Estimation of the Free Energies of Addition of Nucleophiles to Conjugated Carbonyl Compounds and to Acyl Derivatives

J. Fastrez[1]

Contribution from the Laboratoire de Chimie Générale et Organique, Place L. Pasteur, 1, B 1358 Louvain la Neuve, Belgium. *Received November 23, 1976*

Abstract: The free energies of addition of nucleophiles to aromatic and conjugated aldehydes as well as to acyl derivatives have been estimated by an empirical method. The overall free-energy change upon addition is divided into two contributions: the change in free energy associated with the interruption of conjugation between the carbonyl function and the aromatic or ethylenic group or the lone pair of the NR_2, OR, or SR group, called the localization free energy; the change in free energy due to the addition of the nucleophile to the localized form. The localization free energy is obtained for aldehydes and amides from rotational barriers and for other derivatives indirectly from thermodynamic cycles. The free energy of addition to the localized form is calculated by extrapolation of the linear free-energy relationships of addition of the nucleophile to saturated carbonyl compounds. Only the resonance and inductive contributions of the aromatic, ethylenic, or X group have been considered; their steric effect has been neglected. The number of assumptions required for the calculations limits the accuracy of the results in the present form. For simple conjugated carbonyl and acyl compounds, the calculated free energies are generally within 2 kcal of those obtained by direct equilibrium measurements or from the analysis of the kinetics of the corresponding transacylation reactions. For unhindered acyl derivatives, the localization free energies are between 22 and 15 kcal/mol for amides and anilides, between 18 and 14 kcal/mol for acids and esters depending on the structure, and 11 kcal/mol for ethylthioacetate.

The equilibria of addition of nucleophiles to carbonyl compounds have been investigated very actively in recent years and a clear picture is now emerging from the effort devoted to the study of these reactions. It has been suggested for a long time that transacylation reactions go by an addition elimination mechanism through a tetrahedral intermediate. The intermediates at the acyl level of oxidation are generally very unstable and have been isolated or detected in relatively few cases.[2] Their involvement in a transacylation reaction was first proven for the acid and basic hydrolysis of esters by Bender.[3] The demonstration of their existence on the reaction pathway rests for most reactions on the analysis of the kinetics: from the observation of a change in rate-determining step with pH or buffer concentration, or from a variation in product distribution with no change in the overall rate.[4]

Careful analysis of the kinetics of some transacylation reactions has even led to the determination of the equilibrium constant of formation of one of the tautomeric forms of the tetrahedral intermediate lying on the reaction pathway.[5]

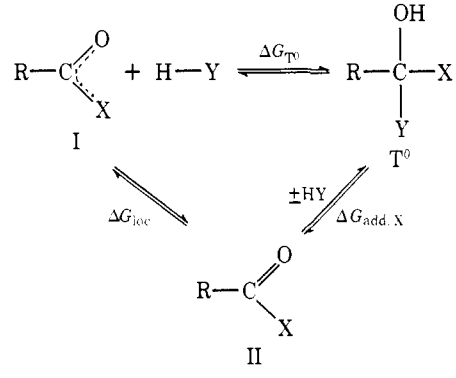
Recently, in a series of papers, Guthrie[6] has developed an interesting method which allows him to obtain the free energies of hydration or alcohol addition to formic and acetic acids, their methyl esters and dimethyl amides, and trifluoroacetic acid and its methyl ester. This method is based on the experimental determination of the heat of hydrolysis of ortho esters and ortho amide-dimethyl acetals, and on the use of a linear free-energy correlation of carbon basicities in alcohol and diol series. This approach rests on a sound thermodynamic basis and leads to a reasonably good determination of the free energies of addition of nucleophiles to the acyl derivatives mentioned. It is nevertheless limited by the fact that few ortho esters or ortho amides can be prepared so that a general picture of the effect of structure on the equilibria of formation of the intermediates by that system alone is difficult to obtain.

We have used a different approach to the same problem, resting on the old idea that the instability of the tetrahedral intermediates at the acyl level of oxidation is due to the resonance energy loss accompanying the addition of the nucleophile. The equilibrium constant of addition of the nucleophile to the nondelocalized form of the acyl derivative is obtained from a free-energy correlation. The same method is applied to the calculation of equilibria of addition of nucleophiles to conjugated aldehydes.

To the extent that both methods are based on different approaches and rest on different sets of experimental data, they appear to be complementary and should contribute to give a more detailed picture of the field.

Method of Calculation. The instability of tetrahedral intermediates of transacylation reactions is due to the fact that the resonance energy of the carboxylic function must be lost during the addition of the nucleophile. For the purpose of estimating the free-energy difference between the reagents and the addition product, the overall process can be divided into two steps (Scheme I), where X and Y can be NR_2, OR, SR,

Scheme I



or halogen. Then we have eq. 1

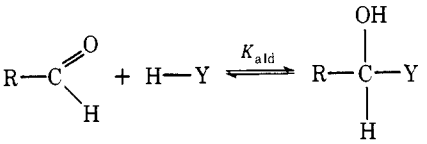
$$\Delta G_{T^0} = \Delta G_{loc} + \Delta G_{add.\ X} \qquad (1)$$

In the first step, the conjugation between the lone pair of the X group and the carbonyl group is interrupted; in the second step, the nucleophile adds to the nonconjugated form of the acyl derivative.

It is thus necessary to find a reliable method for measuring the localization free energy, in other words, the free-energy difference between the conjugated form (I) and the nonconjugated form (II) of the acyl derivative. For the second step, the assumption is made that the nonconjugated form will behave like an aldehyde or a ketone for the addition of the nucleophile. The free-energy difference corresponding to this step can be estimated by the application of linear free-energy re-

lationships for the addition of nucleophiles to aldehydes and ketones.

A. Equilibria of Addition of Nucleophiles to Nonconjugated Forms. The equilibrium of addition of a nucleophile to the nonconjugated form of the acyl derivative will be calculated from the equilibrium of addition of the same nucleophile to the corresponding aldehyde, corrected for the difference in inductive effect between hydrogen and the X group by the application of the linear free-energy relationship (eq 2).



$$\log K_{add.\,X} = \log K_{ald} + \rho^*(\sigma^*_X - \sigma^*_H) \qquad (2)$$

1. The ρ^* Value and the Choice of the Reference Compound. The general picture of substituent effects on the addition of nucleophiles to carbonyl compounds is presently well understood. The best-studied reaction is the hydration reaction for which a large amount of data is available. The equilibrium constants of the hydrations of aldehydes and ketones have been correlated by a Taft equation applicable to derivatives in which the C=O group is not conjugated to a double bond or an aromatic ring. Several correlations have been proposed, the best known ones by Bell[7] and Greenzaid.[8] The latter correlates the hydration equilibrium constants for aldehydes and ketones on separate lines and formaldehyde is considered as a special case

$$-\log K_{diss} = 1.70\,\Sigma\sigma^* + 2.03\Delta - 2.81 \qquad (3)$$

where Δ is the number of aldehydic protons. Accordingly, the large difference between ketones, aldehydes, and formaldehyde will not be attributed to a steric effect but to an adjacent bond interaction effect analogous to a hyperconjugative stabilization. This seems reasonable to the extent that acetone hydrate is isosteric with neopentane which is essentially a strain-free molecule.[9] Also the enthalpy of reduction of acetone is 3.00 kcal less than that of acetaldehyde, itself 3.78 kcal less than that of formaldehyde;[10] here too a steric effect is unlikely.

This interpretation of the difference between ketones, aldehydes, and formaldehyde as an adjacent bond interaction effect has an important consequence for the choice of the reference compound used to calculate the equilibrium constant of addition to the nonconjugated form of the acyl derivative. The corresponding aldehyde (RCOH) and not the methyl ketone ($RCOCH_3$) must be used as a starting point because the methyl group interacts with the C=O group both by inductive ($\sigma^* = 0$) and hyperconjugative effects, and we want to take into account only the difference in inductive effect between the X group and the reference group.

An accurate ρ^* value is not available for the addition of every class of nucleophiles to carbonyl compounds in water. In the aliphatic series, good values are available only for hydration ($\rho^* = 1.70 \pm 0.07$)[8] and hemiacetal formation ($\rho^* = 1.36 \pm 0.19$).[12] In the aromatic series, on the other hand, data are available for oxygen, sulfur, and nitrogen nucleophiles. The following ρ values have been reported: 1.1 for hydration,[13] 1.44 for bisulfite addition,[14] 1.81 for semicarbazide addition in 25% ethanol,[15] and 2.0 for methanol addition in methanol.[16] The last two values appear to be comparatively large but they have been obtained in 25% ethanol and in methanol, respectively. The ρ values tend to increase with the decrease in solvent polarity; in these solvents, the ρ values for the ionization of benzoic acid are 1.27[17a] and 1.537,[17b] respectively. Much of the increase in ρ observed for semicarbazide and methanol addition is likely to be due to a solvent effect. That the ρ value remains relatively constant for most nucleophiles is shown by the observation of Sander and Jencks[18] that the equilibrium constants of addition of nucleophiles to *p*-chlorobenzaldehyde can be correlated by an equation $\log K_{ad} = \Delta\gamma + A$ where γ is the log of the ratio of the equilibrium constants of the addition of the nucleophile and methylamine to pyridine-4-carboxaldehyde. The slope Δ is close to unity. The data for formaldehyde are correlated in the same way although amines and alcohols fall on different lines. We have obtained a similar correlation for acetaldehyde with a Δ value of 1.03 ± 0.12 ($r = 0.983$) with oxygen and nitrogen nucleophiles on the same line.[19]

We feel that in making the approximation that the ρ^* value for the Taft relationship is constant for all nucleophiles only a relatively small error is introduced in the system. An overestimation of 0.4 in the ρ^* value would lead to an underestimation of the equilibrium constant of addition by a factor of 2.2 for amides and aldehydes bearing the most electronegative substituents reported in this paper. This is due to the fact that $(\sigma^*_X - \sigma^*_H)$ remains relatively small for these compounds. For esters and other acyl derivatives, errors in the estimation of the inductive effect of the X group would not affect the calculated value of the equilibrium constants directly but only the value of the localization free energies (see below).

2. Determination of σ^*. Some σ^* values needed for the calculations are not found in standard tables.[23] They can be obtained from the pKa of the correspondingly substituted acetic acid(XCH_2COOH) by application of the following relationship:[24]

$$\sigma^* = (4.77 - pK_a)/0.663 \qquad (4)$$

For basic substituents this method is not suitable, because the substituent is protonated in the pH range corresponding to the pK_a of the carboxylic function. We use then the pK_a of 2-substituted ethylamines ($XCH_2CH_2NH_2$):[25]

$$\sigma^* = (10.50 - pK_a)/0.76 \qquad (5)$$

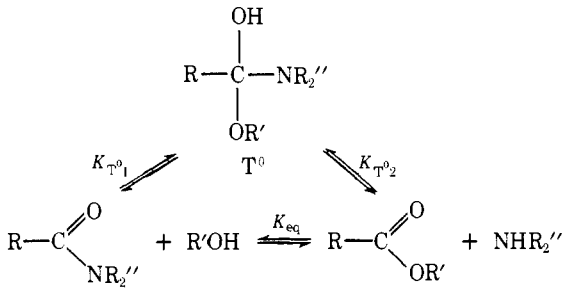
For various NHR groups, the σ^* values can also be obtained from a correlation of the pK_as of substituted hydrazines.[26]

3. Steric Effects. Because relatively unhindered acyl derivatives have been considered so far, no steric correction has been applied for the replacement of the aldehydic hydrogen by an RO- or R_2N- substituent. This approximation is similar to the neglect of the steric correction in Greenzaid's correlation of the hydration data of aldehydes and ketones.[8] Steric corrections could in principle be obtained from molecular mechanical calculations of the steric energies, but the level of refinement of these calculations does not seem to be presently sufficient to make them applicable to the calculation of small energy differences in molecules containing heteroatoms or aromatic rings.[9]

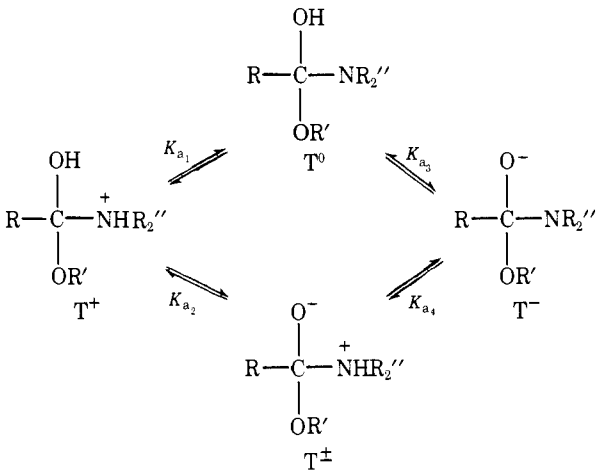
B. Localization Free Energy. 1. Amides and Conjugated Carbonyl Compounds. The rotational barrier of amides and conjugated carbonyl compounds has been taken as a measure of the free-energy loss when the delocalization of the lone pair is interrupted. The rotational barriers have been intensively investigated and good data are available. The barriers for several compounds have been measured in various aprotic or protic solvents though rarely in water; fortunately, the barrier height varies little with the solvent.[27,28] For some of the compounds, only the $\Delta G^{\ddagger}$ value at the coalescence temperature is available; however, the entropy of activation of this kind of process is negligible in most cases investigated so that $\Delta G^{\ddagger}$ does not vary significantly with the temperature.[27-29]

2. Other Acyl Derivatives. For carboxylic acids, esters, and thioesters, rotational barriers can in principle also be measured and some have been obtained by several methods; these measured barriers nevertheless do not correspond to the localization free energies because some conjugation is still present in the perpendicular form. We have then used the following method.

Scheme II



Scheme III



The equilibrium constant of formation of the tetrahedral intermediate for the addition of an alcohol or thiol to an amide is calculated ($K_{T^0_1}$). The equilibrium constant of the corresponding overall transacylation reaction (K_{eq}) is then used to obtain the equilibrium of addition of the amine to the ester ($K_{T^0_2}$) (Scheme II), in which

$$K_{eq} = [\text{amide}][\text{alcohol}]/[\text{ester}][\text{amine}] = K_{T^0_2}/K_{T^0_1} \quad (6)$$

$$K_{T^0_1} = [T^0]/[\text{amide}][\text{alcohol}]$$

$$\text{and } K_{T^0_2} = [T^0]/[\text{ester}][\text{amine}]$$

The free-energy change associated with the addition of the amine to the ester ($\Delta G_{T^0_2}$) can be separated in two contributions as in Scheme I: the free energy associated with the localization of the ester lone pairs and the free energy of addition of the nucleophile to the nonconjugated form of the ester (eq 7).

$$\Delta G_{T^0_2} = \Delta G_{\text{loc ester}} + \Delta G_{\text{add. OR}} \quad (7)$$

The value of $\Delta G_{\text{add. OR}}$ is calculated from the equilibrium constant of the addition of the amine to the corresponding aldehyde corrected for the difference in inductive effects between the RO- group and hydrogen as explained above. From eq 7 and the known $\Delta G_{T^0_2}$ and $\Delta G_{\text{add. OR}'}$ the localization free energy is obtained.

The localization free-energy value obtained in this way can be biased by a systematic error if the ρ^* of addition of amines to the acyl derivative is actually different from 1.70. If the ρ^* value is larger than 1.70, the localization free energy will be too small. For the calculation of the equilibrium constant of addition of another nucleophile, this possible systematic error in ΔG_{loc} will not affect the results if the actual ρ^* value for the reaction with this nucleophile is the same as for amines. Otherwise an error proportional to $\Delta\rho^* \times (\sigma^*_X - \sigma^*_H)$ will be introduced in the equilibrium constant.

C. Charged Forms of Tetrahedral Intermediates. Tetrahedral intermediates can exist in essentially four different forms: neutral (T^0), anionic (T^-), cationic (T^+), and zwitterionic ($T^\pm$) (Scheme III).

When the equilibrium constant of formation of the neutral species is known, the other ones can be obtained if the pK_as of the various intermediates are available. These can be estimated from the plots of the pK_as of various amines and alcohols versus σ^* values.

For alcohols of general structure XYZCOH, a reasonably good correlation is obtained between the pK_as and the sum of σ^* values; the pK_as of diols are correlated by the same line after statistical correction if the σ^* value of OH is taken as 1.81.[30] A ρ^* value of -1.45[31] is found, 10% higher than the value calculated by Sho Takahashi et al.[32] from a more limited series of pK_as.

For amines, two different correlations have been proposed with ρ^* values varying between -1.18[33] and -1.75.[6b] The difference in ρ^* is probably due to the different choice of amines included in the correlation. We have calculated correlation lines for several series of amines based on a large number of individual pK_as and found the following ρ^* values:[34] for $XYZC\text{-}NH_2$, $= -1.53$; for $XYZC\text{-}N(CH_3)_2$, $\rho^* = -1.46$; for $XCH_2\text{-}N(C_2H_5)_2$, $\rho^* = -1.55$; for XCH_2-*N*-morpholines, $\rho^* = -1.50$. The mean value of -1.5 is not significantly different from the value found for alcohols. However, these plots are not very satisfactory because the standard deviations are relatively large (of the order of 0.3-0.5) so that the estimated pK_as could be wrong by as much as one pK_a unit. As a consequence, the equilibrium constants of formation of charged tetrahedral intermediates will be less precise than the values for the neutral forms. To minimize errors, the pK_as of the intermediates should be calculated by choosing a reference compound as closely related to the structure of the intermediate as possible.

Table I. Equilibrium Constants of Addition of Nucleophiles to Aldehydes[a]

Aldehyde	Nucleophile	K_{eq}, M^{-1}
CH_3COH	$(CH_3)_2NH$	61 ± 5.6
CH_3COH	NH_2NH_2	$2.5 \times 10^3 \pm 0.5 \times 10^3$
CH_3COH	CF_3CH_2OH	0.024,[b] 0.021[c]
C_6H_5COH	$(CH_3)_2NH$	1.5 ± 0.1

[a] 25 °C, in water except for the trifluoroethanol addition equilibria measured in the alcohol. [b] Measured by UV spectrophotometry. [c] Measured by NMR.

Results

The equilibrium constants quoted in this paper are based on a standard state of 1 M for all reagents except for water for which the activity of the pure liquid is taken as 1.0.

Most of the equilibrium constants of addition of nucleophiles to carbonyl compounds needed for the calculations have been obtained by several authors. Some new values have been determined for this work; they are given in Table I.

The equilibrium constant of addition of trifluoroethanol to acetaldehyde is very weak and had to be measured in pure trifluoroethanol. When the determination of the equilibrium constant was tried by addition of various quantities of trifluoroethanol to aqueous solutions of acetaldehyde, a larger increase in absorbance than could be accounted for by the decrease in water concentration was observed. The most likely interpretation is that the alcohol decreases both the extent of hydration and hemiacetal formation by a solvent effect. A similar behavior has been found by Jencks with pyridinecarboxaldehyde.[18]

The equilibrium constants of transacylation reactions have been obtained by measuring the rate of approach of the equilibrium from both sides using reactions mixtures identical in

Table II. Equilibrium Constants of Formation of Acyl Derivatives[a]

Acyl deriv	K_{eq} = [RCOX]/[RCOOH][HX], M^{-1}
CH_3COOCH_3	0.107 ± 0.008[b]
$CH_3CONHNH_2$	2.59×10^4
$CH_3CON(CH_3)_2$	7.05×10^4

[a] 25 °C, ionic strength = 1.0, water activity taken as 1. [b] 0.098 for the synthesis and 0.116 for the hydrolysis.

buffer component in large excess over the changing reagents. For slow reactions, the ratio of the initial changes was used to calculate the position of the equilibrium according to the method of Fersht.[36] From the known equilibrium constant of formation of acethydroxamic acid,[37] the equilibrium constants of formation of the acyl derivatives have been calculated; they are reported in Table II.

The equilibrium constant of acethydrazide formation is one fourth that of formhydrazide; the formamides are generally two to three times more stable toward hydrolysis than the other corresponding amides.[36] On the other hand, dimethylacetamide is 86.5 times less stable than dimethylformamide. The value obtained here compares favorably with the value calculated for *N*-dimethylpropionamide at 25 °C from the data of Morawetz and Otaki:[38] 8.4×10^4 M^{-1}. The difference between these amides is likely to be due to steric inhibition of resonance.

Tetrahedral Intermediates Generated by Addition of Nucleophiles to Amides and Aromatic Aldehydes. The principles exposed in the theoretical part can be applied to the calculation of several equilibrium constants. They can first be used to calculate some equilibria of the additions of nucleophiles to conjugated aldehydes. The calculation of the equilibrium constant of hydration of benzaldehyde will be detailed as an example.

According to Scheme I, the formal equilibrium constant of formation of the localized form (II) is first calculated from the rotational barrier, 7.9 kcal:[39]

$$K_{loc} = [II]/[I] = e^{-\Delta G_{loc}/RT} = 1.6 \times 10^{-6}$$

The equilibrium constant of hydration of the localized form is obtained from the equilibrium constant of hydration of formaldehyde (1.8×10^3)[40] corrected for the difference in inductive effect between the phenyl group and hydrogen according to eq 2:

$$\log K_{hydr(II)} = \log K_{hydr(H_2CO)} + 1.7\,(0.6 - 0.49)$$

$$K_{hydr(II)} = [T^0]/[II] = 3.1 \times 10^3$$

The equilibrium constant of hydration of benzaldehyde is then

$$K_{hydr(C_6H_5COH)} = (3.1 \times 10^3) \times (1.6 \times 10^{-6}) = 5.0 \times 10^{-3}$$

Several equilibrium constants of nucleophilic additions to unsaturated carbonyl compounds are collected in Table III where they are compared with experimental values.

The experimental equilibrium constant of hydration of benzaldehyde is within a factor of 2 of the value obtained by Greenzaid.[13] The value for the addition of methanol to benzaldehyde is close to the experimental value. For semicarbazide, on the other hand, a large discrepancy is observed which can be related to the fact that the addition constant of amines to formaldehyde is about 10 times larger than that of an alcohol of identical γ value.[18] This behavior is at present not understood.

The equilibrium constants of addition of nucleophiles to amides are given in Table IV. The values of K_{T^0} are obtained as for benzaldehyde; the values of $K_{T^\pm}$ are calculated from the pK_as of $T^+ \rightarrow T^0$ (pK_{a_1}) and $T^+ \rightarrow T^\pm$ (pK_{a_2})(Scheme III). The equilibrium constant of tautomerization is obtained from the relation $K_{taut} = K_{a_2}/K_{a_1}$.

For morpholine for instance, the following constants are derived from the pK_as of the reference compounds[34,41] and a σ^* value of 4.31 for the morpholinium group calculated from the pK_a of 2-morpholinoacetic acid (1.91)[42] (Scheme IV): pK_{a_1}

Scheme IV

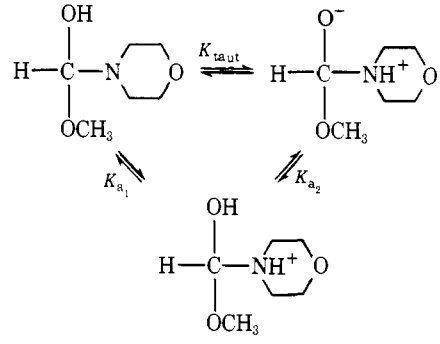
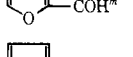
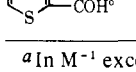
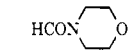
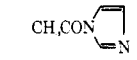


Table III. Equilibrium Constants of Addition of Nucleophiles to Aldehydes at 25 °C

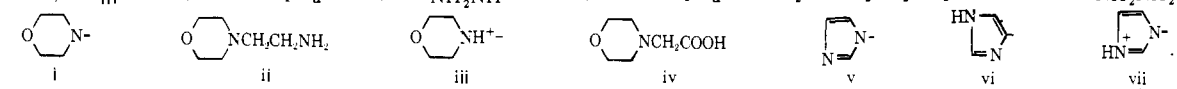
Aldehyde	Nuc	ΔG_{loc}, kcal	K_{T^0} calcd[a]	K_{T^0} exptl[a]	K_{T^-} calcd[q], M^{-1}	K_{T^-} exptl, M^{-1}
C_6H_5COH	H_2O[b]	7.9[c]	5.0×10^{-3}	1.1×10^{-2}[d]	5.3×10^{-2}	1.26×10^{-1}[d] 1.8×10^{-1}[e]
C_6H_5COH	CH_3OH[f]	7.9[c]	3.2×10^{-3}	3.6×10^{-3}[g]		
C_6H_5COH	$NH_2NHCONH_2$[h]	7.9[c]	3.2×10^{1}	1.32[i]		
4-$CH_3OC_6H_4COH$[j]	H_2O[b]	9.2[c]	3.6×10^{-4}		3.0×10^{-3}	1.09×10^{-2}[e]
CH_2=CHCOH	CH_3OH[f]	7.02[k]	1.2×10^{-2}	9.4×10^{-3}[l]		
	H_2O[b]	10.0[n]	9.1×10^{-4}		5.2×10^{-2}	1.7×10^{-1}[e]
	H_2O[b]	10.0[p]	2.1×10^{-3}		2.6×10^{-1}	7.8×10^{-2}[e]

[a] In M^{-1} except for the hydration equilibria for which the activity of pure water was taken equal to 1.0. [b] From the equilibrium constant of hydration of formaldehyde: 1.8×10^3.[40] [c] Reference 39. [d] Reference 13. [e] Reference 64. [f] From the equilibrium constant of addition of methanol to formaldehyde: 1.3×10^3 M^{-1}.[65] [g] Reference 16. [h] From the equilibrium constant of addition of semicarbazide to formaldehyde: 1.4×10^7 M^{-1}.[18] [i] Reference 15. [j] σ^*4-$CH_3OC_6H_4$– calculated from the pK_a of 4-$CH_3OC_6H_4CH_2COOH$, extrapolated in water from values in 10, 50, and 75% ethanol,[66] $\sigma^* = 0.52$. [k] Reference 67a, the $\Delta H^\ddagger$ value was used but the available data indicate that $\Delta S^\ddagger$ is very small.[67a,b] [l] Reference 20. [m] σ^* value for the 2-furyl group (1.1) calculated from the pK_a of 2-furylacetic acid (4.04).[68] [n] $\Delta G^\ddagger$ at 25 °C calculated from the data given in ref 69. [o] σ^* value for the 2-thiophenyl group (1.32) calculated from the pK_a of 2-thiophenylacetic acid (3.89).[68] [p] Reference 82. [q] From the pK_as of the tetrahedral intermediates calculated from the equation given in footnote 31 and a statistical correction of 0.3; $K_{T^-} = (K_{T^0} \times K_a)/K_w$, $\sigma^*_{OH} = 1.81$ (see text).

Table IV. Equilibrium Constants of Addition of Nucleophiles to Amides[a,b]

Amide	Nuc	$K_{add,X}$,[c] M^{-1}	ΔG_{loc}, kcal	K_{T^0} calcd, M^{-1}	$K_{T^\pm}$ calcd, M^{-1}	$K_{T^\pm}$ exptl, M^{-1}
$HCONHNH_2$	CH_3OH	2.6×10^4 [d]	18.3[e]	1.0×10^{-9}	5.2×10^{-14}	2.5×10^{-14} [f]
$HCONHCH_3$	CH_3OH	2.2×10^3 [d]	22.0[g]	1.4×10^{-13}	1.1×10^{-15}	
	CH_3OH	3.6×10^4 [d]	19.5[h]	1.7×10^{-10}	3.1×10^{-15}	1.4×10^{-15} [f]
	NH_2NH_2	1.8×10^5 [i]	10.5[j]	3.7×10^{-3}	1.3×10^{-7}	10^{-6} [k]
$CH_3CONHNH_2$		2.6[l]	18.6[m]	6.1×10^{-14}	2.1×10^{-18}	4×10^{-18} [n]
$CH_3CONHNH_2$	CH_3CH_2OH	1.0×10^1 [o]	18.6[m]	2.3×10^{-13}	7.5×10^{-18}	1.4×10^{-17} [p]
$CH_3CONHNH_2$	CF_3CH_2OH	0.47[q]	18.6[m]	1.1×10^{-14}	3.1×10^{-19}	8.9×10^{-18} [p]
$CH_3CONHNH_2$	C_6H_5OH	2.0×10^{-1} [r]	18.6[m]	4.7×10^{-15}	1.4×10^{-19}	2.9×10^{-19} [p]
$CH_3CONHNH_2$	C_2H_5SH	7.4×10^2 [s]	18.6[m]	1.7×10^{-11}		
$CH_3CONHNH_2$	CH_3OH	1.4×10^1 [t]	18.6[m]	3.3×10^{-13}		
$CH_3CON(CH_3)_2$	CH_3OH	1.2[t]	18.7[u]	2.1×10^{-14}		
$CH_3CON(CH_3)_2$	CF_3CH_2OH	3.8×10^{-2} [q]	18.7[u]	6.9×10^{-16}		
$CH_3CON(CH_3)_2$	C_6H_5OH	1.7×10^{-2} [r]	18.7[u]	2.9×10^{-16}		
$CH_3CON(CH_3)_2$	C_2H_5SH	6.0×10^1 [s]	18.7[u]	1.1×10^{-12}		
$CH_3CON(CH_3)_2$	NH_2NH_2	4.0×10^3 [i]	18.7[u]	7.7×10^{-11}		
$HCON(CH_3)_2$	CH_3OH	2.2×10^3 [d]	21.0[u]	8.1×10^{-13}		
$C_6H_5CON(CH_3)_2$	CH_3OH	6.0×10^{-3} [v]	15.8[w]	1.5×10^{-14}		
$HCONHC_6H_5$	$NH(CH_3)_2$	4.9×10^7 [x]	17.7[y]	5.1×10^{-6}		

[a] In aqueous solution at 25 °C, standard state for solutes 1 M. [b] Apart from standard σ^* values, the following σ^* were used: $\sigma^*_i = 1.34$, from the pK_as of ii;[34] $\sigma^*_{iii} = 4.31$, from the pK_as of iv;[42] $\sigma^*_{NH_2NH-} = 1.26$, from the pK_as of $NH_2NHCH_2CH_2NH_2$ (this work); $\sigma^*_{NH_2NH_2^+-} =$



i ii iii iv v vi vii

4.26, from the relation $\sigma^*_{NR_2H^+-} = \sigma^*_{NR_2-} + (3.0 \pm 0.1)$ obtained from the differences in σ^* values between the protonated and nonprotonated forms of 10 amines; $\sigma^*_{C_6H_5NH-} = 1.24$, from the pK_as of $C_6H_5NHCH_2COOH$;[71] $\sigma^*_v = 1.60$, estimated from the σ^* of vi = 1.0, (obtained from the pK_a of histamine[34]) + 0.6 for the replacement of C by N; $\sigma^*_{vii} = 3.24$ from the pK_as of 1-imidazoleacetic acid.[72] [c] Calculated from the equilibrium constants of addition of the nucleophiles to the aldehydes (K_{ald}) and a correction for the difference in inductive effect between the X group and hydrogen (eq 2, $\rho^* = 1.7$). [d] K_{ald} ($H_2CO + CH_3OH$) = 1.3×10^3 M^{-1}.[65] [e] From the rotational barriers of $HCONHN(CH_3)CH_2$-C_6H_5 or $HCONHN(CH_2C_6H_5)_2$.[73] [f] From the kinetics of aminolysis of methyl formate,[43] the overall equilibrium constant of the reaction[36] and as assumed rate constant of proton transfer of 10^{10} M^{-1} s^{-1} between OH^- and $T^\pm$ and 1.3×10^8 M^{-1} s^{-1} between hydrazine and $T^\pm$ (see text). [g] Reference 74. [h] This work. [i] K_{ald} ($CH_3COH + NH_2NH_2$) = 2.4×10^3 M^{-1} (this work). [j] Reference 75. [k] Mean value between 4.2×10^{-6} and 2.8×10^{-7} M^{-1} obtained from the kinetics of hydrazinolysis of acetylimidazole[44] and assumed limiting values for the rate of proton transfer between $T^\pm$ and hydrazine (see text). [l] K_{ald} (CH_3COH + imidazole) = 0.13 M^{-1}.[76] [m] From the rotational barrier of constants of addition of the nucleophiles to the aldehydes (K_{ald}) and a correction for the difference in inductive effect between the X group and hydrogen (eq 2, $\rho^* = 1.7$). [d] K_{ald} ($H_2CO + CH_3OH$) = 1.3×10^3 M^{-1}.[65] [e] From the rotational barriers of $HCONHN(CH_3)CH_2$-C_6H_5 or $HCONHN(CH_2C_6H_5)_2$.[73] [f] From the kinetics of aminolysis of methyl formate,[43] the overall equilibrium constant of the reaction[36] and an assumed rate constant of proton transfer of 10^{10} M^{-1} s^{-1} between OH^- and $T^\pm$ and 1.3×10^8 M^{-1} s^{-1} between hydrazine and $T^\pm$ (see text). [g] Reference 74. [h] This work. [i] K_{ald} ($CH_3COH + NH_2NH_2$) = 2.4×10^3 M^{-1} (this work). [j] Reference 75. [k] Mean value between 4.2×10^{-6} and 2.8×10^{-7} M^{-1} obtained from the kinetics of hydrazinolysis of acetylimidazole[44] and assumed limiting values for the rate of proton transfer between $T^\pm$ and hydrazine (see text). [l] K_{ald} (CH_3COH + imidazole) = 0.13 M^{-1}.[76] [m] From the rotational barrier of $CH_3CONH(CH_2C_6H_5)_2$.[73] [n] Mean value between 1.8×10^{-17} and 1.2×10^{-18} M^{-1} (see footnote [k]) using the equilibrium constant of the reaction calculated from the free energy of hydrolysis of acethydrazide and of acetylimidazole (this work and ref 77). [o] K_{ald} ($CH_3COH + C_2H_5OH$) = 0.5 M^{-1}.[20] [p] From ref 5 and the equilibrium constant of the reaction calculated from the free energy of hydrolysis of acethydrazide (this work) and the ester[77] (see text). [q] K_{ald} ($CH_3COH + CF_3CH_2OH$) = 0.023 M^{-1} (this work). [r] K_{ald} calculated from the equilibrium constant of addition of phenol to formaldehyde: $K = C_6H_5OCH_2OH]/[C_6H_5OH][H_2CO] = 18$ M^{-1},[78] corrected by a factor of $5.5 \times 10^{-4} \pm 0.2 \times 10^{-4}$ representing the difference in affinity between acetaldehyde and formaldehyde for water or alcohols (from data given in ref 65 and 20). [s] K_{ald} ($CH_3COH + C_2H_5SH$) = 36 M^{-1}.[79] [t] K_{ald} ($CH_3COH + CH_3OH$) = 0.7 M^{-1}.[20] [u] Mean value from ref 27. [v] K_{ald} ($C_6H_5COH + CH_3OH$) = $3.6\ 10^{-3}$ M^{-1}.[16] [w] Reference 28. [x] K_{ald} ($H_2CO + NH(CH_3)_2$) = $2.6\ 10^6$ M^{-1}.[80] [y] Reference 81.

$= pK_a$ (ethylmorpholine) $- 1.50(\sigma^*_{OH} + \sigma^*_{OCH_3} - \sigma^*_H) = 7.70 - 1.5(1.81 + 1.81 - 0.49) = 3.01$; $pK_{a_2} = pK_a$ (ethanol) $- 1.45\ (\sigma^*_{viii} + \sigma^*_{OCH_3} - \sigma^*_H) = 15.9 - 1.45(4.31 + 1.81 - 0.49) = 7.74$; $K_{taut} = 1.86 \times 10^{-5}$.

viii

If the two pK_as are calculated from methylmorpholine and methanol as starting points, they are different, $pK_{a_1} = 3.42$ and $pK_{a_2} = 8.12$ but the value of K_{taut} is hardly affected: 2.0×10^{-5}. To obtain K_{taut}, the reference compounds should be chosen to make similar structural changes in the amine and the alcohol. If the individual pK_as are used to calculate K_{T+} or K_{T-}, it is advisable to calculate the pK_as from several starting points and take the mean value.

The calculated values $K_{T\pm}$ (corresponding to $K_{T\pm1}$ in Scheme V) are compared in Table IV with the values obtained from the kinetics of aminolysis of esters or of acetylimidazole under basic conditions according to the detailed mechanism proposed by Jencks and co-workers (Scheme V).[5,43,44]

For the base-catalyzed reactions, the observed rate constants are equal to

$$k_{obsd} = K_{T\pm2} \times k_b$$

where k_b is a proton-transfer step.

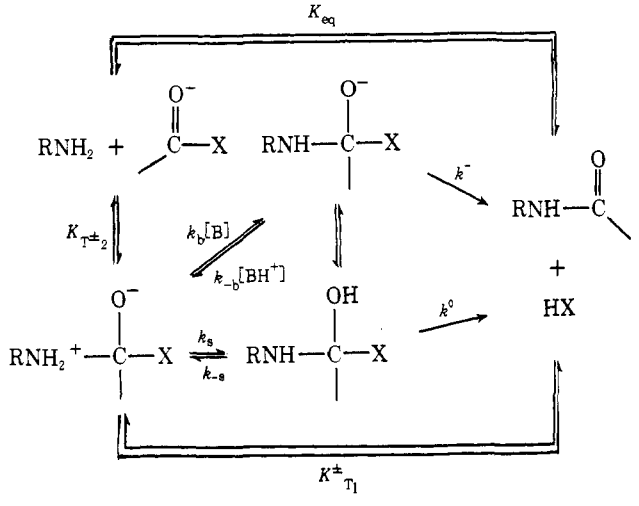
The equilibrium constants $K_{T\pm2}$ have been determined[5] from the kinetics for the addition of hydrazine on methyl-, trifluoroethyl-, and phenylacetate as 6×10^{-12}, 1×10^{-9}, and 2×10^{-9} M^{-1}, respectively, assuming a rate constant of 10^{10} M^{-1} s^{-1} for the deprotonation of $T^\pm$ by OH^- and 1.3×10^8 M^{-1} s^{-1} for the deprotonation by hydrazine. Using the same rates for the proton-transfer step, we have calculated the following $K_{T\pm2}$: 1.4×10^{-15} for the addition of morpholine to methyl

Table V. Calculated Localization Free Energies for Acyl Derivatives[a]

Acyl deriv	Reaction used	Overall K_{eq}[b]	$K_{T^0 2}$,[c] M^{-1}	$K_{add.\ X}$,[d] M^{-1}	ΔG_{loc},[e] kcal
$HCOOCH_3$	$HCOOCH_3$ +	1.83×10^6 [f]	3.3×10^{-4}	3.2×10^8 [g]	16.3
	$HCOOCH_3 + NH_2NH_2$	8.9×10^5 [f]	8.9×10^{-4}	6.8×10^9 [h]	17.6
	$HCOOCH_3 + NH(CH_3)_2$	5.0×10^7 [f]	4.0×10^{-5}	4.6×10^8 [i]	17.8
HCOOH	$HCOOH + NH_2NH_2$	1.07×10^5 [j]	1.6×10^{-4}	6.8×10^9 [h]	18.6
	$HCOOH + NH(CH_3)_2$	6.1×10^6 [j]	7.3×10^{-6}	4.6×10^8 [i]	18.8
CH_3COOCH_3	$CH_3COOCH_3 + NH_2NH_2$	2.4×10^5 [k]	8.0×10^{-8}	4.2×10^5 [l]	17.3
	$CH_3COOCH_3 + NH(CH_3)_2$	6.6×10^5 [k]	1.4×10^{-8}	1.1×10^4 [m]	16.2
CH_3COOH	$CH_3COOH + NH_2NH_2$	2.5×10^4 [k]	1.2×10^{-8} [n]	4.2×10^5 [l]	18.5
	$CH_3COOH + NH(CH_3)_2$	7.1×10^4 [k]	2.3×10^{-9}	1.1×10^4 [m]	17.3
$CH_3COOCH_2CF_3$	$CH_3COOCH_2CF_3 + NH_2NH_2$	1.15×10^8 [p]	1.3×10^{-6}	1.7×10^7 [l,o]	17.9
	$CH_3COOCH_2CF_3 + NH(CH_3)_2$	3.12×10^8 [p]	2.4×10^{-7}	4.4×10^5 [m,o]	16.7
$CH_3COOC_6H_5$	$CH_3COOC_6H_5 + NH_2NH_2$	6.8×10^9 [p]	3.1×10^{-5}	4.8×10^6 [l]	15.2
	$CH_3COOC_6H_5 + NH(CH_3)_2$	1.85×10^{10} [p]	5.9×10^{-6}	1.2×10^5 [m]	14.0
$CH_3COSCH_2CH_3$	$CH_3COSCH_2CH_3 + NH_2NH_2$	4.37×10^7 [p]	7.4×10^{-4}	1.6×10^5 [l]	11.4
	$CH_3COSCH_2CH_3 + NH(CH_3)_2$	1.2×10^8 [p]	1.3×10^{-4}	4.3×10^3 [m]	10.3
$CH_3COOCOCH_3$	$CH_3COOCOCH_3 + NH_2NH_2$	8.5×10^{15} [q]	2.5×10^2 [r]	5.8×10^6 [l,s]	6.0[t]
	$CH_3COOCOCH_3 + NH(CH_3)_2$	2.8×10^{16} [q]	5.8×10^1 [u]	1.5×10^5 [m,s]	4.7[t]

[a] At 25 °C. [b] $K_{eq} = [RCONR''_2][R'OH]/[RCOOR'][HNR''_2]$, unit free except for the equilibrium constants of formation of amides from acids and amines in M^{-1} because the activity of pure water is taken equal to 1.0. [c] Calculated from eq 6 and the $K_{T^0 1}$ values given in Tables IV and VI or in footnotes. [d] Calculated from the equilibrium constants of addition of the nucleophiles to the aldehydes (K_{ald}) and a correction for the difference in inductive effect between the X group and hydrogen (eq 2, $\rho^* = 1.7$ and σ^* values taken from ref 23 except for $\sigma^*_{OH} = 1.81$ (see text). [e] Calculated from $K_{T^0 2}$ and $K_{add.\ X}$ using eq 1 and $\Delta G = -RT \ln K$. [f] From the free energies of hydrolysis of the amide[36] and of methyl formate.[70] [g] K_{ald} (H_2CO + morpholine) = 1.8×10^6 M^{-1}.[40,80] [h] K_{ald} ($H_2CO + NH_2NH_2$) = 4.0×10^7 M^{-1}, from the equilibrium constant of addition of hydrazine to *p*-chlorobenzaldehyde $K = 7.0$ M^{-1} [18] corrected by a factor $(5.7 \pm 2.3) \times 10^6$, representing the difference in affinity of formaldehyde and *p*-chlorobenzaldehyde for amines (from the data given in ref 18). [i] K_{ald} ($H_2CO + NH(CH_3)_2$) = 2.6×10^6 M^{-1}.[40,80] [j] Reference 36. [k] From the equilibrium constants given in Table II. [l] K_{ald} ($CH_3COH + NH_2NH_2$) = 2.4×10^3 M^{-1} (this work). [m] K_{ald} ($CH_3COH + NH(CH_3)_2$) = 6.1×10^1 M^{-1} (this work). [n] $K_{T^0 1} = 4.6 \times 10^{-13}$, calculated from $K_{hydr\ CH_3COH} = 1.04$[20] and $\Delta G_{loc\ CH_3CONHNH_2} = 18.6$ (see footnote *m* Table IV). [o] $\sigma^*_{OCH_2CF_3} = 2.76$, estimated from $\sigma^*_{OCH_3}$ (1.81) + $\sigma^*_{NHCH_2CF_3}$ (1.55[26]) − $\sigma^*_{NHCH_3}$ (0.6) = 2.76; σ^*_{OPh} (2.43) + $\sigma^*_{NHCH_2CF_3}$ (1.55) − σ^*_{NHPh} (1.22, see footnote *b*, Table IV) = 2.76. [p] From the equilibrium constants given in Table II and in ref 77. [q] From the equilibrium constants given in Table II and in ref 83. [r] $K_{T^0 1}$, obtained from the equilibrium constant of addition of acetic acid to acetaldehyde ($K = 0.07$ M^{-1}) under the assumption that the adduct is entirely the nucleophilic addition compound and not the hydrogen-bonded complex of AcOH to acetaldehyde hydrate[84] and using ΔG_{loc} values for $CH_3CONHNH_2$ and $CH_3CON(CH_3)_2$ given in Table IV. [s] $\sigma^*_{OCOCH_3} = 2.48$, calculated from the field component of CH_3COO- substituent effect:[46] $\sigma_I = (0.6 \times 0.679) - 0.01$ and $\sigma^* = 6.23\sigma_I$. [t] Lower limit subjected to condition explained in footnote *r*.

Scheme V



formate (from the observed rate of the OH^--catalyzed pathway[43]) and 2.4×10^{-14} M^{-1} for the addition of hydrazine on methyl formate (from the rate of the hydrazine catalyzed pathway). These $K_{T^\pm}$ values are dependent on the choice of a rate constant of deprotonation of $T^\pm$ by OH^-. A value of 10^{10} M^{-1} s^{-1} was chosen. It could in fact be 2-2.5 times larger[45]; this would decrease the $K_{T^\pm}$ values by a factor of 2-2.5.

For the hydrazinolysis of acetylimidazole, the observed rate constant of the hydrazine-catalyzed pathway can also be used but the value of 1.3×10^8 M^{-1} s^{-1} applicable to the esters for the rate of proton transfer between hydrazine and $T^\pm$ is only a lower limit because of the characteristics of the mechanism of this reaction;[44] an upper limit would be in the range of 2×10^9 M^{-1} s^{-1};[45] accordingly $K_{T^\pm 2}$ is between 4.2×10^{-6} and 2.8×10^{-7} M^{-1}.

The $K_{T^\pm 1}$ constants given in Table IV are calculated from the $K_{T^\pm 2}$ given above and the overall equilibrium constants of the reactions.

The localization free energies have been calculated for several esters and thioesters from the $T_{T^0 2}$ values (Scheme II). They are given in Table V. The localization free energies of esters are ~4 kcal less than those for amides of comparable structure (compare dimethylformamide and methyl formate); the difference between an ester and a thioester is ~5 kcal. These differences seem reasonable in view of the differences in electronegativity and dimension of the atoms involved. For acetic anhydride, the value given is the localization free energy corresponding to the addition of a nucleophile to one of the carbonyl groups. This value is dependent on the assumption given in footnote *r* of Table V, that the equilibrium constant of interaction of acetic acid with acetaldehyde represents really a nucleophilic addition; otherwise this value of the localization free energy for acetic anhydride would be larger.

The localization free energies have been used to calculate the equilibrium constants of hydration and addition of hydroxide ions (Table VI).

Discussion

The comparison between our calculated values and the values obtained by direct measurements of the equilibria for conjugated aldehydes or derived from the kinetics of the reactions for amides shows that the agreement is reasonable in most cases. Although a wide range of equilibrium constants between 2×10^{-6} and 2×10^{-19} M^{-1} is covered for amides,

Table VI. Equilibrium Constants of Hydration of Various Acyl Derivatives[a]

Substrate	$K_{add.\ X}$[b]	ΔG_{loc}, kcal	K_{T^0}	K_{T^-},[c] M^{-1}	$K_{T^0\,calor}$[t]
$HCON(CH_3)_2$	3.0×10^3 [d]	21.0[e]	1.2×10^{-12}	5.1×10^{-12}	1.8×10^{-15}
$HCONHCH_3$	3.0×10^3 [d]	22.0[f]	2.2×10^{-13}	9.4×10^{-13}	
$HCONH_2$	3.0×10^3 [d]	18.7[g]	5.8×10^{-11}	2.5×10^{-10}	
	5.0×10^4 [d]	19.5[h]	2.5×10^{-10}	3.2×10^{-8}	
$HCONHNH_2$	3.7×10^4 [d]	18.3[i]	1.4×10^{-9}	1.4×10^{-7}	
$HCONHC_6H_5$	3.4×10^4 [d]	17.7[j]	3.5×10^{-9}	3.2×10^{-7}	
$CH_3CON(CH_3)_2$	1.7[k]	18.7[d]	3.3×10^{-14}	7.4×10^{-14}	1.3×10^{-15}
$CF_3CON(CH_3)_2$	2.3×10^5 [l]	18.6[m]	5.3×10^{-19}	7.3×10^{-5}	
$CCl_3CON(CH_3)_2$	5.2×10^4 [n]	15.0[m]	5.2×10^{-7}	8.2×10^{-3}	
$C_6H_5CON(CH_3)_2$	1.8×10^{-2} [o]	15.8[p]	4.7×10^{-14}	7.9×10^{-13}	
$CH_2{=}CH{-}CON(CH_3)_2$	3.5×10^{-2} [q]	16.8[r]	1.7×10^{-14}	2.5×10^{-13}	
CH_3COOCH_3	1.8×10^2 [k]	16.8	8.7×10^{-11}	1.1×10^{-8}	1.0×10^{-8}
CH_3COOH	1.8×10^2 [k]	17.9	1.4×10^{-11}	2.5×10^{-9} [s]	4.0×10^{-9}
$CH_3COOCH_2CF_3$	7.5×10^3 [k]	17.3	1.5×10^{-9}	4.4×10^{-6}	
$CH_3COOC_6H_5$	2.1×10^3 [k]	14.6	4.0×10^{-8}	3.8×10^{-5}	
$CH_3COSC_2H_5$	6.9×10^1 [k]	10.8	8.2×10^{-7}	4.3×10^{-5}	
$HCOOCH_3$	3.2×10^5 [d]	17.2	7.7×10^{-8}	4.7×10^{-5}	4.5×10^{-7}
$HCOOH$	3.2×10^5 [d]	18.7	6.1×10^{-9}	5.7×10^{-6} [s]	3.7×10^{-10}

[a] At 25 °C, standard state 1 M for all species except for water activity taken as 1.0. [b] Calculated from the equilibrium constants of hydration of the aldehydes (K_{hydr}) and a correction for the difference in inductive effect between the X group and hydrogen (eq 2, $\rho^* = 1.7$, σ^* values taken from ref 23 except for $\sigma^*_{OH} = 1.81$ (see text) and σ^* values given in footnote *b* of Table IV). [c] From the pK_a of the tetrahedral intermediates calculated from equation given in ref 31 and a statistical correction of 0.3; $K_{T^-} = (K_{T^0} \times K_a)/K_w$. [d] $K_{hydr\ H_2CO} = 1.8 \times 10^3$.[40] [e] Mean value from ref 27. [f] Reference 74. [g] Reference 85. [h] This work. [i] Reference 73 (see footnote *e*, Table IV). [j] Reference 81. [k] $K_{hydr\ CH_3COH} = 1.04$.[20] [l] From the equilibrium constant of hydration of chloral[40] corrected for the difference in steric effect by a factor 5. [m] Reference 86. [n] $K_{hydr\ CCl_3COH} = 3.1 \times 10^4$.[40] [o] $K_{hydr\ C_6H_5COH} = 1.1 \times 10^{-2}$.[13] [p] Reference 28. [q] $K_{hydr\ CH_2=CHCOH} = 2.1 \times 10^{-2}$, calculated as shown in Table III for the addition of methanol on acrolein. [r] Reference 63. [s] Statistical correction of 0.48 on the pK_a of T^0 (see footnote *c*). [t] Values given in ref 6a and 6b and revised in 6c.

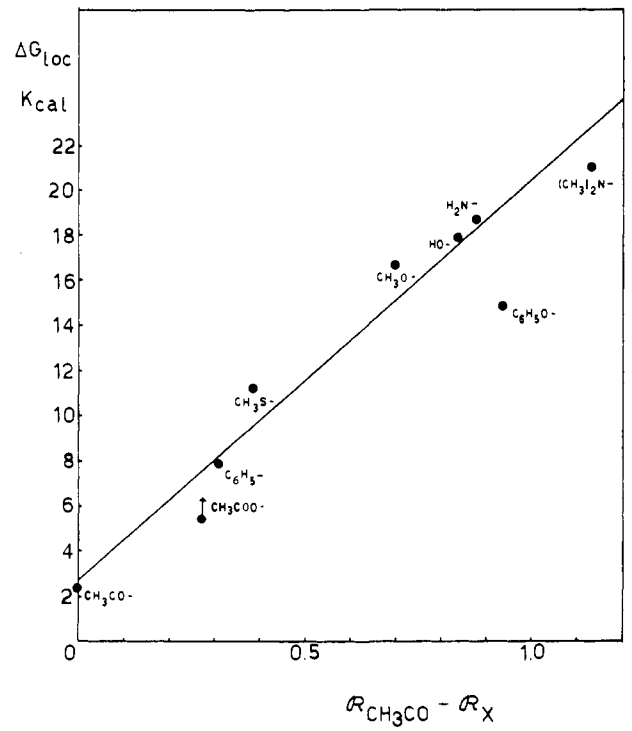


Figure 1. Localization free energies (see text) as a function of the difference in the resonance components of the substituent effect ($\mathcal{R}$) between the X group and the C=O group.

the experimental values are reproduced to within 2 kcal. In view of the many assumptions and approximations made in the calculations, as detailed in the theorical part, the agreement between the experimental values and our calculated values is somewhat comforting. Some compensations of errors are likely to play on our side. It nevertheless seems that it is possible to estimate with a reasonable degree of accuracy the free-energy change involved in the formation of a tetrahedral intermediate which is experimentally not available.

Some of the values reported in this paper have been obtained by a different method by Guthrie.[6] Some of Guthrie's values are given in Table VI for comparison. Relatively large discrepancies exist between Guthrie's revised values and our values for the hydration of acetic acid, methyl acetate, and dimethylformamide and the addition of methanol to dimethylformamide. Guthrie's method is subject to the possibility of error accumulation because many individual measurements contribute to the final value and some experimentally inaccessible data such as solubilities of amide–dimethyl acetals and entropies of formation have to be extrapolated from reasonable models. Our method on the other hand is more empirical and as detailed earlier is dependent on a few assumptions. It is difficult at this stage to decide which method gives the best results because, for the equilibria investigated by the two methods, no direct experimental result is presently available with which to compare the calculated values.

Another estimation of the reliability of the calculations can be obtained by using Scheme II for calculating the localization free energy for one acyl derivative from several transacylation equilibria. Table V includes several data of this kind. It can be seen that the localization free-energy values calculated in this way vary by <2 kcal, although all the errors of the individual steps could accumulate in these values.

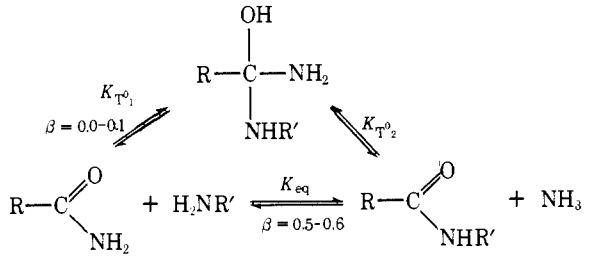
The ΔG_{loc} values can be correlated with the difference in $\mathcal{R}$ substituent constants of Swain and Lupton[46] between the X group and the C=O group[47] (Figure 1). The resonance interaction between two C=O groups is calculated from the difference between the experimental value of the hydration equilibrium constant of 2,3-butanedione (2.0)[8] and the value calculated from the hydration equilibrium of acetaldehyde (1.04),[20] by application of eq 2 with a σ^* value of 1.65 for CH_3CO;[23] the ratio of K_{calcd}/K_{exptl} of 50 corresponds to a localization free energy of 2.3 kcal.[48] The point corresponding to the phenyl ester (OC_6H_5) deviates significantly from the plot; this behavior must be related to the fact that the phenyl

ring in the ester has been shown to lie in a plane perpendicular to the plane of the ester function.[52]

The values of the localization free energy can also be compared with the resonance energy data derived from thermochemical measurements. To the extent that rotational barriers are essentially enthalpic; there should be a reasonable agreement between the two sets of data. The comparison is made in Table VII for several compounds with the resonance energy values obtained by Klage and by Franklin[53] or from comparisons of heats of hydrogenation.

A consideration of the equilibrium constants of formation of tetrahedral intermediates from both sites of the transacylation reaction is instructive. Let us look for instance at several transamidation equilibria from a single amide (Scheme VI).

Scheme VI



It is known that the overall equilibrium constants are correlated by a Bronsted plot: $\log K_{eq} = \beta\, pK_a + C$, with a value of β between 0.5 and 0.6.[36,54] On the other hand, the equilibrium constants of the additions of nucleophiles to carbonyl compounds show very little sensitivity to the pK_as of the nucleophiles.[18,55] Accordingly, the $K_{T^0_1}$ value should depend very little on the pK_a of the amine. The equilibrium constants of addition of one amine to several amides should then vary according to $\log K_{T^0_2} = 0.5\, pK_a + C$, where the pK_a refers to the amine constituting the amide. In the formanilide series, the formal equilibrium constants of formation of the localized forms vary with the pK_as of the constituting anilines with a slope of 0.2.[56] The difference between this value and the overall effect of the substituent, 0.5, is due to the change in inductive effects of the substituents NHPhX on the $K_{add.\ NHPhX}$ values. In other words, electron-withdrawing substituents favor the addition of the nucleophile both by lowering the localization free energy and by increasing the inductive effect on $K_{add.}$. These two factors are nearly equal.

The separation of the overall equilibrium constants of the transacylation reactions into several formal steps leads to a better understanding of the factors involved in the thermodynamic stability of the acyl derivatives. Several anomalies have been reported, for instance in the equilibrium constants of hydrolyses of amides. Formamide is ~3 kcal less stable than predicted from the Brønsted plot relating equilibria of formation of amides to the pK_as of the constituting amines.[36] This difference has been attributed to an anomalously good solvation of ammonia in water. From a consideration of the rotational barriers, it is more likely to be due to a lower delocalization energy compared to *N*-methyl and *N*-dimethylformamide.

Dimethylpropionamide has been reported to be ~3 kcal less stable than dimethylformamide;[38] however, it is generally accepted that the equilibrium constants of hydrolyses of amides do not depend significantly on the structure of the acyl portion of the amide.[36] The previous method of measurement of the equilibrium constants from kinetic data under different conditions for the forward and the reverse reactions made it possible that this difference was in fact illusory. The equilibration in identical buffers for the forward and reverse reactions that we have used here gives more reliable results. It is found that dimethylacetamide is also 2.7 kcal less stable toward hydrolysis than dimethylformamide. Here too the difference is entirely reflected in the difference in the heights of the rotational barriers. The smaller rotational barrier for dimethylacetamide is likely to be due to steric interactions in the planar form of the amide. In fact, secondary amides exist predominently as the *Z* form.[57] This kind of consideration explains why, although dimethylformamide is hydrolyzed faster than dimethylacetamide, because of the difference in steric hindrance; the hydrolysis of the sterically less hindered *N*-methylpropionamide is slower than that of dimethylpropionamide.

So far we have examined relatively simple derivatives for which the approximation made in neglecting the difference in steric effects between the X group and hydrogen is not likely to lead to large errors. For more crowded systems, steric effects could play a significant role both by inhibiting the delocalization in the acyl derivative and by decreasing the equilibrium constant of addition on the localized form. To what extent these two factors would compensate is not known.

The fact that the equilibrium constants of formation of tetrahedral intermediates from conjugated carbonyl compounds and acyl derivatives can be estimated with a reasonable degree of accuracy by considering only resonance and inductive effects for unhindered systems shows that the instability of these tetrahedral intermediates is quantitatively accounted for by the conjugation loss which is relatively large in all cases, between 7 and 11 kcal for conjugated aldehydes and up to 22 kcal for amides.

Table VII. Comparison of Resonance Energies Obtained from Thermochemical Measurements and Delocalization Free Energies Reported in This Work[a]

Compd	E_R, Klage[b]	E_R, Franklin[b]	E_R, hydrogen	ΔG_{deloc}
HCOOH	12	14	17.24[c]	18.7
CH_3COOH	13	14	17.17[c]	17.9
$HCOOCH_3$	15	19		17.2
CH_3COOCH_3	18	19		16.8
$HCONH_2$	22	21	17.56[d]	18.7
$HCONHC_6H_5$	23[e]	23.6[e]		17.7

[a] Kilocalories/mole. [b] Reference 53. [c] Calculated from the difference in enthalpy of formation between the aldehyde, the acid and their reduction product, the alcohol, and the diol at 298 K, vapor phase (data from ref 11). [d] Using the same method as for the acids; the enthalpy of formation of H_2NCH_2OH is obtained indirectly from the experimental value $\Delta H°_f(CH_3ONH_2)$ and its isomerization energy from MO calculations.[87] [e] Resonance energy of the anilide minus the resonance energy of aniline.

Experimental Section

Materials. Acetaldehyde (UCB Analar) was freshly distilled twice under nitrogen from a 40% methanolic solution. Benzaldehyde was freshly distilled under nitrogen before use. Trifluoroethanol (Aldrich Gold Label), hydrazine hydrate (BDH Analar), dimethylamine, a 20% titrated solution in distilled water made from Fluka, water-free dimethylamine, methylacetate, acetic acid, and dimethylacetamide were commercial products used without further purification.

Acethydroxamic acid was prepared according to the method of Jencks[37] and recrystallized from ethyl acetate, mp 89.5–91 °C (lit. 89–92.5 °C).

Acethydrazide was prepared according to the method of Curtius[58] and vacuum distilled. mp 65 °C (lit. 67 °C).

N-Formylmorpholine was prepared from formic acid and morpholine[59] and vacuum distilled bp 235 °C.

2-Aminoethylhydrazine was made by reaction of hydrazine hydrate and ethylenimine[60] and vacuum distilled, bp 86–87 °C (15 mm).

Methods. The pK_as of acethydroxamic acid and 2-aminoethylmorpholine were measured by titration with a radiometer PHM 64 pH meter and a Radiometer GK 2301C glass electrode; 0.1 M solu-

Table VIII. Experimental Conditions for the Determination of the Equilibrium Constants of Transacylation Reactions[a]

Acyl deriv	Buffer composition	Estd $t_{1/2}$, h	Time of measurement, h
CH_3COOH	5 M CH_3OH/46.5 M H_2O/1 M HCl		45[b]
CH_3COOCH_3	5 M CH_3OH/46.5 M H_2O/1 M HCl		45[b]
$CH_3CONHOH$	0.7 M NH_2OH·HCl/0.7 M NH_2NH_2 + 0.3 M HCl	40	125[c]
$CH_3CONHNH_2$	0.7 M NH_2OH·HCl/0.7 M NH_2NH_2 + 0.3 M HCl	40	125[c]
$CH_3CONHOH$	1 M NH_2OH·HCl/1 M $NH(CH_3)_2$	1500	482[c]
$CH_3CON(CH_3)_2$	1 M NH_2OH·HCl/1 M $NH(CH_3)_2$	1500	482[c]

[a] 25 °C, acyl derivative concentration 10^{-2} in all cases. [b] K_{eq} given in Table II. [c] K_{eq} calculated from the ratio of initial changes.[36]

tions in 1 M KCl were titrated with 1 M NaOH or 1 M HCl. The following pK_as were found: acethydroxamic acid 9.35 ± 0.02, 2-aminoethylhydrazine, 9.50 and 8.07.

Equilibria of Addition of Nucleophiles to Aldehydes. The addition of dimethylamine to benzaldehyde and hydrazine to acetaldehyde were measured by UV spectrometry on a Cary 16K spectrometer. For benzaldehyde, 100 μL of a 5×10^{-2} M solution of aldehyde was added to a solution of dimethylamine–80% free base in distilled water. The decrease in absorbance at 280 nm (ΔA) was extrapolated to zero time to take into account the iminium formation. The amine concentration was varied between 4 and 0.33 M. The equilibrium constant was evaluated from a plot of ΔA vs. ΔA/[amine].

For acetaldehyde, the absorbance at 278 nm of several solutions 1.54×10^{-3} M in acetaldehyde and between 6.25 and 1.25×10^{-3} M in hydrazine–50% free base, were measured 10 s after mixing in a 2-cm optical path cell. The equilibrium constant was calculated from the following formula:

$$\frac{[CH_3COH]_0}{[CH_3COH]} = 1 + K_{hydr} + \frac{K_{am}[amine]_0}{1 + K_{am}[CH_3COH]}$$

where K_{hydr} is the hydration equilibrium constant equal to 1.04[20] and K_{am} is the equilibrium constant of amine addition; $[CH_3COH]_0$ refers to the total acetaldehyde concentration, free, hydrated, and complexed with hydrazine; $[amine]_0$ refers to the nonprotonated initial amine concentration; $[CH_3COH]$ is the free acetaldehyde concentration as measured from the optical density of the solution; the extinction coefficient, ϵ, for acetaldehyde in water is the value determined by Kurz,[61] 15.77. Because of the low concentrations used, the equilibrium constant is comparatively less accurate.

The equilibrium constant of addition of dimethylamine to acetaldehyde was measured by recording the pH drop of 1 mL of a 0.05 M solution of dimethylamine–50% free base upon addition of 1 mL of solutions between 1 M and 0.3 M in acetaldehyde and extrapolating to zero time according to the method of Le Henaff.[22]

The equilibrium constant of addition of trifluoroethanol to acetaldehyde was estimated from the integration of the areas of the NMR peaks corresponding to the free aldehyde and the hemiacetal of a 10% trifluoroethanol solution of acetaldehyde and from the apparent ϵ of a 0.13 M solution of acetaldehyde in trifluoroethanol, taking the ϵ for the free acetaldehyde to be equal to the value observed in hexane (16.2).[7]

Equilibria of Transacylation Reactions. The experimental conditions for the determination of the equilibria are given in Table VIII. For the esterification equilibria, the alkaline hydroxamate assay of Hestrin was used.[62] Samples (0.5 mL) were added to 1 mL of a freshly prepared mixture of 1.33 M hydroxylamine hydrochloride and 2.67 M NaOH. After 5 min, 1.5 mL of 20% $FeCl_3 \cdot 6H_2O$ in 4 N HCl was added and the absorbance at 540 nm was measured after 10 min. A calibration curve was made using standard solutions of methyl acetate.

For the hydroxamic acid formation and aminolysis, 0.5 mL of sample solutions were added to 2 mL of 20% $FeCl_3 \cdot 6H_2O$ in 1.4 N HCl. The absorbance at 540 nm was measured against a blank. The pH was read at the end of the experiment and the hydroxylamine content was measured by titration to make sure that the hydroxylamine had not decomposed significantly during the time of the equilibration.

Rotational Barrier. The rotational barrier of *N*-formylmorpholine was determined from the analysis of the proton decoupled ^{13}C NMR spectra of neat samples of methylmorpholine. The analysis was done according to the intensity ratio method[63] between 70 and 100 °C for the β carbons ($\Delta G^{\ddagger} = 19.55 \pm 0.18$ kcal) and 100 and 110 °C for the α carbons ($\Delta G^{\ddagger} = 19.53 \pm 0.08$). The spectra were taken on a Varian CFT 20 NMR spectrometer.

Supplementary Material Available: A list of the pK_a and σ* values used to obtain the pK_a vs. σ* relationships (7 pages). Ordering information is given on any current masthead page.

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(30) This σ^*_{OH} is then equal to the $\sigma^*_{OCH_3}$; this is consistent with the fact that $\sigma^*_{CH_2OH}$ (0.555) is nearly equal to $\sigma^*_{CH_2OCH_3}$ (0.52).
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