Acidic Dissociation Constants of Thiols

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The acidic dissociation constants of a number of thiols have been determined and collated with those already recorded in the literature.

THIOLS are more acidic by several orders of magnitude than the corresponding alcohols. The acidities of individual thiols vary from those which are comparable with phenol ($pK_a \sim 10$) to those which are comparable with the carboxylic acids. The earlier determinations of pK_a values were made by electrometric titrations (*8, 20*). In 1953, Noda, Kuby, and Lardy (*18*) observed that the butanethiolate ion has an ϵ_{240} of $5.4(10^3)$ while butanethiol is optically void at that wave length. In 1955–6 Benesch and Benesch (*1*), DeDeken *et al.* (*5*), and Gorin (*10*), following this lead, introduced a spectrophotometric method based on the fact that thiolate anions absorb much more strongly in the ultraviolet than do the corresponding thiols: the pK_a could be determined by a plot of absorbance *vs.* pH. The Benesches immediately took advantage of this method to resolve the long-standing riddle of the assignment of the three pK_a's of cysteine. Subsequent papers have supplemented their original interpretation (*6, 7, 11, 22, 23*).

While quantitative values for pK_a's of thiols are important in correlating and interpreting the data of reactions in organic chemistry and biochemistry, no compilation of such values has yet been published. Moreover, because of differences in environmental variables (particularly solvent composition and temperature), it is frequently difficult to correlate values for different thiols scattered throughout the literature. In some cases, reported values have impaired usefulness because essential information as to temperature and/or solvent composition has been omitted.

The authors have now reviewed critically the pK_a values for thiols reported in the literature, in some cases they have redetermined them, and in a number of cases, values are being reported for the first time. The procedures, both spectrophotometric and electrometric, employed have already been described (*3*). Values in the literature, for which one or more critical specifications are missing, are not included (Table I) unless the value is the only one ever reported for a given compound. In these cases, attention is called to the lack of specification. When independently concordant values are available they are listed, while one or more discrepant values (differing by more

Table I. Acidic Dissociation Constants of Thiols

Compound	pK_a	Solvent	Temp., °C.	Technique[a]	Reference
1-Octanethiol	11.72	23.0% aq. *tert*-BuOH	25	ET	(*8*)
1-Butanethiol	11.51	23.0% aq. *tert*-BuOH	25	ET	(*8*)
2-Methyl-2-butanethiol	11.35	H_2O	25	UV	(*15*)
2-Methyl-2-propanethiol	11.22	H_2O	25	UV (245)	(*14*)
	11.05	H_2O	25	UV (?)	(*15*)
	11.14	H_2O	20	ET	(*24*)
2-Propanethiol	10.86	H_2O	25	UV (240)	(*14*)
Ethanethiol	10.61	H_2O	25	UV (240)	(*14*)
	10.50	H_2O	20	UV (235–250)	(*3*)
	10.64	H_2O	20	ET	(*24*)
3-Mercaptopropionic acid	10.27	H_2O	20	ET	(*3*)
	10.20	H_2O	20	UV (235–250)	(*3*)
	10.05	H_2O	30	ET	(*9*)
	10.03	H_2O	30	UV (235–250)	(*3*)
	9.85	H_2O	40	UV (235–250)	(*3*)
Mercaptoacetic acid	10.40	H_2O	20	UV (235–250)	(*3*)
	10.32	H_2O	24.5	UV (230–238)	(*1*)
	10.22	H_2O	25	ET	(*17*)
	10.22	H_2O	30	UV (235–250)	(*3*)
	10.20	H_2O	30	ET	(*9*)
	10.05	H_2O	40	UV (235–250)	(*3*)
	10.56	H_2O	25	ET	(*23*)
	9.74	H_2O	60	ET	(*17*)
N-Acetyl-β-mercaptoisoleucine	10.30	H_2O	30	ET	(*9*)
N-Acetyl-2-mercaptoethylamine	9.92	H_2O	25	UV (235)	(*14*)

(*Continued*)

Table I. Dissociation Constants of Thiols (*Continued*)

Compound	pK_a	Solvent	Temp., °C.	Technique[a]	Reference
N-Acetylpenicillamine	9.90	H_2O	30	ET	(*9*)
2-Mercapto-2-methyl-1-propanol	9.85	H_2O	25	ET	(*15*)
2-Mercaptoethanol	9.72	H_2O	25	UV (235)	(*14*)
	9.58	H_2O	20	ET	(*3*)
	9.43	H_2O	25	ET	(*16*)
	9.48	H_2O	20	UV (235–250)	(*3*)
	9.32	H_2O	30	UV (235–250)	(*3*)
	9.17	H_2O	40	UV (235–250)	(*3*)
N-Acetylcysteine	9.52	H_2O	30	ET	(*9*)
1-Thio-D-sorbitol	9.50	H_2O	20	UV (235–250)	(*3*)
	9.35	H_2O	30	UV (235–250)	(*3*)
	9.20	H_2O	40	UV (235–250)	(*3*)
1-Thioglycerol	9.51	H_2O	25	ET	(*16*)
Ethyl 3-mercaptopropionate	9.48	H_2O	25	ET	(*15*)
2-Ethoxyethanethiol	9.38	H_2O	25	ET	(*16*)
α-Toluenethiol	9.4	H_2O	25	UV (?)	(*16*)
2-Mercaptoethanesulfonic acid	9.08	H_2O	20	UV (235–250)	(*3*)
1,4-Dithioerythritol	9.0 (pK_{a_1})	H_2O	?	ET	(*25*)
	9.9 (pK_{a_2})	H_2O	?	ET	(*25*)
2-Mercaptobenzoic acid	8.88	H_2O	25	UV (270)	(*14*)
	8.20	H_2O	27	UV (270)	[b]
	8.40	H_2O	25	ET	(*19*)
	10.69	48.9% aq. EtOH	20–2	ET	(*20*)
1,4-Dithiothreitol	8.3(pK_{a_2})	H_2O	?	ET	(*25*)
	9.5(pK_{a_1})	H_2O	?	ET	(*25*)
2-Pyridylmethanethiol	8.82	H_2O	25	ET	(*15*)
D,L-Homocysteine	8.70	H_2O	30	ET	(*9*)
3-Mercaptopropionitrile	8.6	H_2O	?	ET	(*13*)
Glutathione	8.56	H_2O	30	ET	(*9*)
L-Cysteine	8.53	H_2O	23	UV (230–238)	(*1*)
	8.30	H_2O	25	ET	(*12*)
	8.32	H_2O	20	UV (235–250)	(*3*)
	8.39	H_2O	25	ET	(*23*)
2-Mercaptoethylamine	8.35	H_2O	20	UV (235–250)	(*3*)
	8.35	H_2O	23	UV (230–238)	(*1*)
	8.23	H_2O	25	UV (235)	(*14*)
	8.20	H_2O	30	UV (235–250)	(*3*)
	8.05	H_2O	40	UV (235–250)	(*3*)
4-Mercaptophenol	8.33	48.9% aq. EtOH	20–2	ET	(*20*)
	10.02	95% aq. EtOH	20–2	ET	(*20*)
Mercaptoacetamide	8.2	H_2O	?	ET	(*13*)
N-Ethylmercaptoacetamide	8.14	H_2O	?	ET	(*13*)
β-Mercaptoisoleucine	8.10	H_2O	30	ET	(*9*)
4-Methoxythiophenol	8.08	48.9% aq. EtOH	20–2	ET	(*20*)
	9.76	95% aq. EtOH	20–2	ET	(*20*)
	8.8	MeOH	?	ET	(*4*)
N-Methylmercaptoacetamide	8.05	H_2O	?	ET	(*13*)
Ethyl mercaptoacetate	7.95	H_2O	25	ET	(*16*)
	7.93	H_2O	25	UV (?)	(*16*)
2-Mercaptoethyl methyl sulfone	7.9	H_2O	?	ET	(*13*)
4-Aminothiophenol	7.95	40% aq. EtOH	20	ET	[b]
	7.80	40% aq. EtOH	30	ET	[b]
	9.7	MeOH	?	ET	(*4*)
Penicillamine	7.90	H_2O	30	ET	(*9*)
Mercaptoacetone	7.86	H_2O	25	ET	(*16*)
Methyl mercaptoacetate	7.68	H_2O	20	ET	(*3*)
3-Methoxythiophenol	7.54	48.9% aq. EtOH	20–2	ET	(*20*)
	9.20	95% aq. EtOH	20–2	ET	(*20*)
2,4-Dichlorothiophenol	7.2	MeOH	?	ET	(*4*)
4-Bromothiophenol	7.06	48.9% aq. EtOH	20–2	ET	(*20*)
	8.37	95% aq. EtOH	20–2	ET	(*20*)
4-Iodothiophenol	6.99	48.9% aq. EtOH	20–2	ET	(*20*)
	8.32	95% aq. EtOH	20–2	ET	(*20*)
Methyl 3-mercaptobenzoate	6.98	48.9% aq. EtOH	20–2	ET	(*20*)
	8.40	95% aq. EtOH	20–2	ET	(*20*)
3-Acetylthiophenol	6.93	48.9% aq. EtOH	20–2	ET	(*20*)
	8.35	95% aq. EtOH	20–2	ET	(*20*)
2-Mercaptobenzothiazole	6.93	40% aq. EtOH	27	UV (235–40)	[b]
3-Bromothiophenol	6.90	48.9% aq. EtOH	20–2	ET	(*20*)
	6.77	48% aq. EtOH	25	ET	(*2*)
	8.22	95% aq. EtOH	20–2	ET	(*20*)
3-Chlorothiophenol	6.85	48.9% aq. EtOH	20–2	ET	(*20*)
	8.17	95% aq. EtOH	20–2	ET	(*20*)
3-Iodothiophenol	6.85	48.9% aq. EtOH	20–2	ET	(*20*)
	8.08	95% aq. EtOH	20–2	ET	(*20*)

(*Continued on page 388*)

Table I. Dissociation Constants of Thiols (*Continued*)

Compound	pK_a	Solvent	Temp., °C.	Technique[a]	Reference
Mercaptosuccinimide	6.7	H_2O	?	ET	(*13*)
2-Toluenethiol	6.64	H_2O	26–7	UV (265)	[b]
	7.82	40% aq. EtOH	26–7	UV (265)	[b]
	7.85	40% aq. EtOH	25	ET	[b]
3-Toluenethiol	6.58	H_2O	25	UV (265)	[b]
	7.55	40% aq. EtOH	25	UV (265)	[b]
	7.65	40% aq. EtOH	20	ET	[b]
	7.55	40% aq. EtOH	30	ET	[b]
	7.99	48.9% aq. EtOH	20–2	ET	(*20*)
	9.56	95% aq. EtOH	20–2	ET	(*20*)
2-Aminothiophenol	6.59	H_2O	20	ET	(*3*)
4-Toluenethiol	6.52	H_2O	23	UV (265)	[b]
	6.92	20% aq. EtOH	23	UV (265)	[b]
	7.58	40% aq. EtOH	23	UV (265)	[b]
	7.55	40% aq. EtOH	20	ET	[b]
	7.40	40% aq. EtOH	30	ET	[b]
	8.07	48.9% aq. EtOH	20–2	ET	(*20*)
	9.70	95% aq. EtOH	20–2	ET	(*20*)
	8.4	MeOH	?	ET	(*4*)
Thiophenol	6.5	H_2O	25	UV (?)	(*16*)
	6.62	H_2O	23	UV (265)	[b]
	6.82	20% aq. EtOH	23	UV (265)	[b]
	7.40	40% aq. EtOH	23	UV (265)	[b]
	7.55	40% aq. EtOH	20	ET	[b]
	7.39	40% aq. EtOH	30	ET	[b]
	7.78	48.9% aq. EtOH	20–2	ET	(*20*)
	9.32	95% aq. EtOH	20–2	ET	(*20*)
	7.47	23% *tert*-BuOH	25	ET	(*19*)
L-Cysteine ethyl ester	6.53	H_2O	30	ET	(*9*)
L-Cysteine methyl ester	6.50	H_2O	20	ET	(*3*)
3-Mercaptobenzoic acid	6.32	H_2O	20	ET	[b]
	6.20	H_2O	30	ET	[b]
	6.15	H_2O	28	UV (270)	[b]
	6.60	20% aq. EtOH	28	UV (270)	[b]
	7.0	40% aq. EtOH	28	UV (270)	[b]
	8.07	48.9% aq. EtOH	20–2	ET	(*20*)
Methyl 4-mercaptobenzoate	6.17	48.9% aq. EtOH	20–2	ET	(*20*)
	7.50	95% aq. EtOH	20–2	ET	(*20*)
2-Nitrothiophenol	5.99	48.9% aq. EtOH	20–2	ET	(*20*)
	7.46	95% aq. EtOH	20–2	ET	(*20*)
4-Acetylthiophenol	5.93	48.9% aq. EtOH	20–2	ET	(*20*)
	7.28	95% aq. EtOH	20–2	ET	(*20*)
3-Nitrothiophenol	5.90	48% aq. EtOH	25	ET	(*2*)
4-Chlorothiophenol	5.9	H_2O	23	UV (270–275)	[b]
	6.3	20% aq. EtOH	23	UV (270–275)	[b]
	6.78	40% aq. EtOH	23	UV (270–275)	[b]
	7.06	48.9% aq. EtOH	20–2	ET	(*20*)
	8.45	95% aq. EtOH	20–2	ET	(*20*)
	7.3	MeOH	?	ET	(*4*)
3-Methanesulfonylthiophenol	5.88	48% aq. EtOH	25	ET	(*2*)
4-Mercaptobenzoic acid	5.80	H_2O	25	UV (305)	(*14*)
	5.90	H_2O	25	UV (305)	[b]
	7.85	48.9% aq. EtOH	20–2	ET	(*20*)
4-Mercaptobenzenesulfonic acid	5.73	H_2O	?	UV (285)	(*21*)
4-Mercapto-*N*-trimethylanilinium	5.66	48.9% aq. EtOH	20–2	ET	(*20*)
	6.35	95% aq. EtOH	20–2	ET	(*20*)
4-Methanesulfonylthiophenol	5.57	48% aq. EtOH	25	ET	(*2*)
4-Nitrothiophenol	5.11	48% aq. EtOH	25	ET	(*2*)
	4.95	40% aq. EtOH	20	ET	[b]
	4.77	40% aq. EtOH	30	ET	[b]
	4.99	48.9% aq. EtOH	20–2	ET	(*20*)
	6.48	95% aq. EtOH	20–2	ET	(*20*)
	5.8	MeOH	?	ET	(*4*)
Thiolacetic acid	3.62	H_2O	25	UV (245)	(*14*)
	3.42	H_2O	25	ET	(*15*)

[a] UV (/), spectrophotometric determination at λ_{max} given. ET, electrometric titrations. [b] This investigation.

than 0.1 unit) are not listed. Discrepant values are listed when comparable concordant ones are not available.

Particular attention has been paid to the role of solvent composition. Of course, thiols would be expected to be more acidic in water than in ethanol. The data not only confirm the expectation but indicate the extent of the difference from water to 95% by volume aqueous ethanol. These data are important, for an appreciable number of thiols are not significantly soluble in water. Fortunately, the spectrophotometric method works well in the vicinity of 10^{-4} to $10^{-5}M$ RSH. Kreevoy *et al.* (*16*) have noted that their value for the pK_a for thiophenol differs considerably from that reported by Danehy and Noel (*3*) but, as recorded here, the discrepancy disappears completely when solvent composition is taken into consideration.

The λ_{max} for the thiolate ion varies from one compound

to another over the range of 220 to 305 mμ. In at least three cases (2-mercaptoethylamine, cysteine, and mercaptosuccinic acid), the λ_{max} varies with pH—i.e., with RS^-/RSH. This latter variation may well reflect the concomitant ionization of the ammonium ion in the first two cases, and of the β-carboxyl group in the third case.

Neither of the two methods employed appears to have any intrinsic advantage over the other, at least when the thiol is of high purity. However, if the thiol contains unknown contaminants an electrometric titration cannot be meaningfully carried out, while a spectrophotometric determination may still be successful.

Table I is arranged according to decreasing values for pK_a. This arrangement clearly displays the inductive effect of the substituent groups on the acidities of the thiols, which has been discussed by Kreevoy *et al.* (*15*, *16*). Thus, it should be feasible to make reasonable estimates for the pK_a values of thiols for which experimental determinations have not yet been carried out.

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Latent Heat of Sublimation of Terephthalic Acid from Differential Thermal Analysis Data

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The latent heat of sublimation of terephthalic acid has been calculated from differential thermal analysis data. This value was 33.3 ± 0.9 kcal. per mole from 7.0 to 760 mm. of Hg. In addition, the sublimation temperature of terephthalic acid at 760 mm. of Hg and the melting point in a sealed tube have been observed. These values were 402° and 427° C., respectively.

THE latent heats of sublimation of terephthalic acid as calculated from vapor pressure data reported by Hirsbrunner (*5*), Jordan (*6*), and Kraus *et al.* (*8*) are not in agreement. The value obtained from the equation presented by Hirsbrunner is 23.6 kcal. per mole. The value obtained from a vapor pressure curve in the compilation by Jordan, who cites Hirsbrunner as the source of his data, is 20.2 kcal. per mole. More recently, Kraus *et al.* reported a value of 31.3 kcal. per mole. The work reported here was undertaken to check these values and to extend the range of the vapor pressure–temperature data.

Hirsbrunner (*5*) measured vapor pressures in a sealed tube at different temperatures. Kraus *et al.* (*8*) used a gas saturation method with nitrogen as the carrier gas. The nitrogen was saturated with terephthalic acid vapor by slow passage over the powdered acid, which was maintained at a constant temperature. The acid vapor was caught in alkali, and the vapor pressure was calculated from the amount of acid found by titration. The vapor pressure–temperature data being reported in this paper were obtained by a variable pressure differential thermal analysis (DTA) technique. In this technique, the pressure of the gaseous environment of the sample is controlled by bleeding nitrogen into the sample chamber. At each preset value of the pressure, a thermogram is recorded and the sublimation temperature is obtained from the thermogram. Markowitz and Boryta (*10*) have used this technique to study the sublimation equilibria of ammonium chloride, and Krawetz and Tovrog (*7*) used a similar method to obtain the vapor pressure of toluene. The limitations of the DTA method have been discussed by Sarasohn (*12*).

EXPERIMENTAL

Terephthalic acid produced by catalytic oxidation of *p*-xylene (*11*) was treated with potassium permanganate in ammonia solution to ensure complete oxidation of any intermediate oxidation products that may have been pres-