Effect of Electrophilic and Electrodotic Groups on the Titration of Amides and Other Weak Bases

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The effect of electrophilic and electrodotic groups on the titration of amides in acetic anhydride and combinations of acetic anhydride with chloroform and acetone has been demonstrated. The presence of electrodotic groups enhanced the potentiometric end point, whereas electrophilic groups usually depressed the end point to such an extent that the compound was not titratable. Similar behavior was noted with acetanilide and its derivatives. Examination of the potentiometric first derivative showed an enhancement of the end point when electron donating groups were present.

PRIOR TO Wimer's work (1) on the potentiometric determination of amides in acetic anhydride, little had been reported on the titration of this weakly basic group of compounds. Acetic anhydride has been used alone as a titration medium or in combination with other solvents (2–10). A good summary has been presented by Wimer (1).

It has been demonstrated by Chatten and Harris (11) that the presence of electrophilic groups has a marked influence on the $E_{1/2}$ values of two groups of relatively strong organic bases when they are titrated in certain organic solvents.

It is the purpose of this investigation to demonstrate the influence of electrophilic and electrodotic groups on the titratability of acid amides and other weakly basic compounds. The solvent systems chosen were acetic anhydride alone, acetic anhydride combined with equal parts of chloroform, and acetic anhydride combined with equal parts of acetone.

EXPERIMENTAL

Apparatus

A Metrohm model E336 recording potentiometer, equipped with conventional glass and calomel electrodes, was used in all titrations. The calomel electrode was not modified.

Reagents and Solutions

Acetic anhydride, A.C.S.; chloroform, A.C.S.; acetone, A.C.S.; dioxane, A.C.S.; and perchloric acid, 70%, were employed.

A 0.1 *N* solution of perchloric acid in dioxane was prepared and standardized potentiometrically against primary standard potassium acid phthalate in glacial acetic acid.

All compounds titrated were Eastman Kodak white label grade and were analyzed without further purification.

Procedures

Acetic Anhydride.—A sample of the material to be titrated equivalent to 0.5–1.0 mmole was stirred in 50 ml. of acetic anhydride. Heat was used to aid solubilization if necessary. The sample was titrated with 0.1 *N* perchloric acid in dioxane and titration followed with a Metrohm model E336 recording potentiometer.

Chloroform–Acetic Anhydride System.—A sample of the material to be titrated equivalent to 0.5–1.0 mmole was stirred in 25 ml. of chloroform. Upon dissolving the compound, 25 ml. of acetic anhydride was added and the titration carried out as previously described. For those compounds which were difficult to dissolve in chloroform, heat was used, and the 25 ml. of acetic anhydride was added to assist in solution.

Acetone–Acetic Anhydride System.—The size of sample and quantity of acetone used was identical to *Chloroform–Acetic Anhydride*. Again, where the material did not dissolve in acetone by stirring, heat and the addition of 25 ml. of acetic anhydride were used.

RESULTS AND DISCUSSION

In his report, Wimer (1) showed that a wide variety of acid amides and a few acylated amines could be titrated in acetic anhydride. In addition, he showed that the presence of glacial acetic acid seriously depressed the magnitude of the inflection point if more than 10% of that solvent was incorporated in the titration medium.

In the present study, amides and acylated amines were chosen to contain various electrophilic or electrodotic groups. The influence of these groups on the titratability of the compound will be interpreted in the following discussion.

In addition, the effect of an aprotic solvent, chloroform, and a weakly protophilic solvent, acetone, upon the titration of the chosen substances was interesting.

Table I reports the average of five determinations together with the standard deviation for titrations in acetic anhydride. For the other two solvent systems, the reported recoveries were the average of three determinations. In chloroform–acetic anhydride, the average range for the three determinations was 0.51%, with a low of 0.2 and a high of 0.9. The average range in acetone–acetic anhydride was virtually the same as that in the aforementioned solvent system as was the lowest and highest ranges. In each instance, the $\Delta E/\Delta V$ value was the average of all determinations for a compound in a particular solvent system.

An arbitrary limit of $\pm 5\%$ from theoretical has been selected as satisfactory for the quantitative recovery of the weak bases in this study. Upon examination of the data for the first three compounds, which were all derivatives of formamide, the first two, which have electrodotic groups, gave

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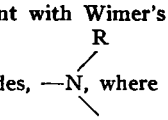
TABLE I.—TITRATION OF AMIDES IN ACETIC ANHYDRIDE ALONE AND IN COMBINATIONS

Compd.	Recoveries, %			$(\Delta E/\Delta V)_{Max.}$		
	Acetic Anhydride	Chloroform–Acetic Anhydride	Acetone–Acetic Anhydride	Acetic Anhydride	Chloroform–Acetic Anhydride	Acetone–Acetic Anhydride
N-Ethylformamide	100.5 ± 0.10	104.9	101.5	215	385	170
N,N-Dibutylformamide	104.5 ± 0.11	108.1	104.4	595	390	235
N,N-Diphenylformamide	No end point	No end point	No end point			
Acetamide	101.4 ± 0.77	No end point	No end point	260	...	...
2-Chloroacetamide	No end point	No end point	No end point			
2-Cyanoacetamide	No end point	No end point	No end point			
N,N-Dimethylacetamide	98.8 ± 0.20	106.5	98.3	185	290	505
N-Ethylacetamide	100.8 ± 0.38	105.1	100.3	150	275	325
N,N-Di-*n*-propylacetamide	102.0 ± 0.25	104.8	101.4	280	360	165
N-*n*-Butylacetamide	103.4 ± 0.32	106.8	103.0	255	325	190
2-Phenoxyacetamide	85.6 ± 0.35	No end point	No end point	110	...	...
1-Naphthaleneacetamide	98.5 ± 0.34	103.7	101.7	235	240	75
N-Methyl-*N*-1-naphthylacetamide	100.6 ± 0.30	102.7	No end point	200	100	...
Thioacetamide	98.7 ± 0.12	98.3	100.8	405	730	420
N,N-Diethylpropionamide	100.7 ± 0.28	102.9	102.8	270	450	210
N,N-Di-*n*-butylpropionamide	104.4 ± 0.35	105.9	102.9	330	315	175
Butyramide	101.6 ± 0.37	101.5	High result	385	315	...
Isobutyramide	100.2 ± 0.20	101.2	High result	285	320	...
Acrylamide	98.3 ± 0.29	98.0	No end point	215	150	...
2-Furamide	70.8 ± 0.93	72.7	No end point	220	150	...
Hexanamide	101.9 ± 0.22	104.9	No end point	280	305	...
N-Butyloctadecanamide	Insoluble	104.5	Insoluble	...	330	...
Benzamide	84.4 ± 0.78	99.7	No end point	245	180	...
o-Ethoxybenzamide	97.8 ± 0.21	99.5	98.3	335	265	165
p-Nitrobenzamide	No end point	No end point	Insoluble	...	...	...
Oxamide	Insoluble	Insoluble	Insoluble	...	...	...
Malonamide	100.4 ± 0.49	Insoluble	Insoluble	335	...	...
Adipamide	Insoluble	Insoluble	Insoluble	...	...	...

satisfactory recoveries in acetic anhydride and acetic anhydride combined with acetone. No explanation can be offered for their somewhat high recoveries in the chloroform–acetic anhydride combination, particularly when one considers the sharpness of the respective end points as illustrated by the $\Delta E/\Delta V$ values. As would be predicted, the third compound on which the nitrogen was substituted by the two electrophilic phenyl groups gave no detectable end point in the three solvent combinations. This finding is in agreement with Wimer's (1) observation that tertiary amides,  , where R is CH_3—C—, exhibited no measurable basic properties. He did not comment on secondary and tertiary amides where the R groups were electron donors. However, Table I shows that the first derivative values were much higher for *N,N*-dibutylformamide than they were for *N*-ethylformamide. This was to be expected. In addition, the $\Delta E/\Delta V$ values at the inflection point should have been greater for the *N*-alkylated acetamide derivatives than for acetamide itself. This was not found experimentally, and no logical explanation can be offered. However, it is worthwhile to mention that the *N*-alkylated derivatives were titratable in the other two solvent systems, which are less acidic and hence less potentrating than acetic anhydride alone, while acetamide was titratable only in acetic anhydride. This would indicate that the *N*-alkyl groups have enhanced the basicity of the amide moiety in these compounds. In addition, there was a further indication of this phenomenon when it was observed that the $\Delta E/\Delta V$ value for *N,N*-di-*n*-butylpropionamide was somewhat greater than that for *N,N*-diethylpropionamide. This was to be expected since the *n*-butyl groups should have a greater electron donating potential than the ethyl moieties.

It was expected that the chloro- and cyano-derivatives would not be titratable in the solvent systems because of the electrophilic influence of these groups. This was demonstrated experimentally. The phenoxy group is less electrophilic than the two aforementioned ones but still sufficiently so to cause depression of the end point which resulted in less than quantitative recovery.

The only compounds of the acetamide series which exhibited anomalous and unpredictable behavior were 1-naphthaleneacetamide and *N*-methyl-*N*-1-naphthylacetamide. One would have expected the naphthalene group to behave as a strong electrophile and thus result in compounds that would be untitratable. While they appeared to be slightly less basic than acetamide when acetic anhydride was the solvent medium, both of them behaved as stronger bases in the chloroform–acetic anhydride system. Naphthylene acetamide even gave a weak but detectable end point in the acetone–acetic anhydride mixture.

The behavior of thioacetamide was predictable since $\rangle C = S$ is less electrophylic than $\rangle C = O$; hence, the thio compound should be more strongly basic than acetamide. This has been demonstrated experimentally.

Wimer (1) has suggested that the low recoveries which he obtained with acrylamide and 2-furamide may have been due to reaction of these compounds with acetic anhydride. In the present work, the

TABLE II.—TITRATION OF ACYLATED AMINES IN ACETIC ANHYDRIDE ALONE AND IN COMBINATIONS

Compd.	Recoveries, %			$(\Delta E/\Delta V)_{Max.}$		
	Acetic Anhydride	Chloroform–Acetic Anhydride	Acetone–Acetic Anhydride	Acetic Anhydride	Chloroform–Acetic Anhydride	Acetone–Acetic Anhydride
Acetanilide	110.5 ± 0.95	[a]	[a]	145	...	...
o-Nitroacetanilide	[a]	[a]	[a]	...	...	...
m-Nitroacetanilide	[a]	[a]	[a]	...	...	...
p-Nitroacetanilide	[a]	[a]	[a]	...	...	...
N-Ethyl-4′-nitroacetanilide	[a]	[a]	[a]	...	...	...
2′-Chloroacetanilide	[a]	[a]	[a]	...	...	...
3′-Chloroacetanilide	[a]	[a]	[a]	...	...	...
4′-Chloroacetanilide	[a]	[a]	[a]	...	...	...
α-Cyanoacetanilide	[a]	[a]	[a]	...	...	...
Acetoacetanilide	[a]	[a]	[a]	...	...	...
o-Hydroxyacetanilide	[a]	[a]	[a]	...	...	...
p-Hydroxyacetanilide	[a]	[a]	[a]	...	...	...
N-*n*-Butylacetanilide	105.4 ± 0.32	109.0	102.8	160	200	120
n-Butyranilide	[a]	[a]	[a]	...	...	...
N-Ethylacetanilide	103.7 ± 0.32	103.8	[a]	290	155	...
O-Acetophenetidide	[a]	[a]	[a]	...	...	...
m-Acetotoluidide	106.2 ± 0.50	104.5	[a]	100	100	...
o-Acetotoluidide	107.9 ± 0.27	103.6	[a]	150	115	...
Benzanilide	[a]	[a]	[a]	...	...	...

[a] No end point.

findings for acrylamide would indicate that such a reaction did not occur since reasonably quantitative recoveries were obtained in two solvent systems. The $\Delta E/\Delta V$ values were smaller for both compounds in acetic anhydride than they were for acetamide, and this was probably due to the existence of a conjugated system of double bonds in both acrylamide and 2-furamide. Such a system would exert an electrophilic effect.

Benzamide would fall into the same category as acrylamide and 2-furamide, since the phenyl group would be conjugated with the carbonyl. It was interesting that quantitative recovery was not obtained for this material in acetic anhydride; but when chloroform–acetic anhydride was used, excellent results were obtained. This would indicate that the presence of an aprotic solvent may be beneficial in some instances. On the other hand, *o*-ethoxybenzamide gave satisfactory results in all three solvent systems; this was to be anticipated because of the electrodotic ethoxy group. As expected, *p*-nitrobenzamide was too weakly basic to be titrated in any solvent system. Salicylamide was investigated also, although it was not included in Table I. The compound was not titratable in the solvent systems used in this investigation, possibly because of hydrogen bonding between the hydroxyl hydrogen and the amide nitrogen.

The solvent system of acetone–acetic anhydride was probably less capable of enhancing the weakly basic properties of the compounds and could account for the failure to reach an end point in many instances. It was noteworthy, however, that when end points were detectable, the quantitative data generally agreed closely with those obtained in acetic anhydride alone.

Although several of the compounds gave recoveries which were above theoretical values, when chloroform–acetic anhydride was the solvent, others gave excellent results with readily detectable end points. While this manuscript was in preparation, Cowell and Selby (12) reported the titration of weak bases in acetic anhydride which contained up to 50% chloroform; they observed that this latter solvent had little effect on the shape of the titration curve. The findings of the present report confirmed this observation. Such a solvent mixture has the added advantage of widening the scope of these titrations, due to the solubilizing properties of chloroform. Such a system, then, should be considered as a desirable alternate to acetic anhydride in the titration of very weak bases.

There was little that could be said concerning the data in Table II, except to observe that acetanilide itself was so weakly basic that it was barely titratable even in acetic anhydride. This phenomenon can be attributed partially to the electrophilic properties of the acetyl group, but the existence of resonance in the molecule may also play an important part in decreasing its basicity. Obviously then, those derivatives which contained additional electrophilic groups such as nitro, chloro, and cyano were even less basic and hence not titratable. Only those derivatives possessing electrodotic groups showed improved titratability, as would be predicted. Data in acetic anhydride were based on five determinations, while the values in the other solvents were the average of three titrations.

CONCLUSION

From the experimental evidence presented in this report, it was concluded that, in most instances, an accurate prediction could be made regarding the titratability of amides and acylated amines by examination of the structure of the compound.

A solvent combination consisting of equal parts of chloroform and acetic anhydride offers a useful alternate medium for the titration of weak bases.

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