on solutions sufficiently acidic to give limiting slow-exchange NMR spectra, and this was then applied directly to the less concentrated solutions. The natural line width, on the other hand, can be expected to vary with acid concentration through its dependence on the viscosity of the medium, which changes appreciably over the range of acidities used. A relationship between natural line width, W, and viscosity, η, of the form $W = a + b\eta/T$,[12] where T is absolute temperature, and a and b are constants, was therefore set up using data (line widths) measured over a range of temperature and viscosity in solutions giving limiting fast and slow-exchange NMR spectra. This expression, $W = (0.35 \pm 0.03) + (34 \pm 2)\eta/T$, was then used to calculate values of W appropriate to the solutions used for the kinetic measurements. Viscosities were interpolated for this purpose by fitting literature data[13] to a polynomial expression in wt % acid and then using this function to calculate the required values.

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(1) This research was supported by the National Science Foundation through Grant No. GP-36004X.
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Extension of the H_A Acidity Function into Oleum Mixtures[1]

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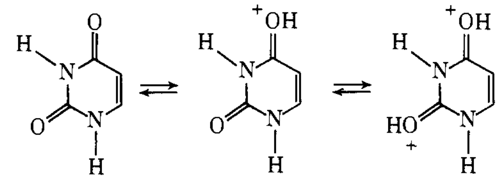
Abstract: The H_A acidity function has been extended from 93% aqueous sulfuric acid to 17% fuming sulfuric acid using weakly basic pyrimidine monocations as indicators. Ionization ratios were determined from ^1H NMR chemical shifts at 25°. The H_A and H_0 acidity functions are briefly compared. The effects of methyl substitution at nitrogen and oxygen are discussed.

Compounds containing $-C(=O)N<$ functional groups (amides, ureas, pyrimidines, purines, etc.) constitute several classes of biologically important compounds. Yates and coworkers[3] developed the amide acidity function, H_A, in order to relate basicities of amide moieties in aqueous sulfuric acid. It was later found that other functional groups follow H_A during protonation. Included are the first protonation of some 2,4-dioxopyrimidines,[4] urea[5] (at the oxygen atom), and N-oxides.[6] In fact, the latter class of compounds has been used to extend H_A from 80 to 93% H_2SO_4.[6] Although amides and N-oxides are quite different structurally, they apparently form a valid set of H_A indicators when judged by the criterion that the ratio of activity coefficients is unity $(\gamma_{NO}\gamma_{HA^+}/\gamma_{NOH^+}\gamma_A)$ in the region of overlap.

In connection with our work on the protonation of uracil and related derivatives, it became necessary to extend H_A into the oleum region. In general, 2,4-dioxopyrimidines protonate sequentially at the 4-oxo and 2-oxo moieties.[7,8] The strength of the acid required for the first protonation can vary considerably, depending on substitution,[4] and the second protonation requires an acid stronger than 90% H_2SO_4. The only acidity function, H_0, which has been extended far beyond 90% H_2SO_4[9] is unsatisfactory for 2,4-dioxopyrimidines.



In searching for a series of indicators with which to extend H_A, the second protonation of 2,4-dioxopyrimidines appeared to be a feasible choice. Both oxo groups are "urea-like" and should be weakly basic since the pyrimidine is already charged as a result of the first protonation. In this paper, we report an extension of the H_A acidity function from 93% H_2SO_4 to 17% (by weight) fuming H_2SO_4. The five pyrimidines used in this study form a valid set of indicators when judged by normal overlap behavior. Although there is always concern when different functional groups are used to construct an acidity function, the overlap of indicators whose structures involve amides, N-oxides, and monoprotonated pyrimidines appears to be satisfactory. Our results for H_A are compared with those recently obtained for H_0 by Gillespie and coworkers.[9]

Experimental Section

Indicators. Uracil and thymine are commercially available from Aldrich and were used without further purification. 2-Methoxy-4-oxopyrimidine,[10] 4-methoxy-2-oxopyrimidine,[11] and 1,3-dimethyluracil[12] were available from a previous study.[13] The ^1H NMR spectra of the pyrimidines were similar to published spectra.[10]

Acid Solutions. The 9.5–96 wt % solutions were prepared by dilution of Baker Analyzed Reagent Grade sulfuric acid (~96%). Concentrations of H_2SO_4 (±0.2%) were calculated by averaging the values derived from 4 to 5 density measurements. For acids stronger than 50 wt % H_2SO_4, the samples for density measurements were diluted by a known amount (approximately 50 wt % H_2SO_4) before the density determinations were made. The weight percent of H_2SO_4 was determined from the density–composition data in the International Critical Tables.[14]

Solutions of 96 wt % H_2SO_4 to 17 wt % fuming H_2SO_4 were

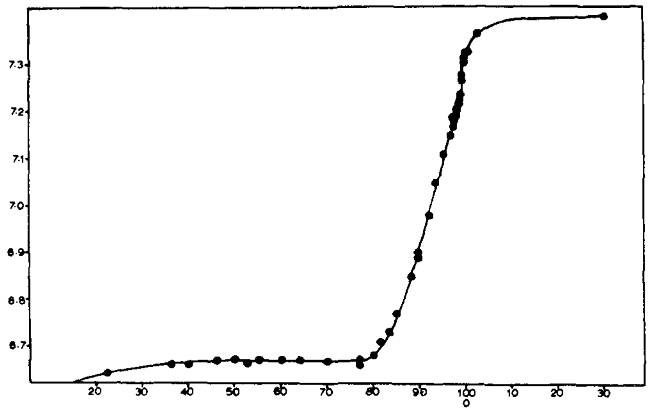


Figure 1. NMR titration curve of 2-methoxy-4-oxopyrimidine [y axis, δ H_5 (ppm); (0-100) x axis, wt % H_2SO_4; 0-20 right part of x axis, wt % SO_3].

prepared by mixing Baker Analyzed Grade (~ 96%) and 15-18% fuming H_2SO_4. Between 96 and 98.1% H_2SO_4, the acid concentrations were determined by freezing weighed portions in a Dry Ice-acetone bath and diluting with weighed amounts of distilled water to ~50 wt % aqueous H_2SO_4. Concentrations of the diluted samples were determined by density measurements as previously described. Maximum deviations were ±0.2%. The method was checked by sodium hydroxide titration of 96.7% H_2SO_4.

Between 97.4% aqueous H_2SO_4 and 17.2% fuming H_2SO_4, the dilution technique was unreliable. As a result, NMR titrations similar to those described later for our indicators were used to determine acid concentrations in this region. The ionization ratios obtained for 0.05 *M* solutions of *p*-nitrotoluene and *p*-nitrochlorobenzene were compared with those obtained by uv techniques.[9] The concentrations of solutions between 97.4 and 98.1% H_2SO_4 were in agreement with the values obtained by density measurements. The concentration of 100% H_2SO_4 was checked by uv spectroscopy. This measurement showed that 0.05 *M* solutions were sufficiently dilute to permit NMR determination of acid concentration within ±0.1%. The concentrations of SO_3 in fuming H_2SO_4 could be in error as much as ±1.5% SO_3 as a result of small solvent effects on the NMR chemical shifts. Precautions described later for NMR sample preparation for indicators were used to prevent dilution by atmospheric moisture.

All prepared acid solutions including commercial 30-33% fuming H_2SO_4 were stored in glass-stoppered acid bottles which were sealed with Parafilm. The acid concentrations were periodically checked by titration with standard sodium hydroxide or the NMR titration method.

NMR Spectra. Spectra of pyrimidine indicators were taken at 25 ± 1° with a Varian A-60 NMR spectrometer equipped with a variable-temperature probe. Samples were 0.1 *M* in the indicator and 0.02 *M* in tetramethylammonium chloride.[15] Immediately before each spectrum was taken, acid was pipetted from the storage bottles to dry NMR tubes which contained the indicator and internal standard. The NMR tubes were sealed with air-tight caps. Contamination by moisture was shown not to be a factor since different samples of the same indicator in the acid of the same concentration prepared on different days gave identical chemical shifts. Tetramethylammonium chloride used as an internal standard was heated at 110° under reduced pressure until dry and was stored in a stoppered bottle which was stored in a desiccator over Drierite.

Chemical Shifts. A permanently degassed sample containing 2 *M* ^1H concentrations of chloroform, methylene chloride, *p*-dioxane, cyclohexane, and tetramethylsilane in CCl_4 was used to calibrate chemical shifts prior to each run. Studies of chemical shift as a function of indicator concentration showed no appreciable effect before, during, or after protonation at lower acid strengths. At 0.1 *M* indicator, the shifts are within 0.01 ppm of the value at infinite dilution. Between 99.4% H_2SO_4 and 3% fuming sulfuric acid, errors of up to 0.08 ppm were found for 0.1 *M* uracil relative to infinite dilution. However, in this region, H_A is changing very rapidly as a function of acid concentration, and the uncertainty in concentration introduces a larger error than the uncorrected chemical shift at 0.1 *M* indicator.

Calculation of Ionization Ratios. The logarithms of the ionization ratios for the second protonation of 2-methoxy-4-oxopyrimidine, thymine, uracil, 4-methoxy-2-oxopyrimidine, and 1,3-dimethyluracil were calculated from ^1H NMR chemical shifts. The mole fraction of diprotonated indicator, $X_{\mathrm{IH_2}^{++}}$, was calculated according to eq 1, where δ_+ represents the ^1H shift of a particular

$$X_{\mathrm{IH_2}^{++}} = \frac{\delta_i - \delta_+}{\delta_{++} - \delta_+} \tag{1}$$

proton in monoprotonated indicator, δ_{++} is the measured shift in diprotonated indicator, and δ_i is the measured shift at a given acid concentration. The mole fraction of monoprotonated indicator is given by eq 2. The logarithm of ionization ratios, log *I*, was then

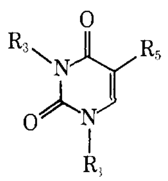
$$X_{\mathrm{IH}^+} = 1 - X_{\mathrm{IH_2}^{++}} \tag{2}$$

calculated from mole fraction data as shown in eq 3.

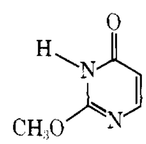
$$\log I = \log \left(X_{\mathrm{IH_2}^{++}}/X_{\mathrm{IH}^+}\right) \tag{3}$$

Results and Discussion

The indicators used in this study, in order of decreasing basicity, were the monocations of 2-methoxy-4-oxopyrimidine (**2**), thymine (**1b**), 4-methoxy-2-oxopyrimidine (**3**), uracil (**1a**), and 1,3-dimethyluracil (**1c**). Ionization ratios for the second protonation of all five indicators were determined at 25° using ^1H chemical shifts.[16] All proton peaks for which chemical shifts could be determined accurately (±0.5 Hz) and which showed small solvent effects (±2 Hz) relative to chemical shift differences between mono- and dications were used. ^1H chemical shifts of "pure" mono- and dications were determined from plots of chemical shift vs. acid concentration, as illustrated for H_5 of 2-methoxy-4-oxopyrimidine in Figure 1. Values for δ_+ and δ_{++} for the five indicators are listed in Table I.



1a, $R_1 = R_3 = R_5 = H$
b, $R_1 = R_3 = H$; $R_5 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_5 = H$



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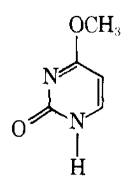


3

The structures of the mono- and dications can be deduced from their pK_a's and NMR and uv spectra. Both methoxy derivatives add a proton to the basic, imidate nitrogens in dilute aqueous sulfuric acid. The monocations of uracil, 1,3-dimethyluracil, thymine, and 4-methoxy-2-oxopyrimidine all have similar uv[4,17] and NMR[18] spectra. Also, the pK_a's for the second protonation of uracil and 4-methoxy-2-oxopyrimidine are identical (see below). Thus, our 2,4-dioxo indicators are mostly monoprotonated at O_4. NMR spectra of the dications of the indicators have been obtained in both H_2O-H_2SO_4-SO_3 and HSO_3F-SbF_5.[7] In the latter solvent, structure determination is facilitated since proton exchange between solute and solvent is sufficiently slow to permit observation of the entire ^1H spectra of the pyrimidine dications. It is obvious from chemical shift and coupling constant comparisons that the second proton is added to the remaining oxo moiety in each of our indicators in H_2O-H_2SO_4-SO_3. Values for the logarithms of the ionization ratios, log *I*, for all of the indicators are presented in Table II. Small differences were seen for log *I*'s evaluated from chemical shifts of different protons in the same molecule, presumably as the result of small solvent effects superimposed on the chemical shift changes which accompany protonation. However, this source of error was not significant during a control experiment in which the NMR titration method was used to reproduce

Table I. Chemical Shifts for Mono- and Diprotonated Indicators[a]

Indicator	Proton observed	δ_+, ppm	δ_{++}, ppm $H_2O-H_2SO_4-SO_3$	δ_{++}, ppm HSO_3F-SbF_5[b]
2-Methoxy-4-oxopyrimidine	H_5	6.67	7.41	7.51
	H_6	7.99[c]	8.64	8.83
Thymine	$-CH_3$	2.22	2.46	
	H_6	7.99	8.45	
Uracil	H_5	6.64	7.33	7.55
	H_6	8.21	8.6[d]	8.81
4-Methoxy-2-oxopyrimidine	H_5	6.66	7.43	7.60
	H_6	8.38	8,7[d]	7.88
1,3-Dimethyluracil	H_5	6.64	7.33	7.53
	H_6	8.15	8.54	8.73
	$1-CH_3$	3.70	4.12	
	$3-CH_3$	3.64	4.06	

[a] Relative to tetramethylsilane with internal tetramethylammonium chloride as a secondary standard (see Experimental Section). [b] Reference 7. [c] In 77.1% $H_2O-H_2SO_4$, subject to solvent shift, 8.12 ppm in 29.9% $H_2O-H_2SO_4$. [d] Broadened due to exchange of the proton at N_1 with solvent.

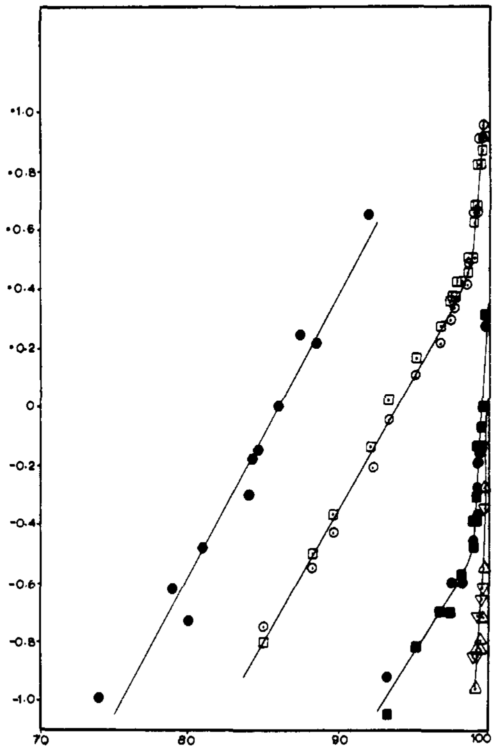


Figure 2. Ionization curves in aqueous sulfuric acid (y axis, log I; x axis, wt % H_2SO_4) for (●) phenazine-5,10-dioxide[6]; (⊡) 2-methoxy-4-oxopyrimidine (based on δ H_5); (⊙) 2-methoxy-4-oxopyrimidine (based on δ H_6); (■) thymine (based on δ CH_3); (●) thymine (based on δ H_6); (△) uracil (based on δ H_5); (▽) 4-methoxy-2-oxopyrimidine (based on δ H_5).

ionization ratios that were also obtained by uv measurements for p-nitrotoluene.[19] Apparently 0.05–0.1 M solutions are sufficiently dilute for measuring ionization ratios in the range we studied.

pK_a's determined by the overlap technique of Hammett and Deyrup using eq 4[20] are shown in Table III. Only

$$\log I_2 - \log I_t = pK_{a2} - pK_{at} = \Delta pK_a \qquad (4)$$

values of log I between +1.2 and −1.2 were used for overlap calculations. Log I and pK_a (−5.12) values for the second protonation of phenazine 5,10-dioxide[6] served to link our indicators to more basic systems. Log I values for our indicators were obtained from curves such as those illustrated in Figure 2.[21] A simplified weighting scheme employed by Gillespie and coworkers[9] was used to obtain values for ΔpK_a.

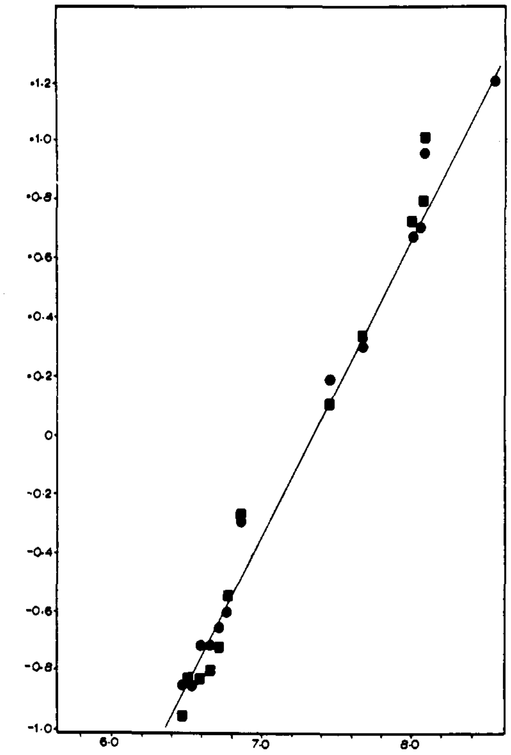


Figure 3. Ionization ratio vs. H_A for the uracil (■) and 4-methoxy-2-oxopyrimidine (●) indicators (y axis, log I; x axis, $-H_A$).

Values for H_A were calculated from pK_a and log I data using eq 5 (see Table IV). In those regions where indicators

$$H_A = pK_a - \log I \qquad (5)$$

overlap, an average value is given. The major source of error results from uncertainties in chemical shifts using solutions of 0.05–0.1 M indicators relative to infinite dilution, especially from 99 to 100% H_2SO_4. A systematic error of ca. 0.1 H_A unit may have been introduced at this point. The precision of NMR "titrations" appears to be acceptable. Figure 3 shows a plot of log I vs. H_A for uracil and 4-methoxy-2-oxopyrimidine which spans the region from 98.4% H_2SO_4 to 7% $SO_3-H_2SO_4$ where precision is most difficult to obtain. The maximum deviation of any point from the least-squares line is 0.2 H_A units, and the standard deviation is 0.1.

The method of Katritzky and coworkers[22] was used to test the validity of our indicators. According to eq 6, a plot

$$\log I_i = a_{i,i\text{-t}} \log I_{i\text{-t}} + pK_{a_{i\text{-t}}} - pK_{a_i} \qquad (6)$$

Table II. Log I in $H_2O-H_2SO_4-SO_3$

2-Methoxy-4-oxopyrimidine Wt % H_2SO_4	Log I (based on H_5 chemical shifts)	Log I (based on H_6 chemical shifts)	Thymine Wt %	Log I (based on CH_3 chemical shifts)	Log I (based on H_6 chemical shifts)
			H_2SO_4		
85.0	−0.75	−0.80	93.3	−1.05	−0.92
88.2	−0.55	−0.50	95.1	−0.82	−0.82
89.6	−0.43	−0.37	96.7	−0.70	−0.70
92.2	−0.21	−0.14	97.4	−0.70	−0.60
93.3	−0.05	+0.02	98.1	−0.57	−0.60
95.1	+0.10	+0.16	98.9	−0.48	−0.46
96.7	+0.21	+0.27	99.0	−0.39	−0.39
97.4	+0.29	+0.35	99.1	−0.39	−0.37
97.6	+0.33	+0.37	99.2	−0.31	−0.28
97.8	+0.37	+0.42	99.3	−0.14	−0.19
98.1	+0.39	+0.42	99.4	−0.14	−0.16
98.5	+0.41	+0.45	99.5	−0.07	−0.13
98.6	+0.48	+0.50	99.6	0	0
98.9	+0.50	+0.50	99.7	+0.31	+0.27
99.0	+0.66	+0.62			
99.1	+0.68	+0.68	SO_3		
99.2	+0.66	+0.68	0.4	+0.48	+0.41
99.3	+0.91	+0.82	1.0	+0.69	+0.61
99.4	+0.91	+0.82			
99.5	+0.91	+0.82			
99.6	+1.00	+0.91			

Uracil Wt %	Log I (based on H_5 chemical shifts)	4-Methoxy-2-oxopyrimidine Wt %	Log I (based on H_5 chemical shifts)
H_2SO_4		H_2SO_4	
99.1	−0.96	99.1	−0.85
99.2	−0.83	99.2	−0.85
99.3	−0.83	99.3	−0.72
99.4	−0.80	99.4	−0.72
99.5	−0.72	99.5	−0.66
99.6	−0.55	99.6	−0.62
99.7	−0.28	99.7	−0.30
SO_3		SO_3	
0.4	+0.10	0.4	+0.18
1.0	+0.33	1.0	+0.29
2.9	+0.72	2.9	+0.66
3.4	+0.79	3.4	+0.69
3.7	+1.00	3.7	+0.95
10.5	+1.19	10.5	+1.19

1,3-Dimethyluracil Wt % SO_3	Log I (based on H_5 chemical shifts)	Log I (based on H_6 chemical shifts)	Log I (based on 1-CH_3 chemical shifts)	Log I (based on 3-CH_3 chemical shifts)
1.0	−0.63	−0.53	−0.50	−0.53
2.9	−0.39	−0.31	−0.34	−0.35
3.4	−0.37	−0.35	−0.31	−0.35
3.7	−0.25	−0.19	−0.21	−0.19
10.5	+0.21	+0.21	+0.25	+0.21
17.2	+0.69	+0.60	+0.63	+0.60

of log I_i vs. log I_{i-1} should ideally give values of unity for $a_{i,i-1}$'s of successive indicators. Values of $a_{i,i-1}$ for our indicators and phenazine-5,10-dioxide which were obtained by a least-squares fit are shown in Table V. All of the $a_{i,i-1}$'s are within acceptable limits (0.88–0.96), although the product of successive $a_{i,i-1}$'s, $\Pi_{a_{i,i-1}}$, shows a 26% reduction from phenazine-5,10-dioxide to 1,3-dimethyluracil over the H_A range of 90% H_2SO_4 to 17% $SO_3-H_2SO_4$.

In Figure 4, the H_A and H_0 acidity scales are compared for H_2SO_4 solutions into the oleum region. Beginning at 20% $H_2SO_4-H_2O$, the acidity functions diverge to a final separation of 4.5 units at 17% $SO_3-H_2SO_4$.[23] Both H_A and H_0 rise steeply near 100% H_2SO_4. Gillespie and coworkers[9] have discussed factors which contribute to the jump in H_0, a similar phenomenon is presumably responsible in both cases. Yates and coworkers[26] have commented on the linear

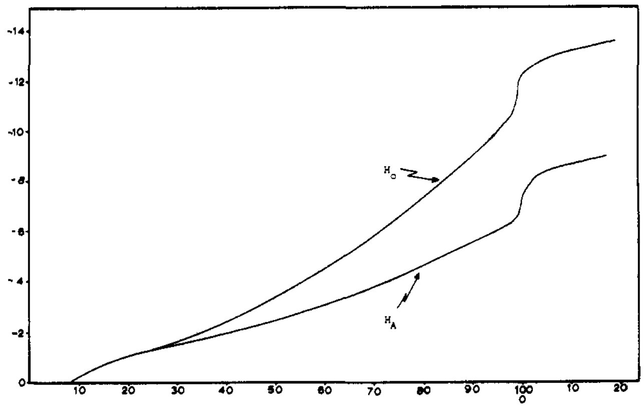


Figure 4. Comparison of the H_0 and H_A acidity functions into fuming H_2SO_4 [y axis, H; (0–100) x axis, wt % H_2SO_4; (0–20 to right) x axis, wt % SO_3].

Table III. pK_a Values for the Second Protonation of the Indicator Bases

Indicator	pK_a
2-Methoxy-4-oxopyrimidine	-5.8_4
Thymine	-6.8_2
Uracil	-7.3_2
4-Methoxy-2-oxopyrimidine	-7.3_2
1,3-Dimethyluracil	-8.3_6

Table IV. H_A Values for $H_2O-H_2SO_4-SO_3$

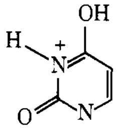
% H_2SO_4	H_A	% SO_3	H_A
85.0	−5.03	0.5	−7.39
86.0	−5.12	1.0	−7.63
87.0	−5.21	2.0	−7.92
88.0	−5.31	3.0	−8.13
89.0	−5.40	4.0	−8.20
90.0	−5.49	5.0	−8.26
91.0	−5.58	7.0	−8.36
92.0	−5.68	10.0	−8.52
93.0	−5.78	13.0	−8.67
94.0	−5.88	17.0	−8.97
95.0	−5.97		
96.0	−6.05		
97.0	−6.13		
98.0	−6.23		
98.5	−6.28		
99.0	−6.43		
99.1	−6.47		
99.2	−6.52		
99.3	−6.59		
99.4	−6.65		
99.5	−6.71		
99.6	−6.78		
99.7	−6.86		
99.8	−6.95		
100.0	−7.24		

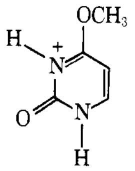
Table V. Test for Parallel Indicator Behavior

Indicators (i − 1→i)	$a_{i,i-1}$	$\Pi_{a_{i,i-1}}$
Phenazine 5,10-dioxide[a]–2-methoxy-4-oxopyrimidine	0.94	
2-Methoxy-4-oxopyrimidine–thymine	0.96	0.90
Thymine–uracil (or 4-methoxy-2-oxopyrimidine)	0.93	0.84
Uracil (or 4-methoxy-2-oxopyrimidine)–1,3-dimethyluracil	0.88	0.74

[a] Reference 4.

correlation between H_0 and H_A in aqueous sulfuric acid. We found excellent linearity between 35 and 98.6% H_2O–H_2SO_4, $dH_0/dH_A = 1.82$ (correlation coefficient 0.999). However, between 99.8 and 100% H_2SO_4, a discontinuity occurs and from 0.3 to 15% H_2SO_4–SO_3, $dH_0/dH_A = 0.84$ (correlation coefficient 0.989). Thus, while H_0 decreases more rapidly than H_A with increasing acidity in aqueous sulfuric acid, the situation is reversed in H_2SO_4–SO_3 mixtures. The transition from H_2O–H_2SO_4 to H_2SO_4–SO_3 must be accompanied by a sizeable perturbation in the relative values of activity coefficients of the indicators used to evaluate H_A and H_0.





Surprisingly, uracil and 4-methoxy-2-oxopyrimidine can be treated as a single indicator (see Figure 3), suggesting that the net difference in stabilization by a methyl substituent at O_4 relative to hydrogen must be negligible. Recently, similar conclusions have been reached with respect to stabilization of methyl vs. hydrogen for protonated *p*-methylanisole and *p*-cresol.[27] The phenomenon may be more general than we anticipated. On the other hand, a methyl group at nitrogen appears to afford a small degree of electronic stabilization, in that during monoprotonation, the 4-oxo group of 1,3-dimethyl ($pK_a = -2.63$)[17,28] is slightly more basic than that of uracil ($pK_a = -2.98$).[4,17,28] However, upon addition of a second proton to the 2-oxo position, the order is reversed, uracil ($pK_a = -7.32$) and 1,3-dimethyluracil ($pK_a = -8.36$). We attribute this to steric hindrance by the methyls at N_1 and N_2 of 1,3-dimethyluracil.

In summary, H_A has been extended into H_2SO_4-SO_3 solvents. The NMR "titration" technique is apparently practical for measuring ionization ratios, even though 0.05–0.1 *M* solutions are required for CW-NMR spectra. The method is advantageous for compounds with several observable nuclei since solvent effects can be minimized by multiple, independent measurements of ionization ratios from a single sample. Increased availability of FT-NMR will allow use of more dilute solutions.

References and Notes

(1) Acknowledgment is made to the American Cancer Society and the Public Health Service, RR07092, for support of this research.
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