ However, there is no such relationship between radicals and their corresponding cations, since the latter are not uniformly charged. In fact, the anions and cations derived from a given radical often have opposite characteristics. An example is OH⁺, soft, and OH⁻, hard.

A noteworthy exception is the hydride ion, which is the softest base listed in Table III, even though η for H is large. The softness of H⁻ resides in its ability to donate charge to an acid for σ -bonding. It is not capable of π -bonding, or π -antibonding. This means that acids with electronic structures suitable for π -bonding may bind less strongly to H⁻ than expected.

Other soft bases in Table III are CN⁻, CF₃⁻, and CH₃CO⁻. Their softness lies mainly in their ability to π -bond by resonance and hyperconjugation.¹⁷ Note that η for CN is quite large (Table I), so that CN⁻ may not be treated as spherical and symmetrical.

For other anions, the nature of the donor atom is dominant. For ambident bases, two different values may be found. For NO₂⁻, Δ_3 is substantially less for the N-bonded isomers than for O-bonded ones. For CN⁻, Δ_3 is smaller for the C- than for the N-bonded isomer. The strength of the H-SCN bond is not known, but Δ_3 for the S-bonded isomers must be less than for the N-bonded ones.¹⁸

Other pairs of acids may also be used to rank order anions. A reasonable amount of data exists for acetyl compounds. Let

$$\Delta_4 = D^\circ_{\text{CH}_3\text{COB}} - D^\circ_{\text{CH}_3\text{B}} \quad (14)$$

The results are shown in Table IV. With one major exception, the ordering is much the same as in Table III. But acetate ion

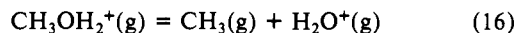
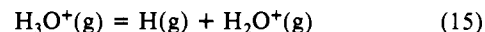
Table V. Empirical Hardness Parameters for Neutral Bases Compared to Global Values^d

| base | $D^\circ_{\text{BH}^+}$ ^a | $D^\circ_{\text{CH}_3\text{B}^+}$ ^a | Δ_5 | η^b |
|-----------------------------------|--------------------------------------|--|------------|----------|
| H ₂ O | 144 | 134 | 10 | 9.5 |
| (CH ₃) ₂ O | ~106 | ~91 | 15 | 8.0 |
| CH ₃ OH | 120 | 106 | 14 | |
| CH ₃ CO ₂ H | 115 | 99 | 16 | |
| H ₂ S | 98 | 96 | 2 | 6.2 |
| C ₂ H ₅ SH | 92 | 89 | 3 | |
| (CH ₃) ₂ S | ~88 | ~84 | 4 | 6.0 |
| NH ₃ | 124 | 111 | 13 | 8.2 |
| N ₂ H ₄ | 93 | 82 | 11 | |
| (CH ₃) ₃ N | 91 | 79 | 12 | 6.3 |
| imidazole | 113 | 96 | 17 | |
| PH ₃ | 106 | 104 ^c | 2 | 6.0 |
| (CH ₃) ₃ P | 110 | 107 | 3 | 5.9 |
| AsH ₃ | ~96 | ~0 | ~0 | 6.0 |

^aSee ref 50. ^bReference 3. ^cEstimated heat of formation for CH₃XH₂. ^dAll data in kcal, except for η in eV.

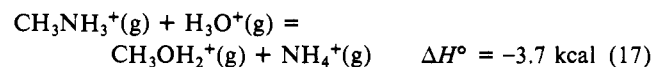
has an unexpectedly small value for Δ_4 . This comes from a low value for the acetyl-oxygen bond. A plausible explanation is that cross-conjugation is weakening the bond. A smaller, but similar effect is seen in acetylacetone. If this explanation is correct, diacetyl-imide should also have a weak acetyl-nitrogen bond.

Neutral Molecules as Bases. Using heats of formation, proton affinities, and ionization potentials, it is possible to calculate D° for reactions such as



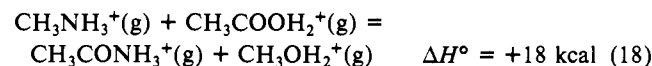
Then defining Δ_5 , analogous to eq 13, as the difference in these bond energies, the results shown in Table V can be found. The ordering given by Δ_5 is that of local hardness, which may be compared with the ordering given by η , the global hardness.

The two orders are qualitatively the same, but there are some deviations. For example, water has a value of Δ_5 which is too small compared to that for (CH₃)₂O or NH₃. The wrong answer would be predicted for the reaction

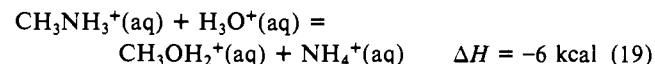


if the normal assumption is made that H₂O is harder than NH₃.

The explanation in this case is most easily seen by considering the effect of replacing a hydrogen atom by a methyl group on the proton affinities of small molecules. The methyl group, because it can delocalize the charge, always increases the proton affinity. But the effect diminishes rapidly as the size of the molecule increases. If we use CH₃CO⁺ and CH₃⁺ as the reference acids, we make the right prediction.¹⁹



The methyl group effect is a gas-phase phenomenon, related to Born charging energies. Thus it should be greatly attenuated in solution. Since the heats of hydration of all the ions in reaction 17 are known,²⁰ we can calculate the following



As expected, the correct prediction is now made. Since practical use of the HSAB principle for ions will normally be in solution, it is safe to assume that H₂O is harder than NH₃.

Complex Ions in Water. The first use of the concept of chemical hardness was to explain complex ion formation in water.⁶ Metal ions were classified as hard or soft according to their preference for certain ligands. Soft metal ions formed more stable complexes

(17) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561-567. Pearson, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 6801-6806.

(18) Jorgensen, K. A.; Lawesson, S. O. *J. Am. Chem. Soc.* **1984**, *106*, 4687-4691.

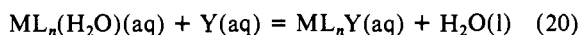
(19) Protonation is probably on the carbonyl oxygen in both the acid and amide. However, protonation on OH and NH₂ is competitive in both cases, and the difference will have only a small value.

with iodide ion, and hard metal ions with fluoride ion.

From heats of formation, it is found that the difference in heats of hydration of F^- and I^- is 53 kcal/mol.^{20,21} Therefore, in Table II, a value of $\Delta_1 = 53$ kcal separates the hard acids from the soft ones, and CH_3^+ is just on the borderline. Cs^+ becomes soft, by this criterion, though normally considered as hard. However, its complexes would be so weak that there seem to be no useful consequences.

There are a great deal of data available, not only on equilibrium constants, but also on heats of reaction between metal ions and various ligands.²² For various practical reasons, it is difficult to find data that can be used even in a comparative sense. Solvation energies are one obvious problem. Only for very restricted cases can we use eq 3 or 4.

Nevertheless, some useful generalizations may be made. Consider the typical reaction for the formation of a complex in water (charges are omitted for simplicity).



There are four interactions in (20) which are acid-base in character. One is the interaction of ML_n with H_2O , the second is the ML_n interaction with Y , the third is the interaction of Y with the solvent, and the fourth is the interaction of water with itself, a constant factor. The solvation energies of the large complex ions, $ML_n(H_2O)$ and ML_nY , are governed by the Born equation primarily.

If ML_n is hard and Y is soft, or vice versa, we can expect ΔH° to be positive, or only a small negative number. Therefore, complexation will not be favorable. Suppose ML_n is hard and Y is hard. Then their interaction will be favorable. But H_2O is a hard molecule, both as an acid and a base. Therefore $Y(aq)$ and $ML_n(H_2O)$ are also stabilized. Overall, only a small negative value for ΔH° can be hoped for and moderately stable complexes.

But if ML_n is soft and Y is soft, then everything works in favor of a large negative value for ΔH° , and very stable complexes. Ahrland has made a detailed study of the available data and has found a remarkable agreement with the above predictions.²³ Hard acids rarely form complexes with soft bases, and hard bases do not form very stable complexes with soft acids, except for strong bases such as OH^- .

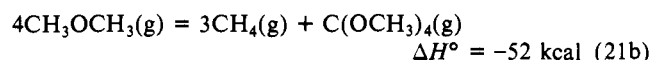
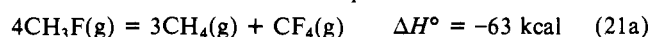
Hard acids form only moderately stable complexes, even with hard bases, and ΔH° is close to zero. Soft acids and soft bases usually form very stable complexes in aqueous solution, and ΔH° is a large negative number. For a soft reference acid, such as Pd^{2+} or CH_3Hg^+ , the order of increasing values of $-\Delta H^\circ$ is $22-24$ $F^- \ll Cl^- < Br^- \sim N_3^- < I^- \sim SCN^- < RS^- < CN^-$. For neutral ligands the order is $H_2O < NH_3 < thiourea < PR_3$. Note that the order for anions is not exactly the same as in Table II because of different hydration energies.

There are not enough comparable data to rank order many metal ions, but the following orders of decreasing values of $-\Delta H^\circ$ can be established: $Hg^{2+} \gg Cd^{2+} > Zn^{2+}; Pt^{2+} \sim Pd^{2+} > Ni^{2+}$. Also the Irving-Williams order²⁵ for formation constants of complexes, $V^{2+} < Cr^{2+} > Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$, follows the experimental values of η for these metal ions.³ As expected, the magnitude of the changes in $\log K_{eq}$ increase with the polarizability of the ligand donor atoms.²⁶

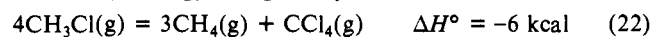
The Symbiotic Effect. It has already been noted that CF_3^+ is much harder than CH_3^+ . This is actually an example of a very general phenomenon, first noted by Jorgensen and called by him

the "symbiotic" effect.²⁷ Soft bases attached to the same central acceptor atom make it a soft acid, and hard bases make it a hard acid. In coordination chemistry, symbiosis explains why some ligands, such as CN^- or phenanthroline, make a metal ion form strong complexes with other soft ligands, whereas F^- and H_2O favor the bonding of other hard ligands.^{27,28} There is also an antisymbiotic effect known.²⁹

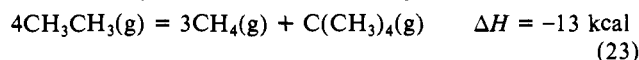
The symbiotic effect is also common in organic chemistry, but here it has been called the clustering, anomeric, or geminal effect.³⁰⁻³² Clustering refers to the stabilization caused by adding several hard substituents to the same carbon atom. Some extreme examples are shown by the following reactions, in which the number of bonds of each kind is preserved.



These large energy changes may be contrasted with

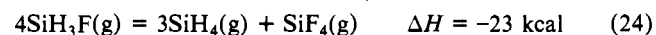


In reaction 21a the comparison is between F^- and H^- , the hardest and softest bases in Table III, and the effect is maximal. In (22) Cl_3^+ is not nearly as hard as CF_3^+ , and the difference between Cl^- and H^- is not as great. In general F^- , OR^- , and NR_2^- give the largest effects, as expected. However, even CH_3^- gives a noticeable symbiotic effect, since CH_3^- is harder than H^- .

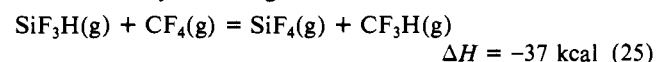


Bases with donor atoms from the later rows give only small effects.^{30,32}

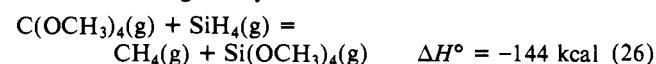
Elements other than carbon may be influenced.^{32,33}



Comparing (24) with (21b) it appears that silicon is less affected than carbon by clustering. But consider the reaction

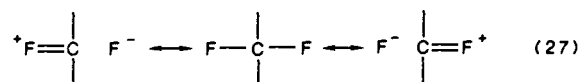


Clearly SiF_3^+ is much harder than CF_3^+ , just as SiH_3^+ is harder than CH_3^+ . An extreme example of the difference between the two elements is given by



This illustrates the great affinity of silicon for binding to oxygen donors.

Two theories have been proposed to explain the clustering effect. The electrostatic theory simply proposes that the carbon atom in CF_4 is much more positive than in CH_3F .³¹ This leads to strong ionic bonding to each fluorine atom, which must be quite negative. The other explanation is double bond-no bond resonance, or negative hyperconjugation.^{30,32}



Such double bonding would be most effective for F , OR , and NR_2 groups, as found.

The explanation, according to the concept of hardness, combines both of these explanations and adds more detail. Since the carbon in CF_3^+ is hard, it resists the addition of electron density and remains positive. This is ideal for bonding to F^- , which favors ionic bonding. The orbital component of hardness in CF_3^+ lies

(20) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109-6114.

(21) This large difference between F^- and I^- may be used to classify water as a hard Lewis acid, as well as a hard base.

(22) Ashcroft, S. J.; Mortimer, C. T. *Thermochemistry of Transition Metal Complexes*; Academic Press: New York, 1970. Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Handbook of Metal Ligand Heats*; Marcel Dekker: New York, 1978.

(23) Ahrland, S. *Helv. Chim. Acta* **1963**, *50*, 306-318.

(24) Gerding, P. *Acta Chem. Scand.* **1966**, *20*, 2771-2776. Hancock, R. D.; Marsicano, F. *J. Chem. Soc., Dalton Trans.* **1976**, 1832-1837.

(25) Irving, H.; Williams, R. J. P. *Nature (London)* **1984**, *162*, 146-148.

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(27) Jorgensen, C. K. *Inorg. Chem.* **1964**, *3*, 1201-1202.

(28) Pratt, J. M.; Thorp, R. G. *J. Chem. Soc. A* **1966**, 187-191.

(29) Pearson, R. G. *Inorg. Chem.* **1973**, *12*, 712-714.

(30) Hine, J. J. *J. Am. Chem. Soc.* **1963**, *85*, 3239-3244. Hine, J.; Klueppel, A. W. *Ibid.* **1974**, *96*, 2924-2929.

(31) Holtz, D. *Prog. Phys. Org. Chem.* **1971**, *8*, 1-74.

(32) Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 7362-7373, and references therein.

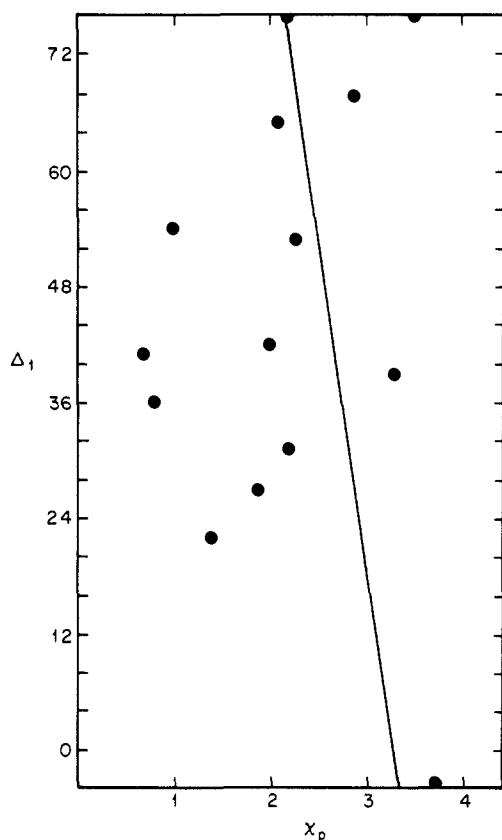


Figure 1. Plot of difference between AF and AI bond energies against the Pauling electronegativities of A. The straight line is the theoretical Pauling equation and the filled circles are the experimental points.

in the LUMO, which is an antibonding π^* orbital. Adding electron density to it cancels the effect of the bonding π orbital. Thus fluorine, being negative in terms of σ -bonding, is a necessary requirement for good π -bonding.

The Pauling Bond Energy Equation. Electronegativity is one of the factors determining bond energies, more electronegative atoms and radicals usually, but not always, forming stronger bonds. Also differences in electronegativity strengthen bonds (ionic resonance energy). Simple MO treatment of bond energies does show a contribution depending on the square of the difference between the absolute electronegativities of the two bonded fragments.^{17,34} However, the coefficient of this term is a very complicated function, different for every case.

Many years ago Pauling proposed his well-known bond energy equation including such a term, and used it to assign electronegativities to the elements.³⁵ His equation assumes that the coefficient is a constant, which is a very crude approximation. Nevertheless, it is conceivable that the Δ values of the tables are due to differences in electronegativity.

The value of any Δ can readily be calculated from the Pauling equation. For Δ_1 we find

$$\Delta_1 = \frac{1}{2}(D_{\text{FF}}^\circ - D_{\text{II}}^\circ) + a(\chi_{\text{F}}^2 - \chi_{\text{I}}^2) - 2a(\chi_{\text{F}} - \chi_{\text{I}})\chi_{\text{A}} \quad (28)$$

χ_{A} is the Pauling electronegativity of the radical A corresponding to the Lewis acid A^+ , and a is a constant equal to 23 kcal/mol. Both χ_{F} and χ_{I} are known (4.0 and 2.5).

Figure 1 shows the theoretical plot of Δ_1 against χ_{A} from eq 28. The straight line predicted may be compared with the points, which represent the experimental values. The discrepancies are very large. Two Lewis acids with the same value of χ_{A} may give

(33) The heat of formation of SiH_3F is that given by: Schlegel, B. *J. Phys. Chem.* **1984**, *88*, 6254–6258.

(34) Pearson, R. G. *J. Chem. Phys.* **1949**, *17*, 969–971. Nelson, P. G. *J. Chem. Res.* (5) **1978**, 378–379.

(35) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Iaca, NY, 1960; pp 88–91.

Δ_1 values differing by 80 kcal/mol. This failure of the Pauling equation when applied to bond energy differences was pointed out some years ago.³⁶

A second test may be made using the values for Δ_3 and Δ_4 . The Pauling equation gives the variation with χ_{B} as

$$\Delta_3 = \text{constant} - 2a(\chi_{\text{H}} - \chi_{\text{CH}_3})\chi_{\text{B}} \quad (29)$$

$$\Delta_4 = \text{constant} - 2a(\chi_{\text{CH}_3\text{CO}} - \chi_{\text{CH}_3})\chi_{\text{B}} \quad (30)$$

The entries in Tables III and IV show that there is indeed a reasonable linear variation of Δ_3 and Δ_4 with χ_{B} , and that the slope is positive for both (29) and (30).

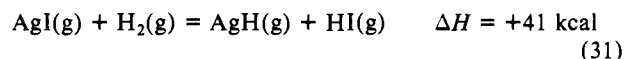
Accordingly $\chi_{\text{CH}_3} > \chi_{\text{H}}$ and $\chi_{\text{CH}_3} > \chi_{\text{CH}_3\text{CO}}$. But this is incompatible with the Pauling electronegativity values assigned to these groups:³⁷ $\chi_{\text{CH}_3} = 2.32$, $\chi_{\text{H}} = 2.08$, $\chi_{\text{CH}_3\text{CO}} = 2.93$. There is no improvement if Mulliken values are used: $\chi_{\text{CH}_3} = 4.96$, $\chi_{\text{H}} = 7.17$, $\chi_{\text{CH}_3\text{CO}} = 4.08$. Electronegativity differences cannot explain the Δ values of the tables.

Bond Energies in Organometallic Compounds. It is interesting to try to apply the HSAB principle to the important case of metal–ligand bond energies in organometallic compounds of the transition metals. While some bond energies are known, there is a great shortage of comparable data. A recent study has provided a useful series of relative bond energies in $\text{C}_5\text{-(CH}_3)_5\text{Ru(P(CH}_3)_3)_3\text{X}$ compounds.³⁸

When the relative Ru–X bond energies are plotted against D_{HX}° (Figure 5 in ref 38) a straight line of unit slope is found whenever X has O or N as the donor atom. But X = CN^- , HS^- , and H^- deviate in the direction of stronger bonds. These results are consistent with $\text{C}_5(\text{CH}_3)_5\text{Ru(P(CH}_3)_3)_2^+$ being a soft Lewis acid.

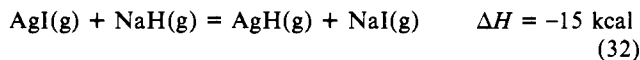
However, there are disturbing discrepancies. The deviations for CN^- and HS^- are much larger than that for H^- , though the latter is the softest base in Table III. Also the Ru– CH_2COCH_3 bond energy falls on the line, even though $\text{CH}_3\text{COCH}_2^-$ is a softer base than HS^- , according to Table III.

The explanation for H^- has already been given. Hydride ion, being a pure σ -donor, does not bond well to a Lewis acid such as Ru^{2+} , with good π -donor properties. The following example shows that it is not the complex nature of the acid which is responsible.



Thus I^- is softer than H^- if Ag^+ is compared to H^+ , the latter being a good σ -acceptor and indifferent to π -bonding.

Another example is also informative.



H^- is softer than I^- , if Ag^+ is compared to Na^+ . The latter, being less electronegative than H^+ , does not bind well to hydride ion. Ag^+ , being more electronegative than Na^+ , binds more strongly, in spite of the lack of π -bonding. Thus bonding of Lewis acids to hydride ion is dominated by the electronegativity of the acid.

A possible answer to the weakness of the bond to $\text{CH}_3\text{COCH}_2^-$ is that a steric destabilization exists, based on the results for CH_3^- binding. In simple M–H and M– CH_3 molecules, the M–H bond is somewhat stronger than the M– CH_3 bond. But adding more ligands to the metal atom greatly increase the difference.³⁹ According to a theoretical analysis by Ziegler, the weaker bond of methyl results from repulsive exchange interactions between the filled valence orbitals of CH_3 and filled d orbitals on the metal

(36) Pearson, R. G. *Chem. Commun.* **1968**, 65–67. Note that the symbiotic effect directly contradicts the Pauling equation. For a discussion see: Evans, R. G.; Huheey, J. E. *J. Inorg. Nucl. Chem.* **1970**, *32*, 373–381. This early paper uses the modern definition of hardness without naming it as such.

(37) See: Mullay, J. *J. Am. Chem. Soc.* **1985**, *107*, 7271–7274, for tabulations of recent values.

(38) Bryndza, H. E.; Fong, L. K.; Paciello, R. A.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1444–1456.

(39) Halpern, J. *Inorg. Chim. Acta* **1987**, *100*, 41–48.

atom.⁴⁰ Repulsive exchange interactions between methyl and the filled orbitals of the ligands accounts for the ligand effect. But this is only the quantum mechanical way of describing steric strain.⁴¹

It is interesting that increasing the positive charge on the metal atom will greatly strengthen the methyl-metal bond relative to hydrogen.^{40,42} This is just the result expected since the metal becomes a harder Lewis acid, and now prefers the harder CH₃⁻ ligand over H⁻. In more elegant language, positive charge on the metal contracts its d orbitals, and reduces the repulsive exchange effects.

Conclusions

It appears to be possible to obtain relative values of local hardness for Lewis acids and bases, which are both rational and consistent. Furthermore, such values, obtained from bond energy differences, are in reasonable agreement with relative values of $\eta = (I - A)/2$. They also show that the chemical hardness of anions, not directly measurable, is not greatly different from that of related neutral molecules.

The consistency suggests that eq 4 is usually reliable and my have useful applications. Exceptions do occur but seem to have reasonable explanations such as steric strain or cross-conjugation. Hydride ion is a special case among bases. It is actually surprising

that specific properties are not invoked more often.

The relative hardness values of F⁻, OH⁻, NH₂⁻, and CH₃⁻ seem to be well correlated with the extent to which their valence shell electrons can produce π -repulsions with the filled valence shells of Lewis acids. Going down a series such as F⁻, Cl⁻, Br⁻, I⁻, these repulsions are diminished and eventually become net stabilizations.⁴³⁻⁴⁴

Finally, it should be mentioned that there is a rapidly growing literature on the modern meaning of chemical hardness. Some of these articles give tables of η , or η , which may be compared with those presented here.⁵¹

Acknowledgment. This work was supported by the U.S. Department of Energy (Contract No. DEAS03-76SF0034).

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(44) Simple polarization also accounts for a stabilization of soft-soft pairs: Bernardi, F.; Bottone, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* **1986**, *108*, 8171-8175.

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(47) Drzaic, P. S.; Marks, J.; Brauman, J. I. *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 21.

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(49) Stull, D. R.; Westrum, Jr., E. F.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969.

(50) Pearson, R. G. *J. Org. Chem.* **1987**, *52*, 2131-2136.

(51) See: Bergmann, D.; Hinze, J. In *Electronegativity*; Sen, K. D., Jorgensen, C. K., Eds.; Springer-Verlag: Berlin, 1987. Komorowski, L. *Chem. Phys., Lett.* **1987**, *134*, 536-540.

(40) Ziegler, T.; Tschinke, V.; Becke, A. *J. Am. Chem. Soc.* **1987**, *109*, 1351-1358.

(41) Halpern, ref 39, has experimental evidence for steric strain.

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Dynamics of Ligand Escape from the Heme Pocket of Myoglobin

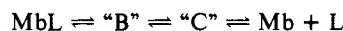
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Abstract: Molecular dynamics calculations are used to study the kinetics of the process by which a dioxygen ligand leaves the heme pocket of sperm whale myoglobin. Umbrella sampling techniques are used to generate free-energy profiles at several temperatures for escape along a path between the distal histidine and valine residues, and methods for assessing the statistical precision of such profiles are explored. The results are used to compute rate constants for ligand escape, both in the transition-state approximation and with full classical dynamics. Corrections to transition-state theory rates (i.e., the transmission coefficients) are in the range 0.8 to 0.9 for this process, and the computed rate constants at room temperature are in good agreement with experiment. Near room temperature the computed activation energy is less than 1 kcal/mol, but at lower temperatures (between 180 and 270 K) this rises to 5 kcal/mol. Potential physical origins of such non-Arrhenius temperature dependence are discussed in light of models of protein fluctuations that accompany ligand escape.

The study of the binding of gaseous ligands to heme proteins has served for many years as an important test case of our ability to understand enzyme-substrate interactions in general. Aside from the simplicity of the ligands (such as O₂, CO, or NO), and the wealth of structural data available for heme proteins, these systems have the important advantage that they can be followed over a wide time domain following photodissociation of the ligand by a short laser pulse. Intermediates in the ligand rebinding process were originally identified in low-temperature studies,¹ and have recently been characterized at room temperature as well.²

There is general agreement that the main features of ligand binding to myoglobin can be described by a (phenomenological) kinetic scheme with two or three intermediate states:^{1,2}



Here, state B has the ligand molecule inside the protein matrix, presumably near the heme group, but not bound to the iron atom.

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