

large as was reasonably compatible with the experimental data. These experiments suggest that any deviation of the index potential exceeding by 2 or 3 tenths of a millivolt its expected theoretical minimum value may be taken as real.

It should now be our task to plot the three normal potentials against  $pH$ , showing all bends corresponding to the various ionization constants of the dye in each of its three levels of reduction, as shown in many previous cases. This cannot be accomplished satisfactorily because one cannot express either the acidity of highly concentrated sulfuric acid solutions in terms of  $pH$  or refer the normal potentials to the standard hydrogen electrode. Here we are faced with a problem of a much more general scope, concerning both the scale of oxidation-reduction potentials, and the scale of acidity, to which we intend to devote a special study.

### Summary

A semiquinone radical is shown to exist as a univalent reduction product for thionine and for methylene blue. In equilibrium with the dye and the leuco dye, it can exist only to a few per cent.

of the total dye *in maximo* over the whole  $pH$  range covered by the customary buffers. In very strongly acid solution, such as from 10 to 26  $N$  sulfuric acid, it is stable to a much higher extent and can be identified by an analysis of the reductive titration curve of the dye and by its color, which is yellow with distinct absorption bands in the blue. The semiquinone formation constant  $k$  reaches for thionine the value 1000 in 26.6  $N$  sulfuric acid but rapidly decreases to values  $< 1$  in less acid solutions. For methylene blue, this constant reaches in 22.9  $N$  sulfuric acid only the value 6. In a wide  $pH$  range around neutrality,  $k$  is for both dyestuffs approximately 0.05. The greater stability of the radical in very acid solution is ascribed to the formation of a bivalent cation having a structure, exhibiting equivalent resonance, of the same type as a Wurster radical.

The existence of this radical is correlated with the reversibility of oxidation-reduction of thiazines, and with their catalytic effect in biological oxidations.

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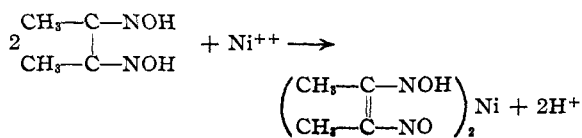
RECEIVED NOVEMBER 1, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY OF THE UNIVERSITY OF MINNESOTA]

## Amperometric Titrations. II. The Titration of Nickel with Dimethylglyoxime Using the Dropping Mercury Electrode as Indicator Electrode

BY I. M. KOLTHOFF AND A. LANGER

In a previous paper<sup>1</sup> the general characteristics of amperometric titrations and the titration of lead with dichromate or chromate have been described. It is expected that many of the modern organic precipitants will be useful in the amperometric titration of several metals, especially since many of these organic reagents are specific for a limited number of inorganic ions. In the present paper the amperometric titration of nickel with dimethylglyoxime is described, using the dropping mercury electrode as indicator electrode. In ammoniacal and weakly acid medium dimethylglyoxime reacts with nickel to form the insoluble red, microcrystalline precipitate of nickel dimethylglyoxime.



(1) I. M. Kolthoff and Y. D. Pan, *This Journal*, **61**, 3402 (1939).

Besides nickel, only palladium and platinum form slightly soluble compounds with dimethylglyoxime. Several metal ions, such as cobalt and ferrous iron, react with the glyoxime to form soluble complexes and may interfere in the titration of nickel. The interference by other metals has been considered in this paper.

### Experimental

The general set-up was similar to that described in a previous paper.<sup>1</sup> The current was measured with a d'Arsonval galvanometer, the sensitivity of which could be changed with an Ayrton shunt. In a few instances a microammeter was used. A saturated calomel electrode connected with the titration cell by means of an agar salt bridge served as an external anode. The applied e. m. f. was measured with the aid of a potentiometer. In most practical work, in which the applied e. m. f., as a rule, has to be known only within 0.05 to 0.1 volt, a suitable voltmeter can be used instead. The reagent was added from a calibrated microburet of the shape given in Fig. 1. The arrangement allowed the storage and the introduction of

the reagent into the titration cell in the absence of air.<sup>2</sup> Before the titration air was removed from the cell by means of a current of nitrogen. For further details, see the previous publication.<sup>1</sup>

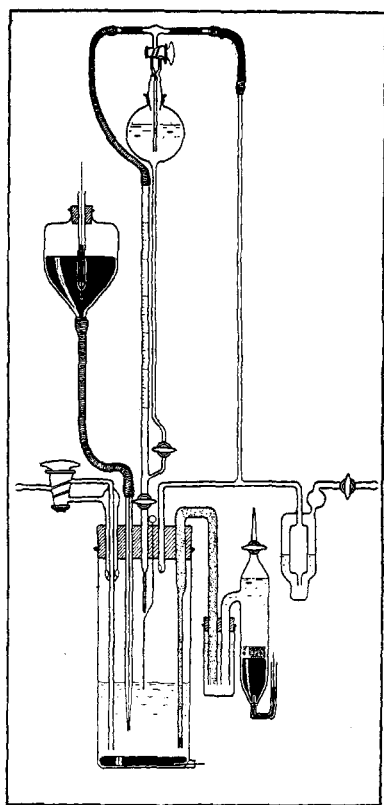


Fig. 1.—Cell allowing the titration to be carried out in the absence of air. The terminal of the agar bridge is made of sintered glass. The gas can pass through or above the solution.

**Chemicals Used.**—All chemicals used were of C. P. quality. If necessary they were further purified by recrystallization. The stock nickel solution was standardized by classical methods. A 0.1 *M* stock solution of dimethylglyoxime in 96% alcohol was prepared. When protected from evaporation this solution could be kept for more than six months without changing its titer.

**Performance of the Titration.**—A measured volume (as a rule 50 ml.) of the standard nickel solution in the proper medium was introduced into the cell, nitrogen was passed through for fifteen to twenty minutes, the proper e. m. f. was applied to the cell and the current was measured. Successive amounts of the alcoholic dimethylglyoxime solution were added from the microburet. After each addition the contents of the cell were mixed by passing nitrogen through for half a minute and the current was recorded after it had become constant (two to three minutes). The tip of the capillary was placed close to the bottom of

the cell, as the red precipitate had the tendency to agglomerate near or at the surface of the solution. No trouble due to obstruction of the capillary was noticed. In all cases the values of the current, corrected for the volume change, were plotted against the amount of reagent added.

### Experimental Results

The most suitable titration medium for nickel was found to be an ammoniacal solution. Consequently, current-voltage curves (polarograms) of nickel and dimethylglyoxime were determined at different concentrations in order to find the most suitable range of values of the applied e. m. f. between which the titrations have to be carried out. In Fig. 2 the current-voltage curve of 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia is given. The wave

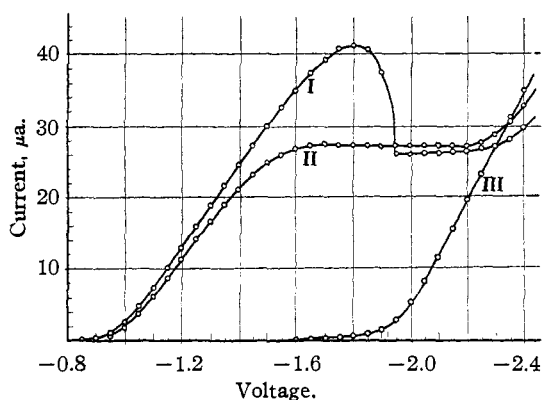


Fig. 2.—Current-voltage curves, temp. 19°, drop time 2.6 sec.: I, 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia; II, same after addition of three drops of 10% gelatin; III, blank.

is drawn out and shows a pronounced maximum (curve I). This maximum can be eliminated by the addition of a trace of gelatin<sup>3</sup> (0.001%), as is evident from curve II; but the wave remains drawn out. In Fig. 3 the current-voltage curves of 0.001, 0.002 and 0.003 *M* solutions of dimethylglyoxime in 0.5 *M* ammonia and 0.1 *M* ammonium chloride are given with the current-voltage curve of the medium alone (curve 1). With the 0.001 *M* dimethylglyoxime solution a diffusion current was obtained at applied values of the e. m. f. between 1.93 and 2.17 volt (curve 2); the 0.002 *M* solution showed a distinct maximum (curve 3), while the 0.003 *M* solution (curve 4) did not give any indication of a diffusion current. At these higher concentrations the current-voltage curve of

(2) Comp. J. Heyrovsky, "Physikalische Methoden der analytischen Chemie," Bd. II, Akademische Verlagsgesellschaft, Leipzig, 1936, p. 284; also M. Spálenka, *Coll. Czechoslov. Chem. Commun.*, **11**, 146 (1939).

(3) Comp. J. J. Lingane; Thesis, University of Minnesota, 1938; I. M. Kolthoff and J. J. Lingane, *Chem. Rev.*, **24**, 1 (1939).

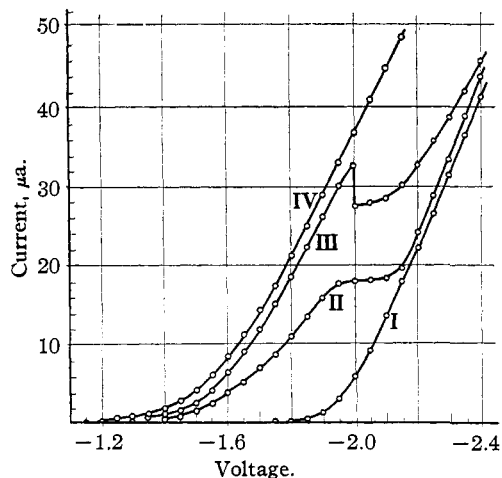


Fig. 3.—Current-voltage curves, temp. 22°, drop time 2.8 sec.: I, 0.1 *M* ammonium chloride and 0.5 *M* ammonia; II, with 0.001 *M* dimethylglyoxime; III, with 0.002 *M*; IV, with 0.003 *M*.

the reagent coincided smoothly with the decomposition current of the medium at higher applied e. m. f. In Fig. 3b it is shown that at an applied e. m. f. of 1.85 volt the dimethylglyoxime current was proportional to the concentration when the latter was smaller than 0.002 *M*. The current

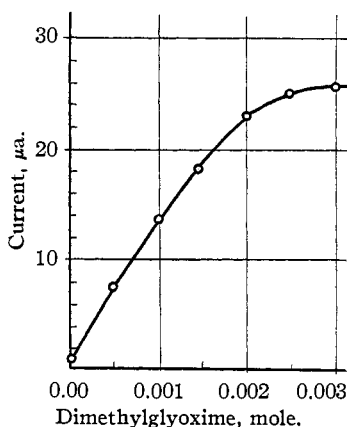


Fig. 3b.—Current at applied voltage of  $-1.85$  v. at different concentrations of dimethylglyoxime in 0.1 *M* ammonium chloride and 0.5 *M* ammonia; temp. 22°, drop time 2.8 sec.

increased only slightly with further increase of the dimethylglyoxime concentration. An applied e. m. f. of 1.85 volt was therefore selected in the performance of the titration. As alcohol was added with the introduction of the reagent, the diffusion current of nickel was determined at  $E_{\text{appl.}} = 1.85$  v. in the above medium in the presence of

different amounts of alcohol. The diffusion current of nickel remained practically unaltered at alcohol concentrations smaller than 12%.

In Fig. 4 are given the data obtained in the titration of a 0.005 *M* nickel solution in 0.1 *M* ammonium chloride and 0.5 *M* ammonia with 0.1 *M* dimethylglyoxime at an applied e. m. f. of 1.85 v. The ordinate gives the values of the current and the abscissa the volume of reagent added. In the titrations the point of intersection was found after addition of 5.00 to 5.03 ml. of reagent. The results are accurate and precise.

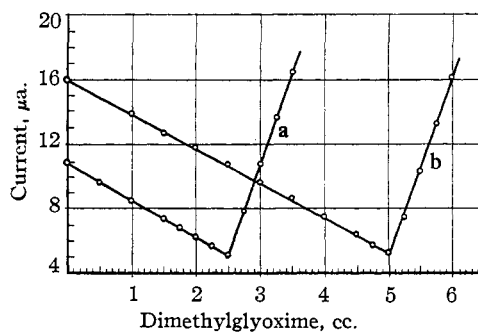


Fig. 4.—Titration curves of 50 ml. of (a) 0.0025 *M*, (b) 0.005 *M*, nickel chloride solutions in 0.1 *M* ammonium chloride and 0.5 *M* ammonia at an applied e. m. f.  $-1.85$  v. with 0.1 *M* dimethylglyoxime; temp. 25°, drop time 2.5 sec.

The concentrations of ammonia and ammonium chloride could be changed within wide limits without affecting the results. Keeping the ammonium chloride concentration equal to 0.1 *M* the residual current at the point of intersection increased only slightly with increasing concentration of ammonia. In 0.5 *M* ammonia it was only 0.85 microampere, in 1 *M* ammonia 1.2, and in 2 *M* ammonia 1.3 microampere. A few data obtained in the titration of 50 ml. of 0.004 *M* nickel chloride with 0.1 *M* dimethylglyoxime in the neighborhood of the end-point are given in Fig. 5. It is seen that in all cases the point of intersection was found after addition of 4.00 ml. of reagent. An increase of the ammonium chloride concentration resulted in a marked increase of the current at the point of intersection. In 0.1 *M* chloride and 0.5 *M* ammonia it was found equal to 0.88 microampere, but in 1 *M* ammonium chloride and 0.5 *M* ammonia it was found equal to 2.2 microamperes. Larger amounts of ammonium chloride apparently increase the solubility of the nickel dimethylglyoxime. In general, it is recommend-

able to keep the ammonium chloride concentration smaller than 0.5 *M*.

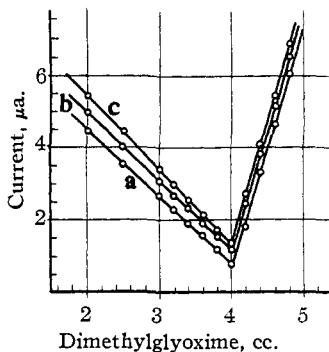


Fig. 5.—Titration curves of 50 ml. of 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and (a) 0.5 *M* ammonia, (b) 1.0 *M* ammonia, (c) 2.0 *M* ammonia solution with 0.1 *M* dimethylglyoxime at an applied e. m. f. of  $-1.85$  v.; temp.  $23^\circ$ , drop time 3.1 sec.

In Fig. 6 are given the data obtained at various applied e. m. f.'s in the titration of 50 ml. of 0.004 *M* nickel in 0.1 *M* ammonium chloride and 0.5 *M* ammonia. The best results were obtained at an applied e. m. f. of 1.6 to 1.9 v. At an applied e. m. f. of 2.0 v. the current at the end-point was relatively great (5.3 microamp.) corresponding to the current of the medium at this voltage. The data obtained at an applied e. m. f. of 1.4 volts varied in an irregular way. These irregularities are caused by stirring effects which are responsible for the occurrence of the maximum

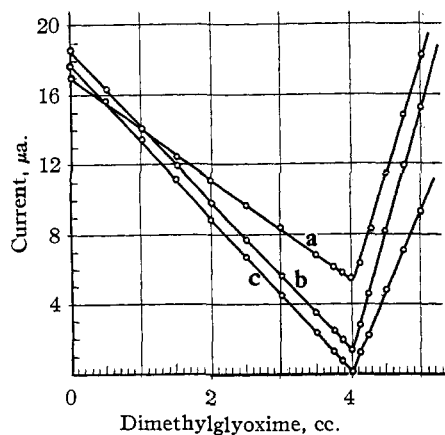


Fig. 6.—Titration curves of 50 ml. of 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia solution with 0.1 *M* dimethylglyoxime at an applied e. m. f. of (a)  $-2.0$  v., (b)  $-1.8$  v., (c)  $-1.6$  v.; temp.  $25^\circ$ , drop time 3.1 sec.

in the nickel curve (see Fig. 2). The stirring effect and also the irregularities were eliminated by the elimination of the maximum as is evident from the results shown in Fig. 7. In this titration

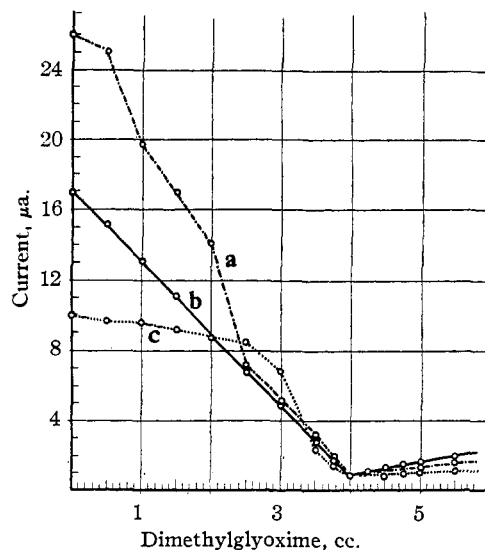


Fig. 7.—Titration curves of 50 ml. of 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia solution with 0.1 *M* dimethylglyoxime at an applied e. m. f. of (a)  $-1.4$  v., (b)  $-1.4$  v. and addition of 1 ml. of 1% gelatin, (c)  $-1.2$  v.; temp.  $25^\circ$ , drop time 3.1 sec.

the maximum was eliminated by the addition of 1 ml. of 1% gelatin. The precipitation line was found to be straight until the end-point. After passing the end-point the current increased only slightly, as at an  $E_{\text{appl.}}$  of 1.4 v. the currents of dimethylglyoxime solutions were very small (see Fig. 3), although proportional to the concentration of the reagent. The data obtained at an applied e. m. f. of 1.2 v. were very irregular (see Fig. 7) for the same reason as at  $E_{\text{appl.}}$  of 1.4 v. A great number of titrations was carried out with 50 ml. of a nickel solution (in 0.1 *M* ammonium chloride, and 0.5 *M* ammonia at  $E_{\text{appl.}} = 1.85$  v.) the concentration of which was varied between 0.01 and 0.001 *M*. The results were precise and accurate within 0.4%. Titrations were also carried out with more dilute solutions, using a 0.01 *M* solution of dimethylglyoxime as reagent. Some data obtained in the titration of 0.0001 *M*, 0.0002 *M* and 0.0004 *M* nickel solutions are given in Fig. 8.

In these highly dilute solutions the solubility of the precipitate at and near the end-point is distinctly noticeable. However, by plotting the

TABLE I

TITRATION OF 50 ML. OF 0.004 *M* NICKEL CHLORIDE SOLUTION IN 0.1 *M* AMMONIUM CHLORIDE AND 0.5 *M* AMMONIA WITH 0.1 *M* DIMETHYLGLYOXIME ( $t = 2.8$  SEC.; TEMP. = 24° C.)

Reagent added, ml.	0.00	1.00	2.00	3.00	3.20	3.40	3.80	3.90	4.00	4.10	4.20	4.40
Current (corr.) $\mu$ a.	18.90 <sup>a</sup>	13.96 <sup>a</sup>	9.66 <sup>a</sup>	5.52 <sup>b</sup>	4.58 <sup>b</sup>	3.64 <sup>b</sup>	2.01 <sup>b</sup>	1.64 <sup>b</sup>	1.50 <sup>b</sup>	2.82 <sup>b</sup>	4.56 <sup>b</sup>	6.44 <sup>b</sup>

<sup>a</sup> Galvanometer at 0.01 sensitivity. <sup>b</sup> At 0.1 sensitivity.

TABLE II

TITRATION OF VARYING AMOUNTS OF NICKEL

Ni taken, mg.	29.34	18.80	14.67	11.74	5.87	2.93	1.76	1.17	0.58
Rel. error, %	+0.14	+0.16	+0.30	$\pm 0.25$	+0.75	-0.3	-1.2	+0.25	-1.0

measurements more than 20 to 40% removed from the equivalence point it is possible to get sufficient data to construct the two straight lines. Although the drop time of the mercury changed somewhat during the titration (up to 10% near the end-point) it was possible to titrate the 0.0001 *M* nickel solution with an accuracy of 1-2%. Solutions more dilute than 0.0001 *M* could not be titrated with a reasonable accuracy, as the solubility effect became too great. The above titrations all have been carried out with a 50-ml. volume of the nickel solution. The accuracy is hardly affected by taking smaller volumes. We have titrated 10-ml. portions containing 0.06 to 0.30 mg. of nickel with an accuracy of 2-3%. By making the proper changes in the apparatus and using still smaller volumes it is possible to use the method for the micro titration of nickel, when the concentration of the nickel is greater than 0.0001 *M* and the volume corrections are considered.

In Table I is given as an illustration the current (corrected for the change of the volume) in the titration of a 0.004 *M* nickel chloride solution.

In Table II is given a summary of some results obtained in the titration of 50-ml. volumes containing varying amounts of nickel. Extensive investigations have been carried out in which attempts were made to titrate the nickel in acetate buffers and in sodium acetate instead of in ammoniacal medium. Although under certain conditions useful results could be obtained in the titration of larger quantities of nickel, the results, quite generally, were much better in ammoniacal medium. For this reason details will not be reported.

**Interference by Other Metal Ions.**—Metal ions which are electroreduced at the applied e. m. f. used in the titration of nickel interfere when present in larger quantities, even if they do not form complexes with the reagent. It is possible to compensate the current caused by the electro-

reduction of the foreign metal ions, but the readings of the current during the titration become less accurate due to the relatively large fluctuations of the current during the formation of a drop of mercury. In general the concentration of foreign ions which are reduced at the applied voltage and which do not react with the reagent should not be many times greater than that of the nickel. It is expected that a stationary electrode may have advantages over the dropping electrode in this respect.

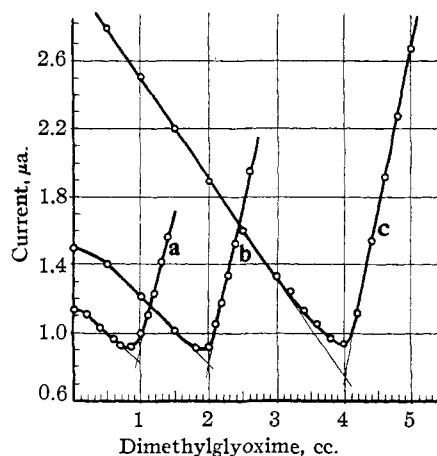


Fig. 8.—Titration curves of 50 ml. of (a) 0.0001 *M*, (b) 0.0002 *M*, (c) 0.0004 *M*, nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia solution at an applied e. m. f. of -1.85 v.; temp. 23°, drop time 2.5 sec.

**Interference by Cobalt.**—A special study was made of the interference caused by cobalt. Cobalt in ammoniacal solution yields a diffusion current at the applied e. m. f. used in the titrations. Moreover, it yields a soluble complex with the dimethylglyoxime. Upon addition of small amounts of the alcoholic reagent to a dilute ammoniacal cobalt solution at an applied e. m. f. of 1.85 v., the current was found to increase in a linear way with the dimethylglyoxime concentration (see Fig. 9). Apparently, the soluble com-

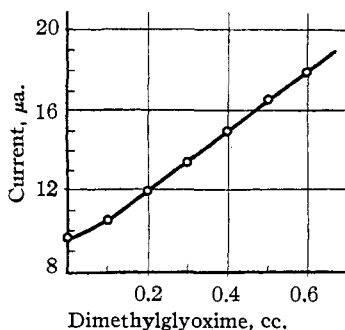


Fig. 9.—Titration curve of 50 ml. of 0.004 *M* cobalt chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia solution with 0.1 *M* dimethylglyoxime at an applied e. m. f. of  $-1.85$  v.; temp.  $25^\circ$ , drop time 2.1 sec.

plex seems to be electroreducible at the applied voltage. Although not expected from this behavior, it was found that small amounts of cobalt interfered with the titration of nickel. Some results are given graphically in Fig. 10. When the ratio of cobalt to nickel in the 0.004 *M* nickel solution was greater than 1:20, the end-point could not be found with accuracy. With larger amounts of cobalt the current changed in a highly irregular way during the titration; and increased from the very beginning. In sodium acetate or in acetate buffers containing 50% of alcohol better results were obtained, but no useful procedure was found for the titration of nickel in the presence of larger quantities of cobalt. Although nickel yields a good current-voltage curve with a diffusion current in cyanide solution, it was found

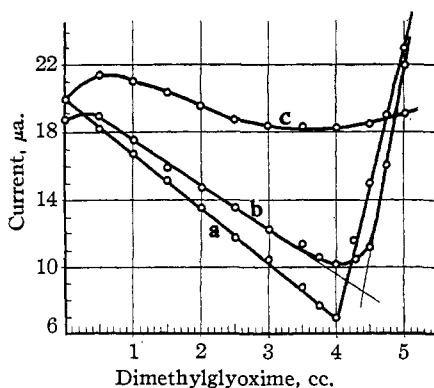


Fig. 10.—Titration curves of 50 ml. of 0.004 *M* nickel chloride in 0.1 *M* ammonium chloride and 0.5 *M* ammonia solution at an applied e. m. f. of  $-1.85$  v. in presence of (a) 0.0002 *M* cobalt chloride, (b) 0.0004 *M*, (c) 0.001 *M*; temp.  $25^\circ$ , drop time 3.1 sec.

that the nickel dimethylglyoxime does not separate from such a medium when little nickel is present. On the other hand it was found that although nickel (and cobalt) do not yield a diffusion current in a solution which was 0.05 *M* in sodium pyrophosphate (see Fig. 11), the nickel complex precipitated readily from such a medium.

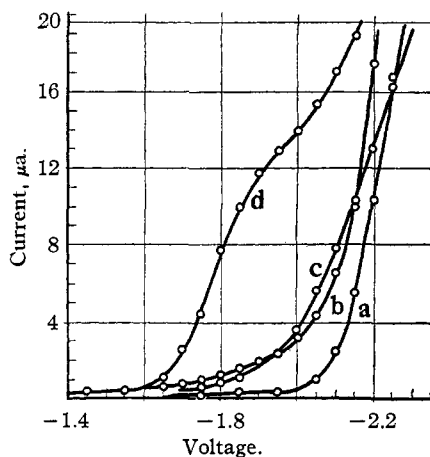


Fig. 11.—Current-voltage curves of: (a) 0.05 *M* sodium pyrophosphate, (b) with 0.004 *M* nickel chloride, (c) with 0.004 *M* cobalt chloride, (d) with 0.004 *M* dimethylglyoxime; temp.  $25^\circ$ , drop time 2.5 sec.

When a nickel titration was carried out in 0.05 *M* sodium pyrophosphate at an applied e. m. f. of 1.7, the titration lines had a slope as given in Fig. 12.

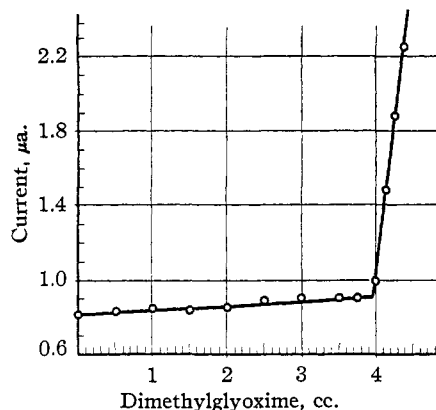


Fig. 12.—Titration curve of 50 ml. of 0.004 *M* nickel chloride in 0.05 *M* sodium pyrophosphate solution with 0.1 *M* dimethylglyoxime at an applied e. m. f. of  $-1.7$  v.; temp.  $24^\circ$ , drop time 2.5 sec.

The end-point could be found with an accuracy of 1-2%. Again, however, relatively small amounts of cobalt interfered. When the amount of cobalt

is more than 5% that of the nickel, it is necessary to remove it by chemical separation. Satisfactory results were obtained by removing the cobalt as potassium cobaltinitrite. To the solution, acidified with acetic acid, was added a large excess of potassium nitrite. After the precipitate had settled it was filtered and washed (or an aliquot part of the filtrate was taken), and the filtrate was evaporated to dryness in the presence of enough hydrochloric acid to remove all of the nitrite. The latter interferes with the nickel titration as it is electroreduced at the applied e. m. f. used in the titrations. The nickel was titrated in ammoniacal medium at an applied voltage of 1.65 in the presence of 1 ml. of 1% gelatin. Taking mixtures with a ratio of cobalt to nickel of 10 to 1, results were obtained which were accurate to within 0.5%. Even when the ratio was 100 to one the results were entirely satisfactory.

**Interference by Other Metal Ions.**—Metal ions, such as ferric iron, aluminum and chromium, which are precipitated in ammoniacal medium can be present in small quantities (about double the amount of nickel). When present in larger quantities low results are found, as the hydrous oxides adsorb nickel. The errors found in the titration of 50 ml. of 0.004 *M* nickel in the presence of 1 ml. of 0.1 *M* solutions of ferric iron, aluminum, chromium and manganese, respectively, were -0.25, -0.5, -2.5, and +0.8%. Larger amounts of the above ions must be removed by classical chemical methods. We have applied the nickel titration to the determination of nickel in nickel steel. After dissolving the sample, oxidation of the iron and reprecipitation from ammoniacal medium in the presence of ammonium chloride, the nickel content was found to be 3.44%, in good agreement with the value 3.47% given by the Bureau of Standards. It is simpler to remove the iron by the ammonium benzoate method.<sup>4</sup> The residue of the solution of the steel (1.16 g.) after oxidation and evaporation was taken up in 0.1 *N* hydrochloric acid, dilute ammonia was added until beginning turbidity, then 5 ml. of glacial acetic acid and 100 ml. of 10% ammonium benzoate. After boiling for five minutes the precipitate was filtered and washed with dilute ammonium benzoate in 30% acetic acid. The filtrate and washings were evaporated, the residue taken up in ammonium chloride and ammonia and

the whole diluted to 250 ml. in a volumetric flask. Fifty-ml. portions were titrated with 0.1 *M* dimethylglyoxime. As an average from four titrations the nickel content was found to be equal to  $3.48 \pm 0.04\%$ .

Cadmium and zinc do not react with the dimethylglyoxime, but they are reduced at the applied e. m. f. at which the titration is carried out. Still, it was found possible to titrate 0.004 *M* nickel solutions in the presence of the same amounts of cadmium and zinc with an accuracy of 1%.

Cupric copper was found to interfere badly. It has to be removed from the solution before titrating the nickel.

**Solubility of Nickel Dimethylglyoxime.**—An attempt has been made to determine the solubility of the red precipitate in various solutions polarographically. The determination should be carried out at an applied e. m. f. at which both nickel and dimethylglyoxime yield a diffusion current. At such an e. m. f. the diffusion current of nickel is:  $i_{dNi} = k_{Ni}C_{Ni}$ , and of dimethylglyoxime  $i_{dD.G.} = k_{D.G.}C_{D.G.}$ . The *k* values can be determined empirically by determining the diffusion currents of nickel and dimethylglyoxime at different concentrations. It is then simple to calculate the solubility from the current measured with the saturated solution (1 Ni + 2 D.G.). Unfortunately, it was hardly possible to find in the various media a suitable value of the applied e. m. f. at which nickel and dimethylglyoxime (or one of them) yield the diffusion current. The best results were obtained with an acetate buffer of pH 4.05 (0.03 *M* in sodium acetate) at an applied e. m. f. of 1.45 v. The results corresponded to a solubility of 9.5 mg. of nickel dimethylglyoxime per liter. The other results are not reported as they are highly approximate for the reasons mentioned above.

### Summary

1. The amperometric titration of nickel in ammoniacal medium with an alcoholic solution of dimethylglyoxime, using the dropping mercury electrode as indicator electrode, yields accurate and precise results.

2. The method is especially useful for the titration of very dilute nickel solutions, good results being obtained in a concentration range between 0.01 and 0.0001 *M*.

3. The interference by other metal ions is

(4) I. M. Kolthoff, V. A. Stenger and B. Moskovitz, *THIS JOURNAL*, **56**, 812 (1934).

discussed. Procedures are described for the determination of nickel after removal of large amounts of cobalt and of iron. The procedure

given for the determination of nickel in nickel steels yields good results.

MINNEAPOLIS, MINN.

RECEIVED OCTOBER 30, 1939

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

## Some Alkamine Esters of Disubstituted Methylcarbamic Acids

BY JOHN J. DONLEAVY AND JAMES ENGLISH, JR.

Most prominent among the various types of simple amines exhibiting local anesthetic properties are the benzohydrilamines. Amines of this type ( $C_6H_5CH(NH_2)R$ ) were first found to be active local anesthetics by Ogata<sup>1</sup> and further study by Fourneau and his collaborators led to the development of a whole series of extremely active local anesthetics including numerous alkoxy-substituted benzohydrilamines.<sup>2</sup> Certain compounds of analogous structure have been studied in this Laboratory and found to be quite active although rather irritating. Experience has shown that in some cases<sup>3</sup> mixed, or aliphatic-aromatic, types are often more active than the diaryl or benzohydrilamine derivatives themselves. Hence typical examples of each of these classes were included in the present investigation.

It was thought possible that the introduction of groups on the nitrogen atom in compounds of this type might act to decrease the irritation produced in the test animals and among the groups considered for this purpose was the COOR group. The present paper describes the preparation of several types of disubstituted methylcarbamates in which R is an aminoalkyl group. It was thought that such compounds might combine the high activity of the benzohydrilamines with that of the amino alcohol carbamates, which are known to be local anesthetics.<sup>4</sup>

The compounds prepared were of the type  $R_1R_2CHNHCOO(CH_2)_nNR_2$  where  $R_1$  and  $R_2$  are either aromatic or aliphatic radicals. Two methods of preparation have been worked out for the isocyanate intermediate in the synthesis of the type in which  $R_1$  and  $R_2$  are both aromatic. The first is based on a modification of the Curtius

reaction of acid azides as developed by Naejeli.<sup>5</sup> This involves the reaction of an acid chloride with sodium azide in dilute acetone solution to give the isocyanate which is immediately treated with the appropriate amino alcohol to give a substituted carbamate. The second method, which was applied also to the aliphatic compounds, consists of the preparation of the isocyanate by the reaction of the alkyl bromide with silver isocyanate and treating this in turn with an amino alcohol. The compounds prepared are listed in Table I.

The pharmacological data will appear elsewhere<sup>6</sup>; it may be said here that the compounds are highly active local anesthetics of toxicity comparable to cocaine; they are somewhat irritating, however.

### Experimental

**Diphenylmethyl Isocyanate.**—Fifteen grams of diphenylmethyl bromide was placed in a flask equipped with a reflux condenser and a mechanical stirrer, care being taken to protect the mixture from moisture at all times. One hundred cc. of anhydrous ether was then added and 12 g. of silver cyanate introduced. The mixture was refluxed and stirred for three hours and refluxing continued overnight. After filtering from the silver bromide, the ether was removed and the product distilled. Diphenylmethyl isocyanate boils at  $148^\circ$  (4 mm.). The yield is 80% of the theoretical.

**Amino Alcohol Carbamates.**—A dry ether solution of the above isocyanate was treated with the calculated quantity of the desired amino alcohol. The solution was refluxed for three hours to ensure completion of the reaction. On passing dry hydrogen chloride into the cold reaction mixture the hydrochloride of the basic urethan precipitated in a fairly pure state. The products can be recrystallized from dry acetone. They are nicely crystalline salts soluble in water and somewhat hygroscopic.

**Amino Alcohol Carbamates from Diphenylacetyl Chloride.**—Twelve grams of diphenylacetyl chloride was dissolved in 80 cc. of acetone and the solution cooled to  $0^\circ$ .

(1) R. Ogata, *J. Pharm. Soc. Japan*, **456**, 81 (1920).  
(2) M. Valette, *Bull. soc. chim.*, (4) **47**, 289 (1930); C. Torres, *ibid.*, (4) **37**, 1591 (1925); Y. Bonnard and J. M. Bulif, *ibid.*, (4) **49**, 1303 (1931).

(3) E. R. Bockstahler, private communication.

(4) A. D. Boese and R. T. Major, *THIS JOURNAL*, **57**, 175 (1935).

(5) C. Naejeli and A. Tyabji, *Helv. Chim. Acta*, **16**, 350 (1933).

(6) The authors are indebted to J. H. Weatherby and H. R. Hulpien and the Pitman-Moore Company for carrying out the pharmacological tests.