THE JOURNAL OF Organic Chemistry

VOLUME 46, NUMBER 22

OCTOBER 23, 1981

Acidities of the H-C Protons in Carboxylic Esters, Amides, and Nitriles

Frederick G. Bordwell* and Herbert E. Fried

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received October 21, 1980

Equilibrium acidities in Me_2SO have been measured for a series of esters, GCH_2CO_2R, and a series of amides, GCH_2CONR_2, where G is Me_3N^+, Ph, PhS, CN, CH_3CO, and 9-fluorenyl and R = Me, Et, or *t*-Bu. These data are compared with data for the corresponding nitriles, $GCH_2C{\equiv}N$. The usual order of acidity found was GCH_2CN > GCH_2CO_2Et (ΔpK_a = 0.8–2) and GCH_2CO_2Et > GCH_2CONMe_2 (ΔpK_a = 3.9–4.5). Extrapolations from these data place the pK_a of CH_3CO_2Et at about 30–31 and that of CH_3CONMe_2 at about 34–35, as compared to the (measured) value of 31.3 for CH_3CN. Measurements in Me_2SO and in H_2O for $CH_2(CO_2Et)_2$ and $(CH_2(CN)_2$ were used as a basis for estimating the pK_a values in water of CH_3CO_2Et (27–28), CH_3CONMe_2 (31–32), and CH_3CN (31.5). These estimates range from 2 to 7 units higher than previous estimates.

The relative acidities of the α-hydrogen atoms in carboxylic esters, amides, and nitriles dictate the relative ease with which these compounds undergo such important reactions as base-promoted metalation, racemization, alkylation, and acylation. Since these compounds are much weaker acids than water, it is impossible to measure their acidities in this solvent, and kinetic acidities have been used to estimate their equilibrium acidities. However, information concerning kinetic acidities is sparse and contradictory. The rate of hydroxide ion catalyzed deuterium exchange for the C–H bond in CH_3CN is about twice that for the C–H bond in CH_3CONH_2. By assuming the same k^{HO^-}/k^{H_2O} ratio (10^{10}) for these compounds as for acetone, these rates were used to estimate the rates for water acting as a base, and equilibrium acidities in water were estimated from a plot of k^{H_2O} vs. pK_a for a series of carbon acids including $CH_2(NO_2)_2$, $(CH_3CO)_2CHBr$, $(CH_3CO)_2CHMe$, $CH_3COCHEtCO_2Et$, $EtCH(CO_2Et)_2$, CH_3COCH_2Cl, and CH_3COCH_3.[1] In view of the diversity in structure of these carbon acids, the uncertainty in pK_a values for many of the acids, and the differences in steric effects at the reaction site, the size of the Brønsted coefficient derived from this plot can be considered to be no more than a rough estimate.[2] Since the k^{H_2O} rates for the C–H acidities of CH_3CN and CH_3CONH_2 are also rough estimates, it is questionable whether the pK_a values derived for these compounds are meaningful. (The same is true for CH_3CO_2Et for which a pK_a was given without a rate.) The pK_a values of 24.5, 25, and 25 for the C–H acidities of CH_3CO_2Et, CH_3CN, and CH_3CONH_2, respectively, that were reported are certainly subject to large errors. Nevertheless, these "pK_a values" are frequently cited in the literature and have been generally accepted.[3]

Other kinetic and equilibrium acidity data do not support the near equivalence of α-C–H acidities for esters, amides, and nitriles. The rate of racemization of PhC*H(Me)CO_2-*t*-Bu-catalyzed by *t*-BuOK in *t*-BuOH hs been found to be about 10^4 greater than that for PhC*H(Me)$CONEt_2$ under the same conditions; the rate for the corresponding nitrile was too fast to measure under these conditions.[4] These data suggest an acidity order of PhCH(R)CN > PhCH(R)CO_2R > PhCH(R)$CONR_2$, but this order needs to be accepted with caution since the relative rates may depend as much on the degree to which the intermediate carbanion is hydrogen bonded to *t*-BuOH as on its stability.[3] The same order is derived from equilibrium acidity data for substituted dinitroalkanes $GCH(NO_2)_2$ in aqueous solution; here the compounds where G is CN, CO_2Me, and $CONH_2$ are reported to have pK_a values of –6.2, 0.98, and 1.30, respectively.[5] Interpretation of these data is difficult, however, since examination of molecular models indicates that steric inhibition of resonance in $GC(NO_2)_2^-$ anions is important and increases in the order CN < $CONH_2$ < CO_2Me. Also, as we will see later, hydrogen bonding may increase the acidity of the amide.

On the other hand, it has been reported that $CH_3CH_2CONEt_2$ incorporates up to 70% of deuterium

(1) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439–2443.
(2) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1973.
(3) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965.
(4) Cram. D. J.; Rickborn, B.; Kingsbury, C. A.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 3678–3687.
(5) Tselinskii, I. V.; Kosmynina, A. S.; Dronov, V. N.; Shokhor, I. N. *Reakts. Sposobn. Org. Soedin.* **1970**, *7*, 50.

0022-3263/81/1946-4327$01.25/0

Table I. Carboxylic Ester, Nitrile, and Amide Acidities in Dimethyl Sulfoxide Solution at 25 °C[a]

compd	indicator	pK_{In}	pK_a[b]	selected pK_a
$[Me_3NCH_2CO_2Et]^+Cl^-$	CNAH	18.9	19.9 ± 0.3[c]	
	2NpANH	20.66	20.03	20.0
$[Me_3NCH_2CONEt_2]^+Cl^-$	TBuFH	24.35	24.90	
	TP2H	25.6	24.90	24.9
$PhCH_2CO_2$-*t*-Bu	MFH	22.34	23.60	
	FH	22.6	23.60	23.6
$PhCH_2CO_2Et$	MFH	22.34	22.57	
	FH	22.6	22.72	22.7[d]
$PhCH_2CONMe_2$	TP2H	25.6	26.64	
	PXH	27.9	26.62	26.6
$PhSCH_2CO_2Me$	2NpANH	20.66	21.3	
	TSXH	21.05	21.4	
	MFH	22.34	21.5	21.4
$PhSCH_2CONMe_2$	MCLPXH	26.6	26.0	
	HB1	26.1	25.8	25.9
9-$CONH_2$-FlH	NBY10	15.01	14.86	
	NBY13	14.1	14.80	14.8
$CH_3COCH_2CO_2Et$	PSFH	15.4	14.37 ± 0.06	
	FMY33	13.8	14.14	14.2
$CH_3COCH_2CONMe_2$	ISFH	16.9	18.18	
	CNAH	18.9	18.18	18.2
$CNCH_2CO_2Me$	ESO2FH	12.4	12.84	
	FMY3S31	11.87	12.74	12.8
$CNCH_2CON(CH_2)_4$	ISFH	16.9	17.24	
	FMY3O	18.1	17.22	17.2

[a] Indicator and standard acid abbreviations: PMPXH, 9-(*p*-methoxyphenyl)xanthene; DDH, tetraphenylmethane; CNAH, 4-chloro-2-nitroaniline; 2-NpANH, 2-naphthylacetonitrile; TBuFH, 9-*tert*-butylfluorene; TP2H, 1,1,3-triphenylpropene; MFH, 9-methylfluorene; FH, fluorene; PXH, 9-phenylxanthene; TSXH, 9-(*p*-toluenesulfonyl)xanthene; MCLPXH, 9-(*m*-chlorophenyl)xanthine; HB1, dibenzo[*b*,*d*]azepine ("iminostilbene"); NBY10, bis(methylsulfonyl)methane (standard acid); NBY13, bis(isopropylsulfonyl)methane (standard acid); PSFH, 9-(phenylthio)fluorene; FMY33, 2-(phenylsulfonyl)-9-phenylfluorene; ISFH, 9-(isopropylthio)fluorene; ESO2FH, 9-(ethylsulfonyl)fluorene; FMY3S31, 2-(phenylsulfonyl)-9-*p*-toluenesulfonylfluorene; FMY30, 9-(phenylsulfonyl)fluorene. [b] Three-point titrations with standard deviations of ±0.05 or less, unless otherwise noted. [c] One-point titrations. [d] Lebedva, T. I.; Petrov, E. S.; Shatenshtein, A. I. *Zh. Org. Khim.* 1977, *13*, 905 (p 829 in the English translation). These authors report 23.3, which is 0.1 unit lower than our value when corrected to an absolute scale.

from CH_3OD under NaOMe catalysis in 1 h, whereas $CH_3CH_2CO_2Et$ fails to undergo exchange under these conditions.[6] This suggests an opposite order of acidifying effects for the carboxamide and carboethoxy functions, i.e., $CO_2R < CONR_2$. This order is supported by the observation that $O_2NCH_2CONH_2$ is 0.57 pK_a unit more acidic than $O_2NCH_2CO_2Et$ in water, and this order is maintained also in the α-Cl and α-F derivatives.[7]

The development of an equilibrium acidity scale in Me_2SO has allowed quantitative measurements to be made for the first time on many very weak acids,[8] including the α-C–H acidities of a number of carboxylic esters, amides, and nitriles. In this paper we present evidence to show that in Me_2SO solution the acidity order is usually $GCH_2CN > GCH_2CO_2R > GCH_2CONR_2$, where G is an acid-strengthening function.

Results

Equilibrium acidities in Me_2SO for the acids GCH_2CO_2R and GCH_2CONR_2, where G is Ph, PhS, CN, CH_3CO, PhCO, or 9-fluorenyl and R is Me, Et, or *t*-Bu, were measured by the method described previously[8] (Table I). The anion conjugate bases of these compounds are stable under the conditions of the measurements, as indicated by constant absorbance readings. Attempts to measure the acidity of ethyl acetate (G = H) were frustrated, however, by rapid decreases in absorbance readings. The absorbance decreased slowly with *tert*-butyl acetate, allowing a pK_a of about 30 to be estimated from extrapolation of absorbance readings back to $t = 0$. Although the value is in the pK_a range expected, as will be brought out later, it is not possible to assign a pK_a value from these results.[9]

Measurement of the acidity of $[Me_3NCH_2CO_2Et]^+Cl^-$ was also complicated by unstable absorbance readings. (This is not uncommon with quaternary ammonium salts.) Only one-point runs were possible with the indicator, 4-chloro-2-nitrophenol, but agreement to within 0.2 pK_a unit was obtained by using 2-naphthylacetonitrile as an indicator, where two three-point titrations gave agreement at $pK_a = 20.0$.

The acidity measurements reported in Table I were made prior to the development of the methods for detecting and measuring the extent of ion pair formation.[12] The anions derived from $CH_3COCH_2CO_2Et$ and $CH_3COCH_2CONMe_2$ are expected to be chelated with K^+, and the pK_a values recorded in Tables I and II may be too low by as much as 0.3 unit. Since the enolate ions derived from acetophenone and cyclohexanone are not ion paired,[12] we do not anticipate ion pairing with the anions derived

(6) Matsuo, H.; Kawozoe, Y.; Sato, M.; Ohrishi, M.; Taksuno, T. *Chem. Pharm. Bull.* **1967**, *15*, 391–398.
(7) Adolph, H. G.; Kamlet, M. J. *J. Am. Soc.* **1966**, *88*, 4761–4763.
(8) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
(9) The uncertainty introduced by the necessity to extrapolate the absorbance reading to $t = 0$ is compounded in this instance by the possibility that the absorbance drop may be caused in part by addition of the indicator anion, In^-, to the carbonyl group of the ester. In THF, *tert*-butyl acetate is known to be deprotonated by LDA to form *tert*-butyl lithioacetate, which has half-life of about 2 h at 28 °C.[10] Similar behavior is likely in Me_2SO since proton transfers are known to be rapid in this medium, but addition of In^- to the carbonyl group of ethyl benzoate is also very rapid.[11]
(10) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688–1690.
(11) Ungermann, T. S., unpublished results.
(12) Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.

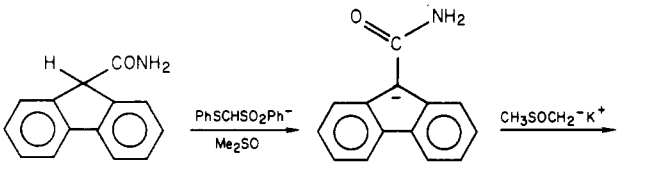
Table II. Comparison of CN, CO_2R, and $CONR_2$ Acidifying Effects in Various Carbon Acid Systems in Dimethyl Sulfoxide

acid	pK_a[a]	$\Delta pK_a(I)$[b]	$\Delta pK_a(II)$[c]
$PhCH_2CN$	21.9[d]		
$PhCH_2CO_2Et$	22.7	0.8	
$PhCH_2CONMe_2$	26.6		3.9
$PhSCH_2CN$	20.8[e]		
$PhSCH_2CO_2Et$	21.4	0.6	
$PhSCH_2CONMe_2$	25.9		4.5
$CNCH_2CO_2Et$	13.1[f]		
$CNCH_2CN$	11.1[d]	2.0	
$CNCH_2CON(CH_2)_4$	17.1		4.0
$PhCOCH_2CN$	10.2[g]		
$CH_3COCH_2CO_2Et$	14.1	3.9	
$CH_3COCH_2CONMe_2$	18.2		4.1
9-CN-FlH[h]	8.3		
9-CO_2Me-FlH[h]	10.35[d]	2.0	
9-$CONH_2$-FlH[h]	14.8		4.5
$[Me_3NCH_2CN]^+Cl^-$	20.6[g]		
$[Me_3NCH_2CO_2Et]^+Cl^-$	20.6	−0.6	
$[Me_3NCH_2CONEt_2]^+Cl^-$	24.9		4.9

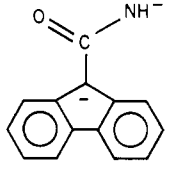
[a] This work (Table I) unless otherwise noted. [b] $\Delta pK_a(I) = pK_a(GCH_2CO_2R) - pK_a(GCH_2CN)$. [c] $pK_a(II) = pK_a(GCH_2CONR_2) - pK_a(GCH_2CO_2R)$. [d] Reference 8. [e] Reference 16. [f] R. Press, unpublished results. [g] Reference 23. [h] FlH = fluorene.

from $PhCH_2CO_2R$ or $PhCH_2CONR_2$. Ion pairing is slight for the enolate ion derived from $PhSCH_2COPh$, even in NMP,[13] so we do not expect ion pairing for the anions derived from $PhSCH_2CO_2R$ or $PhSCH_2CONR_2$ in Me_2SO.

The C–H acidity of 9-carbamoylfluorene (1) was determined without complication from concurrent ionization of the N–H site, which should have a pK_a about 9 units higher. The carbanion was generated in the presence of 1–2 equiv of the standard acid anion, $PhSCHSO_2Ph^-$ (pK_a = 20.34), to avoid possible dianion formation. The resulting visible spectrum of this slightly fluorescent, yellow-green anion (**2A**) displayed a peak at 423 nm and a



1 2A



3A

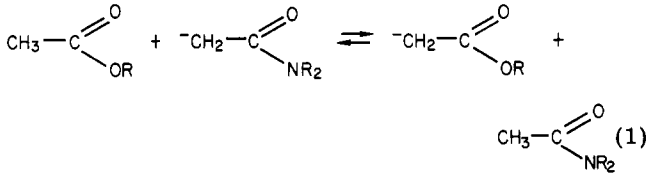
shoulder at 449 nm. Upon addition of excess $CH_3SOCH_2^-K^+$ to the cuvette, the spectrum changed drastically, suggesting formation of dianion **3A**, strong peaks developing at 515, 486, 452, and 425 nm.

Discussion

α-C–H Acidifying Effects of CO_2R, CN, and $CONR_2$ Functions. The data in Table I show that the acidity of GCH_2CO_2R esters depends to some extent on the nature of R. Thus, $CNCH_2CO_2Me$ is 0.3 pK_a unit more acidic than $PhCH_2CO_2$-*t*-Bu. This decrease in acidity of α-C–H with an increase in the size and/or branching in R is in line with greater inductive electron release and/or steric hindrance to solvation in the $GCHCO_2R$ anion.

Examination of Table II shows that esters, GCH_2CO_2R, with R = Me or Et, are less acidic than nitriles, GCH_2CN, by 0.6–1.0 pK_a units for G = Ph, PhS, or CN. (Effects with G = RCO, 9-fluorenyl, and Me_3N^+ will be discussed in a later section.) If a similar difference is assumed between the parent compounds, CH_3CO_2Et and CH_3CN, this would place the pK_a of ethyl acetate at about 32–33 (CH_3CN has a pK_a of 31.3 in Me_2SO). There is reason to believe, however, that substitution of G for a hydrogen atom will have a larger effect in CH_3CN than in CH_3CO_2Et because of the resonance saturation effect.[14] The size of the saturation effect will be determined by the relative charge densities on carbon in the $^-CH_2CN$ and $^-CH_2CO_2Et$ anions, which will be related to the extent of delocalization into the CN and CO_2Et functions. The Taft σ_I/σ_R ratio for CN is 0.56/0.33 = 1.7, as compared to 0.30/0.34 = 0.88 for CO_2R.[15] These numbers indicate resonance saturation will be much greater for CO_2Et than for CN, and that $COCH_3$, for which $\sigma_I/\sigma_R = 0.28/0.47 = 0.60$, is a better model than CN for extrapolations. The Ph and PhS acidifying effects on CH_3COCH_3 are 7.2 and 8.3 pK_a units, respectively.[16] Addition of these numbers to the pK_a values of $PhCH_2CO_2Et$ and $PhSCH_2CO_2Et$, respectively, gives 29.9 and 29.7 as an estimate of the pK_a of CH_3CO_2Et. We conclude that the pK_a of CH_3CO_2Et in Me_2SO is about 30–31.

Examination of Table II shows that carboxamides, GCH_2CONR_2, with G = Ph, PhS, or CN, are less acidic than the corresponding carboxylic esters by about 4 pK_a units in Me_2SO. This would place the pK_a of *N,N*-dimethylacetamide at about 34–35, which is in reasonable agreement with the pK_a of 35 for *N*-methylpyrrolidin-2-one (NMP) estimated by another method.[13] The data indicate that $\Delta G°$ for eq 1 is about −7 kcal/mol.



The position of eq 1 is determined by polar and/or resonance factors. The polar factor could be appreciable, judging from the large difference in σ_I values for OMe (0.27) and NMe_2 (0.06). Conjugative interactions in both the undissociated acids and in the anions could play a role but are difficult to evaluate. If the relative order and magnitude of resonance energies (RE) for CH_3CO_2R and CH_3CONR_2 remain the same in their conjugate bases, the position of eq 1 will not be affected by resonance. It seems likely that the relative RE's of the (less stable) anions will exert the controlling factor, but neither these nor the relative RE's of the undissociated acids have been firmly established. Data from heats of combustion indicate that RE's for amides and esters are comparable in size (16–18 for EtOAc; 16–17 for CH_3CONH_2), but the data are subject to many uncertainties.[17a] A similar conclusion has been

(13) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305–3313.

(14) Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391–2395. Algrim, D.; Bares, J. E.; Branca, J. C.; Bordwell, F. G. *Ibid.* **1978**, *43*, 5025–5026.

(15) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1–78.

(16) (a) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325. (b) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *Ibid.* **1977**, *42*, 326–332.

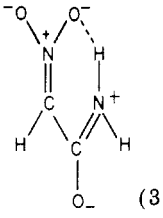
derived recently by relating ΔG_{deloc} to barriers of rotation.[17b] Application of Benson's group additivities[18] indicate that $\Delta G°$ for eq 2 favors the ester by 2.4 kcal/mol.

$$CH_3CONHCH_2CH_2OCH_3 \rightleftarrows CH_3CO_2CH_2CH_2NHCH_3 \quad (2)$$

A similar thermochemical analysis based on model compounds also indicates that the ester function has the larger RE by 2.4 kcal/mol.[19]

The equilibrium acidity order $PhCH_2CN$ > $PhCH_2CO_2Et$ > $PhCH_2CONMe_2$ in Me_2SO (Table II) is the same as that observed for the kinetic acidities in *t*-BuOH for PhCH(Me)CN, PhCH(Me)CO_2-*t*-Bu, and PhCH(Me)$CONEt_2$[4] and for the equilibrium acidities in water for $(NO_2)_2CHCN$, $(NO_2)_2CHCO_2Me$, and $(NO_2)_2CHCONH_2$.[5] The ΔpK_a(I) of 7 for $(NO_2)_2CHCN$ vs. $(NO_2)_2CHCO_2Me$[5] is, however, much larger than any recorded in Table II. (Compare, for example, the ΔpK_a(I) of 1.7 for $CNCH_2CN$ vs. $CNCH_2CO_2Me$.) Also, the ΔpK_a(II) for $(NO_2)_2CHCO_2Me$ vs. $(NO_2)_2CHCONH_2$ of 0.3 is much smaller than the average ΔpK_a(II) of 4.3 derived from the data in Table II. The latter is consistent with ΔpK_2(II) of −0.57 for $NO_2CH_2CO_2Et$ vs. $NO_2CH_2CONH_2$.[7] It seems likely that the relatively high acidity of $(NO_2)_2CHCN$ is associated with the high polarity and low steric demands of the CN group, and that the relatively high acidity of $(NO_2)_2CHCONH_2$ and $NO_2CH_2CONH_2$ is associated with intramolecular hydrogen bonding between $CONH_2$ and $=NO_2^-$. This hydrogen bonding, which is illustrated in eq 3, would amount to about 7 kcal/mol. These hydrogen bonding effects are, of course, absent in amides of the type GCH_2CONR_2.

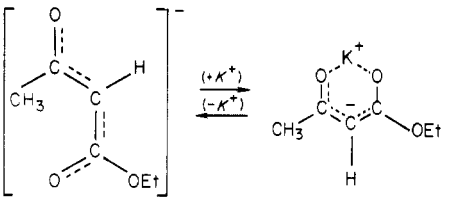
$NO_2CHCO_2Et^-$ + $NO_2CH_2CONH_2$ ⇌ $NO_2CH_2CO_2Et$ +



(3)

Acidities of GCH_2CO_2R, GCH_2CN, and GCH_2CONR_2, with G = RCO, 9-Fluorenyl, and Me_3N^+. The acidifying effects of RCO, fluorenyl, and Me_3N^+ groups are subject to steric and other factors to a much greater extent than is true for Ph, PhS, and CN groups. About 1 pK_a unit of the 3.9 unit greater acidity of $PhCOCH_2CN$ than $CH_3COCH_2CO_2Et$ is due to the inductive effect of Ph vs. CH_3. Ion pairing of the type shown in eq 4 tends to increase the apparent acidity of the ester, but the pK_a value has been corrected for this effect.[12]

The 2.0 pK_a unit greater acidity of 9-cyanofluorene (9-CN-FlH) relative to 9-CO_2Me-FlH is due, at least in part, to the lesser steric demands of the linear C≡N function. Steric inhibition of resonance in the carbanion must act to decrease the acidities of both 9-CO_2Me-FlH and 9-



4 (*E*,*Z*) 5 (*Z*,*Z*) (4)

$CONH_2$-FlH. These steric effects, together with the highly delocalized nature of the fluorenyl anion must serve to minimize the σ_R effects of the CO_2Me and $CONH_2$ functions in these molecules. The fact that ΔpK_a(II) is large in this instance (4.5) supports the conclusion that its size is dictated primarily by the difference in polar effects of OMe and NH_2.

The acidity data for $[Me_3NCH_2CO_2Et]^+$, $[Me_3NCH_2CN]^+$, and $[Me_3NCH_2CONEt_2]^+$ are less reliable than the other pK_a values because of instability of their conjugate bases (ylides). The ΔpK_a(I) and ΔpK_a(II) values obtained are, however, in reasonable agreement with the results obtained with other functions. We note that the acidifying effect of Me_3N^+, which is caused primarily, if not completely, by a polar effect (σ_I = 0.65 in Me_2SO[20]), is slightly greater than that of Ph, which operates principally by a resonance effect (σ_I = 0.10), and slightly greater than that of PhS where a polarizability effect may be dominant ($\sigma_I \simeq 0.30$). The effect of Me_3N^+ is smaller by about 10 pK_a units than that of CN, which has a slightly smaller polar effect (σ_I = 0.56). The large resonance effects of RCO and 9-fluorenyl also leads to much larger acidifying effects for these functions, relative to Me_3N^+.

Medium Effects on Nitrile, Ester, and Amide Acidities. Direct comparisons between acidities in H_2O and Me_2SO are available for malononitrile (pK_a = 11.1 in both H_2O and Me_2SO) and for diethyl malonate (pK_a = 13.3 in H_2O[1] and 16.4 in Me_2SO[12]). When corrected to an absolute scale by subtracting log (55/14) from ΔpK_a,[13] $CH_2(CN)_2$ is 0.6 pK_a unit less acidic in H_2O than in Me_2SO, and $CH_2(CO_2Et)_2$ is 2.5 pK_a units more acidic in H_2O. The latter is a minimum value since ion pairing in the $^-CH(CO_2Et)_2$ anion introduces a conformational effect. We conclude that acetonitrile is likely to be slightly less acidic in H_2O than in Me_2SO and that CH_2CO_2Et and CH_3CONMe_2 are likely to be about 3 pK_a units more acidic in H_2O. This places the pK_a values in H_2O at ~31.5 for CH_3CN, ~27–28 for CH_3CO_2Et, and ~31–32 for CH_3CONMe_2. These are from 2 to 7 pK_a units higher than those estimated earlier.[1]

In the gas-phase $CH_3CO_2CH_3$ is more acidic than CH_3CN by 1.1 kcal/mol, and $CH_3CO_2CH_3$ is more acidic than CH_3CONMe_2 by 2.5 kcal/mol.[21] (For the ester and amide the standard deviations for the measurements are ±4 kcal/mol.)

Experimental Section

Instruments and Analyses. ^1H nuclear magnetic resonance (NMR) spectra were measured on a Varian T60 or on a Hitachi Perkin-Elmer R20B instrument in deuteriochloroform solution (unless otherwise indicated) with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-5 or on a Beckman 283 spectrophotometer.

Analytical vapor-phase chromatography (VPC) was performed on a Hewlett-Packard FM5752A gas chromatograph equipped with a thermal-conductivity detector. Analyses were generally performed by using a 0.25 in. by 10 ft aluminum column packed with 3% Carbowax on acid-washed Chromasorb W (Varian Aerograph). Other columns used included a 0.25 in. by 9 ft column packed with 5% Carbowax on acid-washed Chromasorb W, a 0.25 in. by 10 ft column packed with 2% FFAP on acid-washed

(17) (a) Wheland, G. W. "Resonance in Organic Chemistry"; Wiley: New York, 1955; pp 98–110. (b) Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004–7013.
(18) Benson, S. W. "Thermochemical Kinetics", 2nd ed.; Wiley: New York, 1976.
(19) Liebman, J. F.; Greenberg, A. *Biophys. Chem.* **1974**, *1*, 222–226.
(20) Branca, J. C. Ph.D. Dissertation, Northwestern University, 1979.
(21) Bartmess, J. E.; McIver, R. T. In "Gas Phase Ion Chemistry"; Bowers, M. T., Ed; Academic Press: New York, 1979; Chapter 11.
(22) *Beilstein, 4th ed.* **1978**, *9*, 437.
(23) Bordwell, F. G.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883–1885.

Chromasorb W, and a 0.25 in. by 6 ft column of 10% SE-30 on acid-washed Chromasorb W.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Materials and Syntheses, General Data. All reagents were commercially available reagent grade chemicals unless otherwise noted. Purity of pK_a samples was ascertained by VPC, thin-layer chromatography (TLC; on Eastman Chromagram sheets No. 13181, silica gel with fluorescent indicator), HPLC, NMR, IR, and melting and boiling point, whenever applicable. Thick-layer chromatography was performed by Quantum Industries Quanta/Gram PQ6F or PQ5F plates.

Ethyl Phenylacetate. A commercial sample (Matheson Chemical Co.) was distilled under vacuum [75 °C (1.5 mm)] and found pure by VPC.

***N,N*-Dimethyl-α-phenylacetamide** was prepared from phenylacetyl chloride, and a crystallization from hexane was repeated until no further change in melting point was observed: white needles mp 38–40 °C (lit.[22] mp 43.5 °C); NMR δ 2.92 (6 H, s, $N(CH_3)_2$), 3.65 (2 H, s, $PhCH_2$), 7.15 (5 H, s, Ar).

Methyl Cyanoacetate. A commercial sample (Matheson Chemical Co.) was vacuum distilled [85 °C (~5.5 mm)] and found to be pure by VPC.

1-(Cyanoacetyl)pyrrolidine. A commercially available sample from Parish Chemical Co. was found to be pure enough for the pK_a measurement.

9-Carboxamidofluorene. A sample to 9-fluorenecarboxylic acid generously provided by Professor R. T. Arnold was converted to the amide by using thionyl chloride and a concentrated ammonium hydroxide solution. Multiple recrystallizations from absolute ethanol gave pure white needles: mp 255–256 °C (lit. mp 251 °C); NMR (Me_2SO-d_6) δ 4.54 (1 H, s), 6.9–7.7 (8 H, m).

***tert*-Butyl Acetate.** A commercially available sample (Matheson) was distilled through a 15-cm Vigreux column at atmospheric pressure: bp 95.5 °C; pure by VPC.

***N,N*-Dimethylacetylacetamide.** A commerical sample (Parish Chemical Co.) was vacuum distilled: bp 93 °C (3.8 mm); pure by VPC.

***tert*-Butyl phenylacetate** was prepared from phenylacetyl chloride and *tert*-butyl alcohol. Kugelrohr distillation [80 °C (1 mm)] gave the pure product [lit. bp 110 °C (15 mm)]: NMR δ 1.41 (9 H, s, $C(CH_3)_3$, 3.51 (2 H, s, $PhCH_2$), 7.28 and 7.35 (5 H, 2 s).

Ethyl (trimethylammonio)acetate (chloride salt) was prepared from chloroacetate and anhydrous trimethylamine in ethanol. The white solid was recrystallized twice from acetonitrile and dried under vacuum [100 °C (1.5 mm)] for 30 h: mp 151–153 °C; NMR (D_2O) δ 3.27 (9 H, s, $N(CH_3)_3$), 1.30 (3 H, t, CH_2CH_3), 4.22 (2 H, s, $Me_3NCH_2^+$), 4.21 (2 H, q, CH_2CH_3).

***N,N*-Dimethyl-α-(trimethylammonio)acetamide (chloride salt)** was prepared from chloroacetic acid, thionyl chloride, and diethylamine in benzene.

The oily amide was added directly to a solution of trimethylamine in absolute ethanol, and the solution was refluxed for 6 h, cooled to room temperature, and concentrated in vacuo to yield a brown water-soluble solid. Recrystallization of the product from ethyl acetate/ethanol followed by repeated trituration with hot ethyl acetate afforded a white, granular solid. The product dried in a drying pistol (100 °C, 36 h) under vacuum, melted at 214.5–16.0 °C (with evolution of gas): NMR (D_2O) δ 1.20 (2 t, 6 H), 3.24 (s, 2 H), 3.44 (s, 9 H), 3.44 (m, 4 H).

Ethyl phenylthioacetate and *N,N*-dimethylphenylthioacetamide were prepared by standard procedures from phenylthioacetic acid (Parish Chemical Co.).

Equilibrium acidity measurements were carried out by the method described earlier.[8,12] As pointed out by the referees, it is possible that addition to the carbonyl functions in these compounds may complicate the measurements. Addition of the 9-phenylxanthenyl carbanion to the carbonyl group of benzophenone or ethyl benzoate occurs rapidly, but the equilibrium concentration of adduct is low with the more weakly basic indicator anions that were used in the pK_a measurements reported in Table I.[11] For this reason, and because of the internal consistency of the results, we do not believe that carbonyl addition competes appreciably with the equilibrium deprotonation of esters or ketones in the pK_a range below 25.

Acknowledgment. We are grateful to the National Science Foundation for support of this investigation. We thank Timothy Ungermann for measurements of the acidities of $PhSCH_2CO_2Me$ and $PhSCH_2CONMe_2$ and acknowledge a generous gift of dimethyl sulfoxide from the Chemical Products Division of Crown Zellerbach.

Registry No. Phenylacetyl chloride, 103-80-0; 9-fluorenecarboxylic acid, 1989-33-9; *N,N*-diethylacetamide, 685-91-6; $[Me_3NCH_2CO_2Et]^+Cl^-$, 3032-11-9; $[Me_3NCH_2CONEt_2]^+Cl^-$, 69371-33-1; $PhCH_2CO_2$-*t*-Bu, 16537-09-0; $PhCH_2CO_2Et$, 101-97-3; $PhCH_2CONMe_2$, 18925-69-4; $PhSCH_2CO_2Me$, 17277-58-6; $PhSCH_2CONMe_2$, 78698-19-8; 9-$CONH_2$-FlH, 7471-95-6; $CH_3COCH_2CO_2Et$, 141-97-9; $CH_3COCH_2CONMe_2$, 2044-64-6; $CNCH_2CO_2Me$, 105-34-0; $CNCH_2CON(CH_2)_4$, 14227-95-3; $PhSCH_2CO_2Et$, 7605-25-6; 9-CO_2Me-FlH, 3002-30-0.

Deaminative Rearrangements of 1-Phenylthio- and 1-Oxy-Substituted Chrysanthemylamines

Christopher K. VanCantfort[1] and Robert M. Coates*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received March 19, 1981

Metalation of chrysanthemic nitrile **1** with lithium diisopropylamide followed by sulfenylation with diphenyl disulfide or oxygenation with a molybdenum peroxide complex gave chrysanthemic nitrile derivatives bearing phenylthio (**3** and **4**) or hydroxyl (**6**) substituents at C-1. These compounds provided access to the following series of 1-substitued chrysanthemylamines: 1-(phenylthio)chrysanthemylamine (**5**), 1-methoxychrysanthemylamine (**8**), 1-methoxydihydrochrysanthemylamine (**10**), and the *N*-nitrosooxazolidinone (**13**) derived from 1-hydroxychrysanthemylamine (**11**). Nitrous acid deamination of **5** and **8** and hydrolytic deamination of **13** gave acyclic alcohols (**14**, **17**, and **18**) related in structure to yomogi alcohol as major products by cleavage of the 1–3 cyclopropane ring bond. Products formed by cleavage of the 1–2 cyclopropane ring bond (**15** and **24**) and related in structure to santolinatriene were obtained in lesser amounts from the deamination of **5** and **13**. Pinacol-type ring expansion to the isomeric cyclobutanones **19** and **20** was observed as a minor reaction pathway in the deaminations of **8** and **13**. In contrast, deamination of **10** gave dihydrocyclobutanones **21** and **22** as the major isolated products.

The heterolytic reactions of chrysanthemol derivatives have been studied extensively in recent years as a model reaction for the biogenesis of acyclic terpenoids and as an interesting substrate for investigation of cyclopropyl car-

0022-3263/81/1946-4331$01.25/0