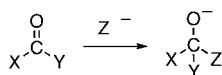# Addition of Anions to Carbonyl Compounds: An Ab Initio Study

Robert Evan Rosenberg

Transylvania University, Department of Chemistry, 300 North Broadway, Lexington, Kentucky 40508

rrosenberg@transy.edu

Received March 25, 2008

X,Y = H, CH$_3$, NH$_2$, OH, F, CF$_3$, CHCH$_2$, CHO, CCH, CN

Z = H, CH$_3$, NH$_2$, OH, F, CHCH$_2$, CHO, CCH, CN

Calculation of $\Delta H_{reaction}$

Energies for the addition of anionic nucleophiles, Z$^-$, to carbonyl compounds, XYCO, are calculated at the G2(MP2) level of theory. The substituents X, Y, and Z are taken from the set {H, CH$_3$, NH$_2$, OH, F, CF$_3$, CHCH$_2$, CHO, CCH, and CN}. The basicity and, to a lesser extent, ionization potential of Z$^-$ were found to correlate with the enthalpy of addition of Z$^-$ to H$_2$CO. The enthalpy of addition of Z$^-$ to XYCO relative to H$_2$CO is largely independent of Z. The ordering of the enthalpies of addition for the series of XYCO's is rationalized. By using a thermodynamic cycle, the independence of this ordering from Z is attributed to the additivity of the inductive stabilization of XYZCO$^-$ by X and Y versus H$_2$ZCO$^-$. A method for estimating the enthalpy of addition for nucleophile/carbonyl combinations not studied above is described and shown to give good results on a model system.

Introduction

Reactions of nucleophiles with carbonyl compounds are of great significance in both organic chemistry and biochemistry.[1] One approach toward a better understanding of these reactions is to examine the relevant species in the gas phase, thereby removing the complications brought by solvation. This methodology has been used with great success in the past in the study of organic acids and bases.[2] However, two factors hinder the use of experimental gas phase data to study carbonyl addition reactions: there is relatively little data[3] and the reaction pathways in the gas phase are often different than those in solution.[4] Since it is well established that ab initio calculations can reproduce gas-phase thermochemical data, it is surprising that only a few such studies on the reaction of nucleophiles with carbonyl compounds exist.[5]

This study examines the enthalpy of addition of nucleophiles, Z$^-$, to carbonyl compounds, XYCO, to form the tetrahedral adducts XYZCO$^-$. The substituents X, Y, and Z were chosen from the set {H, CH$_3$, NH$_2$, OH, F, CF$_3$, CHCH$_2$, CHO, CCH,

and CN} with an emphasis on reactions of Z$^-$ with HCOX and CH$_3$COX. Substituents X, Y, and Z that contained third-row elements such as Cl and SH were omitted from this work. In these cases, the corresponding addition compounds XYZCO$^-$ were computationally unstable toward decomposition into their ion—dipole complexes between the appropriate carbonyl compound and an anion that contained the third-row element, e.g., Cl$^-$ or HS$^-$. Energies were calculated using the G2(MP2) model chemistry, in part so that these data could be compared with previous computational work. The G2(MP2) methodology has been shown to give proton affinities, dissociation energies, ionization energies, and electron affinities with an average absolute deviation from experimental values of 1.58 kcal/mol.[6] Calculation with the somewhat superior G3(MP2) model chemistry is unlikely to change the conclusions of this study.[7]

It should be noted that both theory and experiment show that the gas-phase mechanism for the reaction of Z$^-$ with XYCO

(1) (a) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53–113. (b) Patai, S., Ed. *The Chemistry of Carbonyl Group*; Interscience: New York, 1966, 1970; Vols. 1 and 2. (c) Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770–4777. (d) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.
(2) Ervin, K. M.; DeTuri, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947–9956.
(3) Adler, M.; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005**, *18*, 193–209.
(4) Frink, B. T.; Hadad, C. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2397–2407.

(5) (a) Madura, J. D.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 2517–2527. (b) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1987**, *109*, 3856–3861. (c) Yamabe, S.; Minato, T. *J. Org. Chem.* **1983**, *48*, 2972–2975. (d) Yamabe, S.; Minato, T.; Kawabata, Y. *Can. J. Chem.* **1984**, *62*, 235–240. (e) Lee, I.; Lee, D.; Kim, C. K. *J. Phys. Chem. A* **1997**, *101*, 879–885. (f) Lee, I.; Kim, K. C.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B.-S. *J. Am. Chem. Soc.* **2000**, *122*, 11162–11172.
(6) (a) G2(MP2): Curtiss, L. A.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1993**, *98*, 1293–1298. (b) G2: Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221–7230.
(7) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764–7776.

TABLE 1. Correlation of the Enthalpy of Addition of Z⁻ to H₂CO with Various Parameters (kcal/mol)

Z⁻	enthalpy[a]	acidity[b]	acidity[c]	IP[d]	IP[e]	IP[f]	hardness[g]	hardness[h]
H	−55.7	418.9	400.3	2.3	−7.3	−0.7	157.0	233.0
CH₃	−48.1	416.8	416.8	25.2	15.3	1.0	92.0	87.8
NH₂	−38.2	402.1	403.7	30.1	18.0	18.4	122.0	115.3
OH	−30.9	389.1	390.8	66.3	44.4	43.3	129.0	163.7
F	−20.9	371.1	371.4	111.3	81.6	79.5	161.0	224.5
CHCH₂	−48.0	406.9	406.1	50.5	18.5	17.5		94.3
CHO	−48.5	394.1	393.4	31.0	14.3	7.6		91.7
CCH	−20.4	376.0	376.7	77.9	79.1	71.4		102.7
CN	−8.2	349.3	351.1	117.6	116.9	91.3	122.0	132.2
CF₃	−36.3	379.0	376.9	97.2	73.1	41.3		129.1
CH₂CHCH₂	−28.3	388.7	390.8	11.9	18.4	12.7		72.4

[a] G2(MP2)-calculated heat of reaction of Z⁻ with H₂CO to form H₂ZCO⁻. [b] G2(MP2)-calculated acidities of HZ. [c] Experimental gas phase acidities of HZ, ref 14. [d] MP2/6-311+G(3df,2p)//MP2/6-31G*-calculated ionization potential = $-e_{HOMO}$, ref 17. [e] MP2/6-311+G(3df,2p) single-point calculations. Ionization potential = energy (Z·) − energy (Z⁻), where Z· and Z⁻ are both at the MP2/6-31G*-optimized geometry of Z⁻. [f] G2(MP2)-calculated adiabatic ionization potential of Z⁻. [g] Values of absolute hardness taken from ref 18b. [h] Absolute hardness using Pearson's formulation, and taking ionization potential = $-e_{HOMO}$ and electron affinity = $-e_{LUMO}$ using MP2/6-311+G(3df,2p).

can be complex if either X or Y can act as a leaving group. In these cases, the structure XYZCO⁻ is not always present as a stationary point on the potential energy surface. Specifically, in the gas-phase reaction of Cl⁻ with CH₃COCl, there was no evidence for the intermediate CH₃CCl₂O⁻.[8] Instead, the reaction proceeded through two ion−dipole complexes. This conclusion has been buttressed and extended by a recent high-level computational study.[9] More generally, the mechanism of acyl transfer can proceed either by a textbook addition−elimination sequence[10] or through an S_N2- or S_N1-like mechanism.[11]

Despite the mechanistic ambiguities above, this study takes the approach that reaction of Z⁻ with XYCO leads to a structure XYZCO⁻ that is a genuine stationary point (intermediate or product) on the potential energy surface. For compounds XYCO where neither X or Y is a leaving group (X, Y = H, CH₃, CHCH₂, CHO, CF₃), it is clear that Z⁻ will form an addition product XYZCO⁻. For the remaining compounds XYCO, the corresponding XYZCO⁻'s are expected to be genuine intermediates. Here, the potential leaving groups (NH₂, OH, F, CCH, CN) are significantly less labile than those found in the compounds above that did not follow the textbook addition− elimination pathway. Indeed, all compounds XYZCO⁻ in this study are stationary points that are computationally stable to decomposition. As there are nearly 200 compounds XYZCO⁻ in this study, a complete potential energy surface analysis of each reaction Z⁻ + XYCO in the manner of ref 9 was not performed.

Results and Discussion

A. Addition of Z⁻ to H₂CO. Table 1 lists the calculated enthalpy of reaction for addition of Z⁻ to H₂CO. This enthalpy will be used in pairwise comparisons between basicity (by the acidity of HZ), ionization potential (Z⁻), and absolute hardness (Z⁻), values of which are also listed in Table 1. While these comparisons are all of intrinsic interest, the specific parameters

were also chosen because they each have previously been explicitly or implicitly associated with nucleophilicity. Here, it was assumed that reaction enthalpy and nucleophilicity might be correlated since the high exothermicity of these reactions should lead to late transition states. This assumption is indirectly supported to the extent that nucleophilicity and reaction enthalpy have similar pairwise comparisons.

Though imprecise, the connection between basicity and nucleophilicity is made early on in the training of every organic chemist. When solvent effects are removed, this connection becomes even stronger. In gas-phase kinetic work on the S_N2 reaction, Depuy showed that increasing basicity was synonymous with increasing nucleophility for a variety of nucleophiles.[12] For the calculated values in this work, increasing base strength of Z⁻ (from acidity of HZ in data column 2 in Table 1) correlates reasonably well ($r^2 = 0.85$) with more negative values of the enthalpy of addition of Z⁻ to H₂CO (data column 1 in Table 1). Had the nucleophiles Z = CHO and CF₃ been omitted from this work, this correlation would appear to be significantly stronger ($r^2 = 0.96$). However, there is no clear justification for removing these two species. It is worth noting that the calculated values[13] for the acidity of HZ are very close to the experimental values (data column 3 in Table 1),[14] with H₂ being the only outlier (average deviation = 2.8 kcal/mol, or 1.2 kcal/mol if data for H₂ is removed).

Recently, chemical theorists have tried to create nucleophilicity indices based on measurable physical properties of the nucleophile[15] such as ionization potential (IP).[16] Here, the IPs were calculated in three ways: (1) the vertical IP was set equal to the negative of the energy of the HOMO of Z⁻ according to Koopmans' theorem,[17] (2) the vertical IP was calculated by subtracting the energy of Z⁻ from that of Z· frozen at the anion's geometry, and (3) the adiabatic IP was found by subtracting the energy of Z⁻ from that of Z·, each at its optimized geometry. These data are shown in Table 1 in data columns 4, 5, and 6,

(8) Wilbur, J. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 5839–46.

(9) Fox, J. M.; Dmitrenko, O.; Liao, L.-A.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317–7328.

(10) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: NewYork, 1992; pp 330−335. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987. (c) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981**, *14*, 306–312. (d) McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983**, *16*, 394–399.

(11) (a) Bentley, T. W.; Llewellyn, G.; McAlister, J. A. *J. Org. Chem.* **1996**, *61*, 7927–7932. (b) Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 2124–2127. (c) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387–392. (d) Also see ref 9 and references therein.

(12) Depuy, C. H.; Gronert, S.; Mullin, A.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1990**, *112*, 8650–8655.

(13) Gronert, S. *J. Am. Chem. Soc.* **1993**, *115*, 10258–10266.

(14) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. "Gas phase Ion and Neutral Thermochemistry". *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl 1.

(15) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (b) Roy, D. R.; Parthasarathi, R.; Padmanabhan, J.; Sarkar, U.; Subramanian, V.; Chattraj, P. K. *J. Phys. Chem. A* **2006**, *110*, 1084–1093.

(16) Contreras, R.; Andres, J.; Safont, V. S.; Campodonico, P.; Santos, J. G. *J. Phys. Chem. A* **2003**, *107*, 5588–5593.

(17) Koopmans, T. A. *Physica* **1933**, *1*, 104–113.

TABLE 2. Enthalpy of Addition of Z^- to XYCO To Form XYZCO$^-$, Experiment and Theory[a]

X	Y	Z^- (expt)[b] H$^-$	Z^- (calcd)[c] H$^-$	Z^- (expt)[d] CH$_3^-$	Z^- (calcd)[c] CH$_3^-$
H	H	−40.9 (0.0)	−55.7 (0.0)	−48.9 (0.0)	−48.1 (0.0)
H	CH$_3$	−38.6 (2.3)	−54.2 (1.5)	−48.2 (0.7)	−47.1 (1.0)
CH$_3$	CH$_3$	−38.6 (2.3)	−53.8 (1.9)	−46.7 (2.2)	−46.5 (1.6)

[a] Values are in kcal/mol. Enthalpies relative to addition of Z^- to H$_2$CO are shown in parentheses. [b] Values are taken directly form ref 19. [c] The calculated values are G2(MP2). [d] Values are derived from quantities found in ref 19. The details of the derivation are described in the Experimental Methods.

respectively. Here, the first method shows only modest correlation ($r^2 = 0.57$) between the IP and enthalpy of addition of Z^- to H$_2$CO. The more rigorous calculation of the vertical IP in the second method leads to a much better correlation ($r^2 = 0.78$). A somewhat better correlation is achieved using the adiabatic ionization potential ($r^2 = 0.82$). As with the discussion of basicity above, removal of data, in this case the allyl anion (Z =CH$_2$CHCH$_2$), raises the correlation of each method significantly (method 1 ($r^2 = 0.77$), method 2 ($r^2 = 0.89$), method 3 ($r^2 = 0.95$)). It is tempting to speculate that the delocalization of the allyl anion is somehow related to the poor correlation, though the specifics of this connection are unclear. Taken as a whole, these data show that there is a crude correlation between ionization potential and the enthalpy of addition of Z^- to H$_2$CO, though the strength of this relationship is highly dependent on the method of calculating the ionization potential and on the nucleophiles that are included.

The concept of hardness was introduced over 40 years ago and continues to be relevant to a wide variety of chemical systems.[18] Values for hardness from Pearson and calculated values are shown in Table 1 in data columns 7 and 8, respectively. In this study, however, the correlation between the enthalpy of reaction of Z^- and H$_2$CO and hardness of the nucleophile was extremely poor ($r^2 = 0.00$).

B. Addition of Z^- to XYCO.

1. Before looking at the calculated values for the addition of Z^- to XYCO, it is worthwhile to examine Table 2, which contains the available gas-phase experimental heats of reaction[19] along with the appropriate calculated enthalpies. For Z = H, the calculated values are nearly 16 kcal/mol more exothermic than the experimental values. The weak agreement here can be attributed to the inadequate description of H$^-$ in the calculation, which, in turn, is due to the relatively small number of basis functions used. The poor description of H$^-$ is presumably also the cause of the 18.6 kcal/mol discrepancy between the calculated and experimental acidity of H$_2$ seen in Table 1. All other Z^-'s feature at least one second-row atom and are thus better modeled than H$^-$. Thus, for Z = CH$_3$, the agreement between calculated and experimental reaction enthalpies is very good.

As will be seen, the major result of this work is not based on the absolute enthalpy of reaction, but instead on the relative enthalpy of reaction. Here, relative enthalpy is defined as the enthalpy of addition of Z^- to XYCO minus the enthalpy of

addition of Z^- to H$_2$CO. The use of relative enthalpies allows for the cancelation of systemic errors in the calculations, such as occurred for H$^-$. Thus, the agreement between the calculated and experimental relative enthalpies for addition of H$^-$ to CH$_3$CHO and to CH$_3$COCH$_3$ is actually quite good. As might be expected from the absolute reaction enthalpies, the agreement between the calculated and experimental relative enthalpies for the addition of CH$_3^-$ to CH$_3$CHO and CH$_3$COCH$_3$ is also quite good.

2. Table 3 lists the calculated enthalpies of addition of Z^- to XYCO relative to H$_2$CO. For the first row of Table 3, the absolute values for addition of Z^- to H$_2$CO are shown. For all other XYCO's, the absolute value of addition can be obtained by summing the data in the appropriate row with the value in the first row. The columns of Table 3 (except for the first entry) contain the relative values for addition of a given Z^- to a variety of XYCO's. Analysis of the data in the rows and then the columns of Table 3 proceeds below.

Perhaps the most interesting feature of the data in the rows of Table 3 is that the identity of Z^- has little effect on the relative enthalpy of addition of Z^- to XYCO. This does not mean, however, that the enthalpy of addition of H$^-$ to HFCO (−67.7 kcal/mol) is the same as that for the addition of F$^-$ to HFCO (−32.7 kcal/mol). Instead, the enthalpy *difference* between H$^-$ adding to HFCO versus H$^-$ adding to H$_2$CO (−12.0 kcal/mol) is similar to the *difference* between F$^-$ adding to HFCO versus F$^-$ adding to H$_2$CO (−11.8 kcal/mol). The constancy of the relative enthalpy of addition with respect to variation in Z^- is best illustrated for XYCO's with nonpolar groups such as HCOCH$_3$, HCOCHCH$_2$, CH$_3$COCH$_3$, and CH$_3$COCHCH$_2$. Incorporation of highly polar groups into XYCO such as CF$_3$, CN, or F leads to slightly more fluctuation in the data. The highest variation from the mean of a row is seen for F$_2$CO. Even here, the standard deviation is only 3.3 kcal/mol, which is just over 10% of the mean value for addition. Overall, the average standard deviation across all rows is just 2.1 kcal/mol. Although the data for each row is mostly constant, values for the highly basic H$^-$ tend to be lower than average and those for the weakly basic CN$^-$ tend to be higher than average. This trend and other subtle features of the data in Table 3 will be discussed further in section C.

The data above leads to an important conclusion: the ordering of the enthalpy of addition of compounds XYCO with an anionic nucleophile does not depend on the identity of the nucleophile. Compounds XYCO can be placed into three broad groups. The most negative enthalpies of addition are for carbonyl groups substituted with strongly electron-withdrawing groups such as CF$_3$, CN, CHO, CCH, and F.[20] Intermediate enthalpies are found for carbonyl groups substituted with CH$_3$, CHCH$_2$, or OH, all of which have enthalpies similar to that of H$_2$CO. Finally, carbonyl groups substituted with NH$_2$ have the most positive enthalpies of addition. In the broadest sense, it appears that electron withdrawal activates the carbonyl group toward nucleophilic addition, while electron donation stabilizes it. The reasons behind these groupings is postponed to section C.

3. The data in Table 3 also allow one to confidently estimate the addition enthalpies for compounds not studied here. Both the estimates and the actual reaction enthalpies for 16 additional

(18) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516. (c) Ayers, P. W.; Parr, R.G.; Pearson, R. G. *J. Chem. Phys.* **2006**, *124*, 194107/1–194107/8.

(19) Linstrom, P. J.; Mallard, W. G., Eds. *NIST Chemistry WebBook, NIST Standard Reference Database, Number 69*; National Institute of Standards and Technology: Gaithersburg, MD, 2005. http://webbook.nist.gov.

(20) Though it has no heteroatoms, the substituent CCH can be said to be strongly electron withdrawing based on its σ^* value of 2.18, slightly larger than CHO, which has an σ^* of 2.15. Perrin, D. D.; Dempsey, B.; Serjeant, E. P. pK$_a$ Prediction for Organic Acids and Bases; Chapman and Hall: London and New York, 1981; pp 111, 113.

TABLE 3. Enthalpies of Addition of Z^- to XYCO Relative to Addition of Z^- to H_2CO^a

X	Y	H	CH$_3$	NH$_2$	OH	F	CHCH$_2$	CHO	CCH	CN	avg	sd
H	H^b	−55.7	−48.1	−38.2	−30.9	−20.9	−48.0	−48.5	−20.4	−8.2		
H	CH$_3$	1.5	1.0	1.2	0.2	0.6	1.9	1.0	1.5	2.2	1.3	0.6
H	NH$_2$	9.7	9.4	11.6	8.5	7.3	11.0	10.2	11.6	12.6	10.2	1.7
H	OH	2.3	1.0	1.1	0.2	0.7	3.9	2.3	4.7	5.7	2.5	1.9
H	F	−12.0	−12.9	−14.4	−13.7	−11.8	−9.9	−10.2	−8.6	−6.7	−11.1	2.5
H	CHCH$_2$	−1.6	−1.2	−0.3	0.0	0.5	0.1	−1.0	0.6	1.7	−0.2	1.0
H	CHO	−18.4	−18.9	−18.0	−18.4	−16.6	−17.8	−14.5	−16.2	−13.4	−16.9	1.9
H	CCH	−11.1	−11.1	−9.2	−8.8	−7.7	−8.9	−8.8	−6.4	−4.4	−8.5	2.1
H	CN	−28.2	−27.5	−25.3	−24.8	−22.8	−24.8	−23.2	−21.5	−18.0	−24.0	3.1
H	CF$_3$	−26.4	−25.6	−23.6	−24.0	−21.5	−23.4	−21.4	−21.2	−18.3	−22.8	2.5
CH$_3$	CH$_3$	1.9	1.6	5.5	6.4	1.1	3.2	1.9	2.4	3.6	3.1	1.8
CH$_3$	NH$_2$	9.3	12.6	16.2	8.5	13.2	11.2	10.0	11.8	13.0	11.7	2.4
CH$_3$	OH	2.2	7.4	2.4	7.3	2.1	4.6	2.9	5.3	6.4	4.5	2.2
CH$_3$	F	−10.7	−11.1	−6.2	−11.2	−3.7	−8.1	−8.6	−6.9	−4.7	−7.9	2.8
CH$_3$	CHCH$_2$	−1.9	−1.5	−0.6	−1.2	−0.6	0.1	−1.6	0.2	1.7	−0.6	1.1
CH$_3$	CHO	−16.3	−16.4	−15.4	−16.4	−14.6	−15.1	−12.9	−13.7	−10.7	−14.6	1.9
CH$_3$	CCH	−7.8	−7.7	−5.5	−6.0	−4.8	−5.2	−5.6	−3.2	−0.9	−5.2	2.1
CH$_3$	CN	−24.0	−23.6	−21.3	−21.8	−19.7	−20.7	−19.7	−17.9	−14.2	−20.3	3.0
NH$_2$	NH$_2$	12.7	17.5	13.6	17.0	10.2	14.7	12.1	16.2	16.0	14.4	2.5
OH	OH	−5.5	0.4	−1.7	−0.6	−0.3	−1.8	0.4	0.6	2.3	−0.7	2.2
F	F	−35.5	−29.6	−26.9	−25.4	−28.4	−31.2	−26.8	−28.0	−24.7	−28.5	3.3

^{a} Calculated using G2(MP2). Values are in kcal/mol. ^{b} Values in this row are the absolute enthalpies of addition of Z^- to H_2CO, identical to those from Table 1.

TABLE 4. Calculated and Predicted Enthalpies of Addition of Z^- to XYCO^a

XYCO	H	CH$_3$	F	CN	c-C$_3$H$_5$^{b}	c-C$_3$H$_3$^{b}
H$_2$CO	−55.7	−48.1	−20.9	−8.2	−52.5	−56.2
HFCO	−67.7	−61.0	−32.7	−14.9	−64.6	−68.6
					(−63.6)	(−67.3)
HCONH$_2$	−46.0	−38.7	−13.6	4.4	−43.4	−46.7
					(−42.3)	(−46.0)
C$_3$H$_4$O^b	−72.9	−65.3	−30.5	−23.5	−69.6	−73.6
		(−64.2)	(−36.1)	(−20.1)	(−69.6)	(−73.3)
C$_3$H$_2$O^b	−59.3	−50.9	−15.5	−8.9	−55.2	−59.7
		(−50.5)	(−22.4)	(−6.5)	(−56.0)	(−59.7)

^{a} Calculated using G2(MP2). Values are in kcal/mol. Predicted values (see text) are in parentheses. ^{b} Abbreviations. c-C$_3$H$_5$ = cyclopropanide, c-C$_3$H$_3$ = cycloprop-2-en-1-ide, C$_3$H$_4$O = cyclopropanone, C$_3$H$_2$O = cycloprop-2-en-1-one.

combinations of Z^- and XYCO are shown in Table 4. The discussion of how these estimates are made follows.

Using Table 3, the enthalpy data for reaction of a new nucleophile Z^- with the entire set of XYCO's in this work can be obtained from the value of Z^- adding to a single XYCO. Thus, the predicted value for the addition of cyclopropanide ($C_3H_5^-$) to HFCO is found by adding the row average for HFCO in Table 3 to the value for the addition of cyclopropanide to H_2CO. As seen in Table 4, the predicted result is only 1 kcal/mol off from the calculated value. Additional examples for this Z^- and for $Z^- =$ cycloprop-2-en-1-ide ($C_3H_3^-$) adding to both HFCO and HCONH$_2$ are shown in Table 4. As can be seen, the agreement between the calculated and predicted values is excellent.

Additionally, enthalpy data for a new XYCO could be approximated for the set of Z^-'s in this work merely by obtaining a single data point. For example, data for addition of CH_3^- to cyclopropanone could be obtained using the data in Table 3 by adding the Δ(column average) for CH_3^- vs H^- (= 8.7 kcal/mol = avg$_{XYCO}$ {ΔH (CH_3^- + XYCO) − ΔH (H^- + XYCO)}) to the value for the addition of H^- to cyclopropanone. The predicted result is just a little more than 1 kcal/mol above the calculated value. Additional examples for Z = CH_3, F, and CN adding to cyclopropanone and cycloprop-2-en-1-one are

shown in Table 4. For Z=CH$_3$ the agreement between the predicted and calculated value is excellent. For Z = CN (Δ(column average) CN$^-$ vs H$^-$ = 52.8 kcal/mol) the predicted value is about 3 kcal/mol less negative than the calculated value, an acceptable difference given that the mildly stabilizing interaction of CN with the cyclopropyl ring is ignored in the estimate.[21] For Z = F (Δ(column average) F$^-$ vs H$^-$ = 36.9 kcal/mol), the predicted value is about 6 kcal/mol more negative than the calculated value. However, if one corrects for the 5.85 kcal/mol of strain calculated (G3(B3LYP)) for a fluorine atom directly bound to a cyclopropane, the predicted value is quite good.[22]

Finally, notice that once a new Z^- and a new XYCO are added to the data set, an estimate for the reaction enthalpy between the two new species becomes available. Combining the examples above, the energy for addition of cyclopropanide to cyclopropanone would be estimated by taking the value of cyclopropanide adding to H_2CO and summing the enthalpy difference between H^- adding to cyclopropanone versus H_2CO. The predicted result is fortuitously equal to the calculated value. Additional values for addition of cyclopropanide and cycloprop-2-en-1-ide adding to cyclopropanone and cycloprop-2-en-1-one are shown in Table 4 below. In all cases, the agreement between the predicted and calculated value is excellent.

C. Analysis of the Data Using Isodesmic Reactions.

1. In this section, an explanation is sought for why the relative enthalpies of addition of Z^- to XYCO from Table 3 should not vary with Z^-. To accomplish this, a cycle of four reactions is created, shown in Scheme 1. Reactions A and B reflect the addition of Z^- to XYCO and H_2CO, respectively. Reactions 1 and 2 are isodesmic reactions that show the effect of substituents X, Y on XYCO and XYZCO$^-$, respectively. By inspection, it is seen that

$$\Delta H_{\text{reactionB}} = \Delta H_{\text{reaction1}} + \Delta H_{\text{reactionA}} - \Delta H_{\text{reaction2}} \quad (1)$$
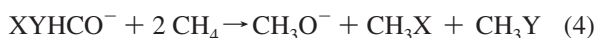
Rearranging slightly gives

$$\Delta H_{\text{reactionB}} - \Delta H_{\text{reactionA}} = \Delta H_{\text{reaction1}} - \Delta H_{\text{reaction2}} \quad (2)$$

Equation 2 shows how the data in Table 3 ($\Delta H_{\text{reactionB}} - \Delta H_{\text{reactionA}}$) can be reduced to a difference between the enthalpies

SCHEME 1. Isodesmic Reactions Used To Analyze the Addition of Z⁻ to XYCO
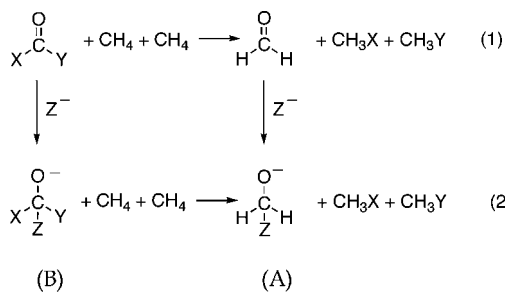
of two isodesmic reactions ($\Delta H_{reaction1} - \Delta H_{reaction2}$). Furthermore, of the two isodesmic reactions, only reaction 2 depends on Z. The constancy in the relative enthalpy of addition of Z⁻ to XYCO is reflected entirely in reaction 2, values of which are placed in Table 5. Notice that the standard deviation from the mean for each row in Table 5 is identical to the corresponding value in Table 3, validating the manipulations above. The advantage of analyzing reaction 2 as compared to reaction B is that only in the former does the functional group remain the same.

$$XYZCO^- + 2\,CH_4 \rightarrow CH_2ZO^- + CH_3X + CH_3Y \quad (3)$$

$$XYHCO^- + 2\,CH_4 \rightarrow CH_3O^- + CH_3X + CH_3Y \quad (4)$$

Reaction 2 (eq 3) can be analyzed by noting its similarity to a reaction studied earlier, shown in eq 4.[23] Indeed, eq 4 is just a specific case of eq 3, where Z = H. For the isodesmic reaction in eq 4 it was found that the stabilization of C—O⁻ by X, Y was proportional to their electron withdrawing abilities. Moreover, the enthalpic effects of X and Y were roughly additive as the substituents X, Y were judged to be largely independent of one another. By extension, the three substituents on XYZCO⁻ from eq 3 should also be independent of one another and the ability of X, Y to stabilize XYZCO⁻ relative to H₂ZCO⁻ should also be proportional to their ability to withdrawal electrons. This reasoning is backed up by the data in Table 5 as judged by the similarity of the leftmost column (Z = H) to the other columns (Z ≠ H). Thus, the invariance of the relative enthalpy of addition of Z⁻ to XYCO with respect to Z is completely reflected in the independence of X, Y, and Z on the inductive stabilization of C—O⁻.

In the previous analysis of eq 4, it was noted that the effects of X and Y were not completely independent. There were some saturation effects: the effects of X and Y acting together on the stabilization of C—O⁻ were often less than the sum of the individual stabilizations of X and Y. Saturation effects can be applied to explain a subtle trend noticed in section B, that relative enthalpies for Z = H tended to be lower (less positive or more negative) than average, while those for Z = CN tended to be higher than average. When Z is a weakly stabilizing group such as H, the full effects of X and Y are seen, leading to more exothermic enthalpies of addition. When Z is a strongly electron-withdrawing substituent such as CN, the stabilization from X, Y is lessened, resulting in less exothermic enthalpies of addition. (Since reaction 2 has a sign inversion relative to reaction B, lower values in Table 3 are equivalent to higher values in Table 5.)

2. Now it is time to examine the relative ordering of the enthalpies of addition to XYCO mentioned in section B. Since Z is invariant to this ordering, the conclusions from our earlier work for Z = H can be extended to all Z.[23] In short, the enthalpy of addition of Z⁻ to XYCO relative to H₂CO can be expressed as the difference of the two isodesmic reactions from Scheme 1, reactions 1 and 2. Reaction 2 (eq 3) shows that electron withdrawal stabilizes C—O⁻, discussed above. Reaction 1 was first analyzed by Wiberg et al.[24] Summarizing, both π donation and electron withdrawal (through either the σ or π system) stabilize the carbonyl carbon relative to H, while attachment of a partially positive atom to the carbonyl carbon is destabilizing relative to H. Compounds XYCO with X, Y containing CF₃, CN, CHO, and CCH all have large, negative enthalpies of anionic addition. This is due to the C=O being destabilized in the starting material (partially positive attached carbon in X, Y) and inductively stabilized in the product. Compounds XYCO with X, Y equal to F also have large, negative enthalpies of addition. Here, the substituent stabilizes the C—O⁻ more than C=O. Compounds XYCO with X, Y equal to NH₂ have the most positive enthalpies of addition. In this case, the π donation that stabilizes C=O in the starting material is lost in the product alkoxide. Compounds XYCO with X, Y containing H and CH₃ have similar reaction enthalpies due to the nonpolar nature of the substituents. Compounds XYCO with X, Y containing CHCH₂ or OH appear to be similar to the nonpolar compounds. Here, the π donation, which argues for more positive enthalpies, and the electron withdrawal, which argues for more negative enthalpies, roughly cancel each other out.

D. Electrophilicity Indices

The results above argue that carbonyl compounds have an intrinsic electrophilicity or that values of electrophilicity might be tabulated. Indeed, such a scale was developed[25] and has recently been reviewed.[26] Here, electrophilicity is derived in terms of the ionization potential, I, and electron affinity, A. Thus, electrophilicity, ω, equals $\mu^2/2\eta$ where μ is the chemical potential equal to $[(I + A)/2]$ and η is the chemical hardness equal to $[I - A]$. In this work, the values for I and A are calculated using Koopmans' theorem.[17] Values for ω are contained in Table 6. Despite the numerous previous successes of ω, here there is little to no correlation ($r^2 = 0.0026$) between ω and ΔH for the addition of H⁻ to XYCO.

Conclusions

The enthalpy of addition of a series of anionic nucleophiles (Z⁻) to H₂CO has a very good correlation with basicity of Z⁻ and a fair correlation with the ionization potential of Z⁻. Attempts to create a nucleophilicity index using these two measures may show promise for systems where the reaction enthalpy of addition is similar to the kinetic barrier. There was a poor relationship between enthalpy of addition and absolute hardness. The enthalpy of addition of Z⁻ to XYCO relative to H₂CO is insensitive to Z⁻. This result can be used as the basis for providing reliable estimates of the enthalpies of addition of complex systems by using suitable model compounds. An

(21) Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* **1985**, *107*, 3811–3819.
(22) Novak, I. *J. Org. Chem.* **2002**, *67*, 6279–6281.
(23) Rosenberg, R. E. *J. Am. Chem. Soc.* **1995**, *117*, 10358–64.

(24) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644–8654.
(25) Parr, R. G.; v.; Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922–1924.
(26) Chattaraj, P. K.; Sarkar, U.; Roy, D. R. *Chem. Rev.* **2006**, *106*, 2065–2091.

TABLE 5. G2(MP2)-Calculated Enthalpies for $XYZCO^- + 2\ CH_4 \rightarrow H_2ZCO^- + CH_3X + CH_3Y$ (kcal/mol)

X	Y	H	CH_3	NH_2	OH	F	$CHCH_2$	CHO	CCH	CN	avg	sd
H	CH_3	9.6	10.0	9.8	10.8	10.4	9.1	10.0	9.6	8.8	9.8	0.6
H	NH_2	21.8	22.1	19.9	23.0	24.2	20.5	21.3	19.9	18.9	21.3	1.7
H	OH	31.0	32.2	32.2	33.1	32.6	29.3	30.9	28.6	27.6	30.8	1.9
H	F	38.1	39.0	40.5	39.8	37.9	36.1	36.3	34.7	32.8	37.3	2.5
H	$CHCH_2$	13.7	13.3	12.4	12.0	11.6	12.0	13.0	11.5	10.3	12.2	1.0
H	CHO	21.6	22.1	21.1	21.6	19.7	21.0	17.6	19.3	16.6	20.1	1.9
H	CCH	14.2	14.2	12.3	11.9	10.8	12.0	11.9	9.5	7.5	11.6	2.1
H	CN	25.8	25.1	22.9	22.4	20.4	22.4	20.8	19.1	15.6	21.6	3.1
H	CF_3	23.3	22.5	20.6	20.9	18.4	20.4	18.4	18.1	15.3	19.8	2.5
CH_3	CH_3	19.6	19.9	16.0	15.1	20.4	18.3	19.6	19.1	17.9	18.5	1.8
CH_3	NH_2	31.6	28.3	24.7	32.4	27.7	29.7	30.9	29.1	27.9	29.2	2.4
CH_3	OH	41.8	36.5	41.6	36.7	41.9	39.4	41.1	38.7	37.6	39.5	2.2
CH_3	F	48.6	49.0	44.1	49.1	41.6	46.0	46.5	44.8	42.6	45.8	2.8
CH_3	$CHCH_2$	22.8	22.5	21.5	22.1	21.5	20.8	22.5	20.7	19.2	21.5	1.1
CH_3	CHO	31.6	31.7	30.7	31.7	29.9	30.4	28.2	29.0	26.0	29.9	1.9
CH_3	CCH	23.8	23.7	21.5	22.0	20.8	21.3	21.6	19.2	16.9	21.2	2.1
CH_3	CN	34.6	34.2	31.9	32.4	30.3	31.3	30.2	28.5	24.8	30.9	3.0
NH_2	NH_2	41.7	37.0	40.9	37.5	44.3	39.7	41.9	38.2	38.4	40.0	2.4
OH	OH	64.0	58.1	60.2	59.1	58.8	60.3	57.6	57.9	56.2	59.1	2.2
F	F	76.1	70.2	67.5	66.0	69.0	71.7	66.9	68.6	65.3	69.0	3.3

TABLE 6. Comparison of the Electophilicity Index, ω, to Enthalpy of Addition of H^- to XYCO (kcal/mol)[a]

X	Y	ω	ΔH	X	Y	ω	ΔH
H	H	53.92	−55.74	CH_3	CH_3	49.77	−53.82
H	CH_3	52.57	−54.23	CH_3	NH_2	49.57	−46.46
H	NH_2	50.11	−46.03	CH_3	OH	54.02	−53.54
H	OH	57.27	−53.42	CH_3	F	55.23	−66.41
H	F	58.32	−67.78	CH_3	$CHCH_2$	48.15	−57.64
H	$CHCH_2$	48.88	−57.38	CH_3	CHO	44.29	−63.65
H	CHO	42.20	−74.19	CH_3	CCH	49.10	−63.50
H	CCH	47.93	−66.85	CH_3	CN	51.07	−79.78
H	CN	44.87	−83.94	NH_2	NH_2	50.21	−43.03
F	F	60.99	−91.26				

[a] Values of I and A are calculated using Koopmans' theorem, ref 17. The orbital energies come from MP2/6-311+G(3df, 2p)//MP2 = full/6-31G* calculations.

enthalpic ordering of XYCO's toward addition of anionic nucleophiles has been constructed and rationalized. Surprisingly, this ordering does not correspond to a scale of electrophilicity developed by Parr. It will clearly be of interest to see how neutral nucleophiles or the inclusion of solvent affect the conclusions above.

Experimental Methods

Calculations were done using the Gaussian 98 suite of programs.[27] Unless otherwise noted, energies were calculated at the G2(MP2) level of theory.[6] The identity of stationary points as local energy minima were verified by frequency calculations.[28] Vertical

(27) Gaussian 98, Revision A.11.4: 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.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; 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.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc.; Pittsburgh PA, 2002.
(28) Foresman, J. B.; Frisch, A. E. *Exploring Chemistry with Electronic Structure Methods*; Gaussian Inc.: Pittsburgh, PA, 1996; pp 70−74.

ionization potentials (IPs) calculated using Koopmans' theorem[17] used the density from MP2/6-311+G(3df,2p) single points on the MP2/6-31G*-optimized geometries. Vertical IPs (for anions Z^-) that calculated radical energies explicitly used MP2/6-311+G(3df,2p) single points on the MP2/6-31G*-optimized geometries of the anions. Absolute hardness was calculated using the equations of Pearson, $\eta = (I - A)/2$, where I and A were taken from the appropriate orbital energies of the MP2/6-311+G(3df,2p) single points on the MP2/6-31G*-optimized geometries of the anions.[18] The Parr function for electrophilicity was calculated using the orbital energies from MP2/6-311+G(3df,2p)// MP2=full/6-31G* calculations.[25]

Experimental data for Table 2 are taken from the NIST WebBook.[19] All data are for gas phase species. Standard enthalpies of addition (ΔH_r°) of H^- to H_2CO, CH_3CHO, and CH_3COCH_3 were available directly. To derive the ΔH_r° for addition of CH_3^- to XYCO to form $XYCH_3CO^-$, the following reaction scheme was used.

$$\Delta H_r^\circ = \Delta H_f^\circ (XYCH_3CO^-) - \Delta H_f^\circ (XYCO)$$
$$- \Delta H_f^\circ (CH_3^-) \quad (5)$$

$$\Delta H_f^\circ (CH_3^-) = \Delta H_f^\circ (CH_4) - \Delta H_f^\circ (H^+) + acidity\ CH_4 \quad (6)$$

$$\Delta H_f^\circ (XYCH_3CO^-) = \Delta H_f^\circ (XYCH_3COH)$$
$$- \Delta H_f^\circ (H^+) + acidity\ XYCH_3COH \quad (7)$$

$$acidity\ HX = \Delta H_r^\circ\ for\ the\ reaction\ (HX \rightarrow H^+ + X^-) \quad (8)$$

The values from the NIST WebBook that are used in the scheme above include the ΔH_f°'s of carbonyl compounds (H_2CO, CH_3CHO, CH_3COCH_3), the ΔH_f° of H^+, the ΔH_f°'s of alcohols (CH_3CH_2OH, $CH_3CH(OH)CH_3$, $CH_3C(CH_3)_2OH$), and the gas phase acidities of species (CH_4, CH_3CH_2OH, $CH_3CH(OH)CH_3$, $CH_3C(CH_3)_2OH$).

Supporting Information Available: Structures and energies of compounds XYCO and $XYZCO^-$. Energies for compounds Z^-, $Z^\bullet$, and HZ. HOMO and LUMO orbital energies for Z^-. HOMO and LUMO orbital energies for compounds XYCO. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800664K