[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY]

Improved Hydroxylamine Method for the Determination of Aldehydes and Ketones. Displacement of Oxime Equilibria by Means of Pyridine

BY W. M. D. BRYANT AND DONALD MILTON SMITH

The value of hydroxylamine and its salts as quantitative reagents for aldehydes and ketones has long been recognized. Brochet and Cambier[1] used hydroxylamine hydrochloride for the volumetric analysis of formaldehyde solutions. They titrated the hydrochloric acid liberated in the reaction $HCHO + HONH_3Cl = CH_2{=}NOH + H_2O + HCl$ and used this as a measure of the formaldehyde present. Bennett[2] and his collaborators modified the analytical procedure and investigated the behavior of several aldehydes and ketones. The most generally applicable procedure in this group is that of Bennett and Donovan, in which most of the hydroxylamine base is first liberated from the hydrochloride by the addition of alcoholic sodium hydroxide and then allowed to react with the carbonyl compound. At the completion of the reaction the remaining unused hydroxylamine is determined alkalimetrically. Schultes[3] has quite recently added some additional carbonyl compounds to the list of substances that can be analyzed by the hydroxylamine method.

The present research arose from the need of an analytical method that would be applicable to a large number of aldehydes and ketones of widely varied constitution. The procedures of Brochet and Cambier, and of Bennett and Donovan were both tried and found to be unsatisfactory in their original form. In the former procedure, equilibrium conditions were often such that complete reaction could not be attained, while the latter was characterized by a slow rate of reaction and erratic losses of hydroxylamine probably resulting from spontaneous decomposition.

In evolving the improved procedure, a special effort was made to extend the scope of the method without adding to its complexity. It was consequently retained in its original form[1] as an acidimetric method employing hydroxylamine hydrochloride. The principal improving feature resulted from the use of pyridine for the double purpose of forcing oxime formation to completion and of rendering the initial reaction mixture neutral to brom phenol blue, thus eliminating the need of a blank titration. Although pyridine exerts a slight buffer action which makes the indicator color change less sensitive, its value in displacing unfavorable oxime equilibria compensates for the diminished sensitivity. The reaction environment of 90–95% alcohol, suggested by Bennett's work, is valuable as a solvent for water-insoluble samples. Over thirty aldehydes and ketones were analyzed by the new procedure and results close to the theoretical obtained.

The method is applicable to aldehydes and ketones of aliphatic, alicyclic and aromatic character. A great many substituted aldehydes and ketones can be estimated although this does not apply to the carboxyl or amide type of carbonyl group. Structural peculiarities of carbonyl compounds have a marked effect upon the rate of reaction with hydroxylamine hydrochloride, although this factor alone is seldom sufficient to render the method inapplicable.

In order to determine the most satisfactory analytical conditions for individual ketones of the less reactive class, the relative rates of reaction were measured at room temperature. These experiments show the effect of chemical constitution upon the reactivity of carbonyl compounds, and lead to some interesting qualitative generalizations regarding steric hindrance of the —CO— group by other organic radicals.

The average precision of the new hydroxylamine method is about $\pm 1\%$, and the results are stoichiometric within the experimental error in practically all cases.

Experimental

Reagents.—The hydroxylamine solution (0.5 *N*) is prepared by dissolving 35 g. of Eastman Kodak hydroxylamine hydrochloride in 160 cc. of distilled water and diluting to 1 liter with 95% ethanol. A solution of 20 cc. of J. T. Baker's C. P. pyridine and 0.25 cc. of 4% alcoholic brom phenol blue indicator made up to 1 liter with 95% ethanol is used in conjunction with the above. The sodium hydroxide for acidimetry is a standardized 0.5 normal solution of sodium hydroxide in 90% C. P. methanol (methanol is preferable to ethanol for this purpose since the resulting solution does not color with age).

(1) A. Brochet and R. Cambier, *Compt. rend.*, **120**, 449 (1895).

(2) A. H. Bennett, *Analyst*, **34**, 14 (1909); A. H. Bennett and F. K. Donovan, *ibid.*, **47**, 146 (1922); A. H. Bennett and M. S. Salamon, *ibid.*, **52**, 693 (1927); A. H. Bennett and T. T. Cocking, *ibid.*, **56**, 79 (1931).

(3) H. Schultes, *Z. angew. Chem.*, **47**, 258 (1934).

The hydroxylamine hydrochloride used should not contain excessive amounts of free acid. It may be tested for acidity as follows: 10 g. of $HONH_3Cl$ crystals when dissolved in 50 cc. of distilled water should not require more than 8 cc. of 0.5 *N* sodium hydroxide solution to produce a neutral (green) end-point with brom phenol blue.

Carbonyl Compounds Investigated.—Most of the aldehydes and ketones used in the present work were Eastman chemicals and were employed without further purification. Some of the compounds were obtained by fractional distillation of technical products from various sources, in which case the boiling points are recorded in Table I. The purity of all but a few of the substances used was probably 98% or better. The remaining few were at least 95% pure.

Analytical Procedure.—Using suitable dispensing cylinders or burets, 30 cc. of hydroxylamine hydrochloride reagent and 100 cc. of pyridine–brom phenol blue solution are run into a clean 300-cc. "Citrate of Magnesia" bottle. After mixing the solutions, the indicator color should be a greenish-blue. The sample is then weighed or pipetted into the mixture, preferably in such proportions that half of the reagent (and never less than one-third) remains after the reaction is complete. The pressure bottle is then capped and either allowed to stand at room temperature or heated in a steam-bath at 100°, for the length of time recommended for the particular aldehyde or ketone under investigation (see Table I). Two hours of heating at 100° is generally sufficient. Heated samples should be allowed to cool spontaneously to within about 5° of room temperature (time required about one hour). The preceding step is necessary because the indicator color goes through a reversible change on heating and cooling. Run at least one blank for use as a color standard with each set of determinations. The pyridine hydrochloride in the reaction mixture is titrated with 0.5 *N* sodium hydroxide in 90% methanol until the indicator color just matches that of the blank. The bottle should only be shaken gently to produce a "swirling" motion during the titration. Violent agitation of the solution often causes salt precipitation which may partially obscure the end-point. The number of moles of sodium hydroxide used is a direct measure of the amount of carbonyl radical, —CO—, or in the case of simple aldehydes and ketones, a direct measure of the number of moles of aldehyde or ketone in the sample as shown by the equations

$$RCHO + HONH_3Cl + N\langle\bigcirc\rangle = RCH{=}NOH + H_2O + ClHN\langle\bigcirc\rangle$$

$$RCOR' + HONH_3Cl + N\langle\bigcirc\rangle = RC(=NOH)R' + H_2O + ClHN\langle\bigcirc\rangle$$

It should be borne in mind that the normality of a reagent in strong alcohol solution changes roughly five times as rapidly with temperature as the corresponding aqueous solution.

It is important to keep the volumetric ratios of reagent to pyridine solution constant in order to maintain the sensitive greenish-blue color in the blank. This color is largely dependent upon the water content of the final mixture. The introduction of appreciable amounts of water over those included in the reagents increases the alkaline buffer properties of the pyridine, thus interfering with the acidimetric titration. The addition of water (*e. g.*, present in the sample) up to 1 cc. to the reaction mixture does not affect the indicator noticeably. As much as 5 cc. can be introduced provided an equal amount is added to the blank. Impurities in the hydroxylamine salt or pyridine also affect the indicator color.

In addition to the reversible color change of the indicator (blue to yellow, on heating) with temperature, a gradual permanent shift of the indicator color toward the yellow occurs after long heating at 100°. This change is probably caused by a slow breakdown of the hydroxylamine salt with the liberation of hydrochloric acid. Heating periods up to five hours at 100° give satisfactory green colors in the blank. No decomposition of this sort is noticeable in the cold even after a month. Thermal decomposition of the reagent is more pronounced and erratic in the method of Bennett and Donovan.

Analytical Results

Table I shows the results obtained with the above quantitative procedure for aldehydes and ketones as applied to over thirty pure carbonyl compounds. With the exception of the solids all samples were measured volumetrically in pipets. The temperatures of the liquid samples were noted and the weights calculated from the densities and volumes of the respective materials. The accuracy of these measurements was found to be consistent with that of the analytical procedure.

Time Requirements and Structure.—Inspection of Table I discloses that twelve of the thirteen aldehydes reacted practically to completion in thirty minutes in the cold. The exception was glucose which required two hours of heating. All of the substances listed except benzophenone and camphor had finished reacting after two hours at 100°. A few other materials required additional time in the cold because of unfavorable equilibrium conditions at 100°. Camphor required five hours' heating with a 0.5-g. sample; benzophenone reacted completely after three hours of heating using a 1-g. sample.

As an aid in selecting the most favorable analytical conditions for some of the less reactive ketones, groups of experiments with each of these materials were started in the cold and analyzed individually at successive intervals, time being the only variable. Curves of percentage reaction *versus* time were constructed from these numerical data and when plotted on the same scale (Fig. 1) show some interesting qualitative relationships between reactivity and chemical constitution. Steric hindrance of the —CO— group by adjacent substitu-

TABLE I

ANALYTICAL DATA FOR ALDEHYDES AND KETONES

Figures in parentheses indicate number of determinations

Substance (purity 98–100% except where noted)	Source (obsd. b. p., °C.)	% of theoretical carbonyl content: Cold experiments (30 min. except where noted)	% of theoretical carbonyl content: Hot experiments (2 hours at 98–100° except where noted)
Propionaldehyde	48		(3) 98.8 ± 2.0
Acetone	J. T. Baker's C. P.	(3) 99.0 ± 0.7; (3) 99.1 ± 0.2 (5–10 min.)	(2) 99.2 ± 1.1
Isobutyraldehyde	63.0–63.6	(2) 98.3 ± 0.3 (5–10 min.)	(3) 99.0 ± 1.0; (2) 99.5 ± 0.0; (3) 98.5 ± 0.3
Pentanone-2	Eastman Kodak	(2) 99.3 ± 0.5	(1) 100.0 (1 hr. 98–100°)
Pentanone-3	Eastman Kodak	(2) 99.1 ± 0.2	
Hexanone-2	Eastman Kodak	(2) 98.8 ± 0.3	
2-Methylpentanone-3	114.5–114.6	(1) 99.4 (27 hrs.)	(2) 100.5 ± 0.8; (2) 101.6 ± 0.4
2-Methylpentanone-4	115.9–116.1		(3) 100.0 ± 1.1
2,2-Dimethylbutanone-3	Eastman Kodak	(2) 95.8 ± 0.0	(2) 98.4 ± 0.3 (1 hr. 98–100°)
2,4-Dimethylpentanone-3	124–126	(2) 99.9 ± 0.0 (48 hrs.)	(3) 94.9 ± 0.6[b]; (2) 95.5 ± 0.4[b]; (2) 100.8 ± 0.0 (stood 18 hrs. in cold after heating)
2-Methylhexen-(3)-one-5	93.5 (100 mm.)		(1) 101.5 (30 min. 98–100°); 102.5 ± 0.4 (1 hr. 98–100°)
2,4-Dimethylhexanone-3	147–148	(1) 98.4 (17 hrs.)	(2) 93.6 ± 0.4[b]; (2) 97.5 ± 0.5 (stood 20 hrs. in cold after heating)
Octanone-2	Resinous Products Co.	(2) 99.8 ± 0.0	(3) 98.7 ± 0.8
d-l-Camphor	Eastman Kodak	(2) 93.5 ± 0.0 (34 days)	(2) 98.8 ± 0.2 (0.5 g. sample, 5 hrs. 98–100°)
Furfural	Eastman Kodak	(2) 99.2 ± 0.6	
Benzaldehyde	112.5–113 (100 mm.)	(2) 101.6 ± 1.4	(3) 100.7 ± 2.0
p-Toluic aldehyde	134–134.5 (100 mm.)	(2) 101.0 ± 0.8	
Dimethylbenzaldehyde	151–152.5 (100 mm.)	(2) 101.8 ± 0.6	
Cinnamic aldehyde	Eastman Kodak	(2) 98.3 ± 0.4	(2) 99.2 ± 0.2
Acetophenone	Eastman Kodak	(1) 98.4 (3 hrs.)	(2) 100.2 ± 1.0
Salicylic aldehyde	Eimer and Amend	(3) 98.0 ± 0.6 (2 days); (1) 96.4 (30 min.)	(2) 98.0 ± 0.3 (1 hr. 98–100°)
o-Nitrobenzaldehyde	Eimer and Amend	(1) 99.1	
p-Chlorobenzaldehyde	144–144.5 (100 mm.)	(1) 98.7 (10 min.)	
Benzophenone	Eastman Kodak		(1) 100.9 (3 hrs. 98–100°)
Benzoin	Eastman Kodak	(1) 97.5 (14 hrs.)	(2) 102.4 ± 1.1 (1 hr. 98–100°)
Benzil (basis of one reactive CO group)	Eastman Kodak	(1) 100.4 (14 hrs.) (1) 101.8 (2 days)	(2) 105.2 ± 1.2 (1 hr. 98–100°)
2-Methylpenten-(2)-al-1[a]	138–139	(3) 98.2 ± 0.5; (2) 96.3 ± 0.7	(2) 97.6 ± 0.4
Heptanone-4[a]	Eastman Kodak	(3) 95.1 ± 0.5	(2) 95.4 ± 0.7
2-Ethylhexanal-1[a]	163–165	(3) 95.2 ± 0.7	
Acetylacetone[a]	Eastman Kodak	(2) 95.5 ± 0.2 (2 days)	
Acetonylacetone[a]	Eastman Kodak	(2) 97.2 ± 0.4	
Anhydrous glucose[a]	Eastman Kodak	(1) 95.9 (43 hrs.)	(2) 96.3 ± 0.4; (2) 97.2 ± 0.1 (stood 69 hrs. in cold after heating)
Carvone[a]	Eastman Kodak	(2) 95.2 ± 0.0 (24 hrs.)	(2) 95.5 ± 0.0

[a] Purity better than 95%. [b] Equilibrium for hot sample; goes to completion in cold.

ent groups is a likely explanation for the slow rate of reaction of certain ketones.

Skeleton formula	% Reaction (30 minutes, cold)
C—C—CO—C—C (Pentanone-3)	99
C—C—CO—C(C)—C (2-Methylpentanone-3)	93
C—C(C)—CO—C(C)—C (2,4-Dimethylpentanone-3)	18
C—C(C)—C—CO—C—C (2,4-Dimethylhexanone-3)	22

Pentanone-3, for example, reacts almost instantaneously with hydroxylamine hydrochloride and pyridine. 2-Methylpentanone-3 with a methyl group adjacent to the carbonyl is definitely less reactive, and 2,4-dimethylpentanone-3 and 2,4-dimethylhexanone-3 with a methyl group ad-

jacent on each side are both very sluggish. On the other hand, 2-methylpentanone-4, where the methyl side chain is not directly adjacent to the carbonyl, reacts rapidly. Hence it is concluded that methyl and probably other alkyl groups adjacent to a carbonyl radical produce a steric blocking effect. Phenyl groups linked directly to the carbonyl in ketones also decrease the rate of reaction (*e. g.*, acetophenone, benzophenone). The effect of constitution upon rate is evident in the case of benzoin, benzil, carvone and camphor.

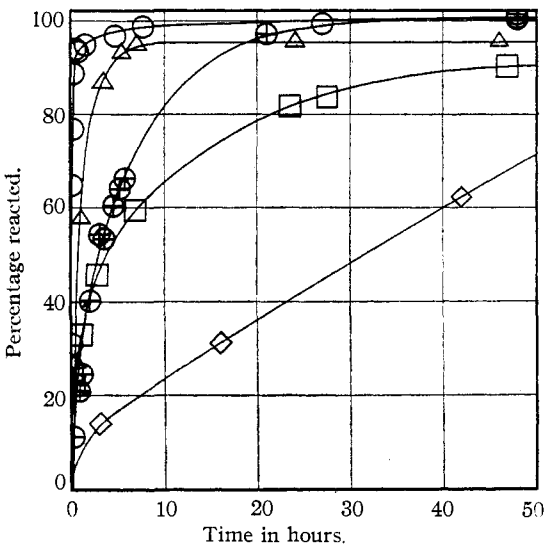

Fig. 1.—Relative reaction velocities of various ketones with hydroxylamine hydrochloride and pyridine: ○, 2-methylpentanone-3; ⊕, 2,4-dimethylpentanone-3; □, 2,4-dimethylhexanone-3; ◬, carvone; ◇,*d*,*l*-camphor.

Effect of Pyridine on the Oxime Equilibria.—The reaction of hydroxylamine salts with carbonyl compounds to form oximes is sometimes incomplete as a result of unfavorable equilibrium rather than slow reaction rate. This is definitely the case with the 2,4-dimethylpentanone-3 when it reacts with hydroxylamine hydrochloride in the absence of pyridine. If 1 cc. of the ketone is allowed to react with the usual 30 cc. of 0.5 *N* $HONH_3Cl$ solution, equilibrium is reached at only 50.1% reaction in the cold or 38.5% hot (hot samples reacted at 100°, but the equilibrium probably represents a somewhat lower temperature because of cooling). By repeating the experiments with the same amounts of ketone and reagent but adding also the usual 100 cc. of pyridine solution, the equilibrium conversion of 2,4-dimethylpentanone-3 becomes 99.9% cold or 95.3% hot. 2,4-Dimethylhexanone-3 in the presence of pyridine reacts 98.4% in the cold or 93.6% hot. Although more nearly quantitative results are obtained in the cold with these substances, the rate of reaction is much slower than at 100°. For the above two difficult cases a compromise can be made conveniently. Good results have been obtained by heating two hours at 100°, cooling and allowing the samples to stand for eighteen to twenty hours (overnight) at room temperature before titration. Although there is evidence that other substances fail to react completely with hydroxylamine hydrochloride alone[4] because of an unfavorable equilibrium, no other examples were found in developing the pyridine method, unless possibly the case of benzil (Table I).

Precision of the Method.—The precision of the hydroxylamine–pyridine method depends to a large extent upon the ability of the analyst to match the blue-green or indigo color of the blank with that of the sample during titration. The color change of brom phenol blue in the reaction environment is gradual and consequently the end-point is only reproducible to about ±0.1 cc. in the titer. If the optimum size of sample is chosen, the precision of the method is usually ±1% or better.

Interfering Substances.—Since the above analytical method for aldehydes and ketones is acidimetric in principle, the presence of acidic or basic compounds in the sample leads to erroneous results. Large amounts of inert organic solvents are undesirable because of their possible effect upon the indicator. Volumes of pure dry alcohols up to 10 cc. produce no noticeable effect upon the end-point.

Small amounts of ferric hydroxide, iron rust, and possibly ferric salts in general, induce a decomposition of the reagent and so lead to apparent high results. Samples containing metal salts or oxides should be distilled before analyzing by the above method.

Summary

1. An improved acidimetric method for the determination of aldehydes and ketones has been developed using hydroxylamine hydrochloride and pyridine as reagents. The method has been used successfully for the analysis of over thirty carbonyl compounds of aliphatic, alicyclic and aromatic structures.

2. Experiments on the relative reaction ve-

(4) M. Marasco, *Ind. Eng. Chem.*, **18**, 701 (1926); Kolthoff and Furman, "Volumetric Analysis," John Wiley and Sons, New York, 1928, Vol. I, p. 206.

locities of certain ketones with the above reagents have been made. The results suggest that steric hindrance of the carbonyl group is responsible for wide variations in the rate of reaction.

3. It has been shown that the addition of pyridine displaces the oxime synthesis equilibrium in the direction of completion.

WILMINGTON, DEL. RECEIVED OCTOBER 26, 1934

[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY]

Rapid Determination of Hydroxyl by Means of Acetyl Chloride and Pyridine

BY DONALD MILTON SMITH AND W. M. D. BRYANT

The most widely used quantitative procedures for determining the hydroxyl radical in organic compounds are probably those based on the use of acetic anhydride with or without the addition of pyridine.[1,2,3,4] When carried out in the approved manner, these methods though precise are time-consuming, due either to the slow rate of reaction or the elaborate precautions necessary in analyzing volatile materials.

Although the use of acetyl chloride as a qualitative reagent for alcohols and certain amines is described in most laboratory texts, less information is available regarding the quantitative value of this substance. One textbook, that of Thorpe and Whiteley,[5] recommends the use of acetyl chloride in the identification of alcohols. The authors claim quantitative yields of ester in one case, but their procedure is apparently preparative rather than analytical in character.

In the present research advantage was taken of the high rate of reaction of acetyl chloride with hydroxyl compounds, and a quantitative titrimetric method of exceptionally wide scope developed. The method is rapid, requires only simple apparatus and yields results which compare favorably with the less rapid acetic anhydride methods.

The new acetyl chloride procedure is applicable to monohydroxy primary and secondary alcohols, both aliphatic and aromatic, to phenols, and to such polyhydroxy compounds as are appreciably soluble in the reagent. Primary and secondary hydroxyl groups present with other functional groups in such molecules as hydroxyglycerides react quantitatively. Tertiary alcohols do not in general react quantitatively. The active hydrogen in mercaptans and primary and secondary amines could probably be estimated by this method, although no experiments with these classes of compounds were included in the present program.

In principle the procedure is similar to the acetic anhydride–pyridine method of Verley and Bölsing,[2] but offers certain advantages not found in their method. Under similar conditions of concentration and temperature, acetyl chloride is considerably more reactive than acetic anhydride. The more recent modifications of the acetic anhydride–pyridine procedure require more time for the reaction to go to completion.[1,3,4] Also, the interference of aldehydes is less pronounced where acetyl chloride is employed.

Comparative experiments indicate that the absolute accuracy is as good as that of the acetic anhydride–pyridine method. The average precision of the acetyl chloride method, however, is slightly less ($\pm 0.5\%$ compared with $\pm 0.2\%$ for the older method).

Experimental

Reagents.—The acetylating reagent was prepared by mixing 1.5 moles (approx. 118 cc.) of Eastman Kodak acetyl chloride (No. P-334) with dry J. T. Baker's C. P. toluene sufficient to make 1 liter of solution. Dry Baker's C. P. pyridine was used in conjunction with the above reagent.

Compounds Investigated.—A few alcohols and all of the phenols were obtained from the Eastman Kodak Co. and used without further purification. The remaining alcohols used were obtained from various sources and carefully purified by fractional distillation. The boiling ranges of the purified compounds are included in Table I. The fractionated alcohols were mostly of 99% purity or better. 2-Methylbutanol-1, hexanol-1 and 2-ethylbutanol-1 could not be freed completely of contaminants by distillation but were probably at least 97% pure.

Analytical Procedure.—Ten cc. of 1.5 molal acetyl chloride in toluene is pipetted into a dry 250 cc. g. s. volumetric flask (calibration unnecessary) using a Lowy auto-

(1) W. Normann and E. Schildknecht, *Fettchem. Umschau*, **40**, 194 (1933).

(2) A. Verley and Fr. Bölsing, *Ber.*, **34**, 3354 (1901).

(3) V. L. Peterson and E. S. West, *J. Biol. Chem.*, **74**, 379 (1927).

(4) S. Marks and R. S. Morrell, *Analyst*, **56**, 428 (1931).

(5) J. F. Thorpe and M. A. Whiteley, "A Students' Manual of Organic Chemical Analysis," Longmans, Green & Co., Ltd., London, 1926.