Summary

Syntheses of I^{131}-labeled monoiodotyrosine, diiodotyrosine and thyroxine of high specific activity have been carried out on a microgram scale. The products have been separated from their reaction mixtures and identified through the use of paper chromatography. A semi-quantitative estimation of the products has been made by spectrophotometry.

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[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Structures of Cyanamide and Carbodiimide

BY WILLIAM C. SCHNEIDER

In a recent paper by Hunter and Rees[1] it was suggested that a tautomerism between cyanamide and its isomer carbodiimide seems quite probable. Since the observed[2] electric moment of cyanamide, 3.8, is similar to other nitriles, it was felt that a redetermination of the electric moment of cyanamide combined with an evaluation of the electric moments of a dialkylcyanamide and some carbodiimide derivatives should indicate readily any tautomerism between cyanamide and carbodiimide. It was not possible to measure the electric moment of carbodiimide itself since the compound is not known to exist. In addition, the dipole moment of dicyandiamide was obtained as an aid in determining the structure of this important dimer of cyanamide.

TABLE I

Compound	M. p., °C.
Cyanamide[a]	
Dicyandiamide[a]	
Diisopropylcyanamide[b]	B. p. 70° at 15 mm.
Diisopropylcarbodiimide[b]	B. p. 155°; 40° at 10 mm.
p,p'-Dichlorophenylcarbodiimide[b]	55–57°

[a] Purified as discussed by Salley and Gray, THIS JOURNAL, 70, 2650 (1948). [b] Prepared by Dr. I. Hechenbleikner, Research Division, These Laboratories.

TABLE II

w	*E*	*d*	*w*	*E*	*d*
Cyanamide (dioxane)			Cyanamide (benzene)		
0.0	(2.1930)[a]	1.01627	0.0	2.2540	0.86304
.0004609	2.2203	1.01633	.0005396	2.2771	.86316
.0008338	2.2422	1.01639	.001077	2.2958	.86330
.001808	2.2980	1.01659	.001433	2.3104	.86337
.002442	2.3347	1.01664			
Dicyandiamide			Diisopropylcarbodiimide		
			0.0	(2.1974)	1.01624
0.0	2.1907	1.01637	.0005048	2.1996	1.01610
.0001633	2.2085	1.01651	.001102	2.2014	1.01590
.0003247	2.2205	1.01648	.0001630	2.2031	1.01577
			.002156	2.2053	1.01560
Diisopropylcyanamide			*p,p'*-Dichlorophenylcarbodiimide		
0.0	2.1968	1.10623	0.0	(2.2154)	(1.01424)
.0003577	2.2045	1.10606	.0004333	2.2152	1.01435
.0006434	2.2099	1.10592	.0008125	2.2154	1.01447
.0009944	2.2170	1.01589	.001009	2.2143	1.10448
.001282	2.2236	1.01592	.001804	2.2155	1.01470

[a] Values in parentheses obtained by extrapolation.

Experimental

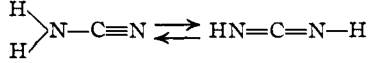
The apparatus and measuring technique have been described previously.[3] The compounds investigated are listed in Table I. Table II lists the experimental values of E, dielectric constant; d, density; and w, weight fraction, for dioxane solutions of the compounds at 35°. Dipole moments were calculated by a modified Hedestrand method similar to that introduced by Halverstadt and Kumler,[4] differing in that densities were used rather than specific volumes. The empirical equation used may be written as

$$ {}_{\infty}p_T = \frac{\epsilon_0 - 1}{\epsilon_0 + 2} \times \frac{1}{d_0}\,[1 - \beta/d_0] + \frac{3\alpha}{(\epsilon_0 + 2)^2\, d_0} \quad (1) $$

where ϵ_0 = extrapolated dielectric constant of solvent
d_0 = extrapolated density of solvent
${}_{\infty}p_T$ = specific polarization at infinite dilution
α = slope of dielectric constant *vs.* weight fraction curve
β = slope of density *vs.* weight fraction curve

The total molar polarization, ${}_{\infty}P_T$, is obtained from the specific polarization by multiplying by the molecular weight. Atomic polarization was neglected, and molecular refractions were calculated from the atomic refractions listed in the "Landolt-Börnstein Tabellen." The values obtained from these calculations are listed in Table III, where P_D and P_O refer to the distortion and orientation polarizations, respectively.

Discussion

Any tautomeric equilibrium between cyanamide and carbodiimide,  $\begin{matrix}H\\H\end{matrix}\!\!>N{-}C{\equiv}N \rightleftarrows HN{=}C{=}N{-}H$ seems quite improbable if one compares the electric moments of cyanamide, 4.52D, diisopropylcyanamide, 4.76D, and diisopropylcarbodiimide, 2.08D. The close agreement between cyanamide and its diisopropyl derivative indicates essentially identical structures. Although one might argue that the small discrepancy, 0.24D, could be interpreted as resulting from tautomerism, it seems more probable that the observed increase from cyanamide to diisopropylcyanamide results from replacing the hydrogen atoms of the amide group by the more negative isopropyl group, causing a small

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[1] Hunter and Rees, *J. Chem. Soc.*, 617 (1945).

[2] Devoto, *Gazz. chim. ital.*, **63**, 491 (1933).

[3] Schneider and Halverstadt, THIS JOURNAL, **70**, 2626 (1948).

[4] Halverstadt and Kumler, *ibid.* **64**, 2988 (1942).

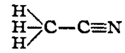
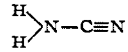
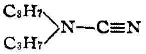
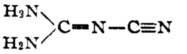
TABLE III

Compound	α	β	$_\infty p_T$	Mol. wt.	$_\infty P_T$	P_D	P_O	$\mu \times 10^{18}$
Cyanamide (benzene)	39.43	0.2303	7.824	42	328.6	7.8	320.8	4.00
Cyanamide (dioxane)	57.75	.1515	9.935	42	417.3	7.8	409.5	4.52
Dicyandiamide	95.14	.5000	16.13	84	1355	21.8	1333	8.16
Diisopropylcyanamide	20.90	− .3417	3.879	126	488.7	35.2	453.5	4.76
Diisopropylcarbodiimide	3.61[8]	− .2968	0.9689	126	122.1	35.2	86.9	2.08
p,p'-Dichlorophenylcarbodiimide	0.0	.2550	0.2128	263	55.9	56.5	(−0.6)	0.0

additional polarization in the molecule. A similar effect is noted when one compares hydrogen chloride, $\mu = 1.32D$, with methyl chloride, $\mu = 1.86D$.

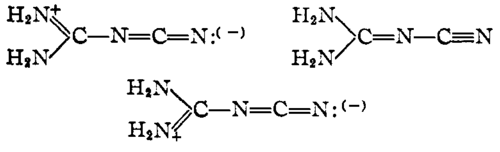
The large dipole moment of the cyanamide molecule undoubtedly results from resonance in the cyano group to give a structure $R{-}C^+{=}N^-$. Although this resonance precludes the making of any bond moment calculations, it is still possible to obtain some qualitative data concerning the relative contribution of the ionic resonance structure as R is made successively more negative. The pertinent data are summarized in Table IV. It can be seen that as the substituent group becomes more negative, the dipole moment increases in small steps which are of the same order of magnitude as the electronegativity differences between the atoms attached to the cyano group except for the last compound dicyandiamide.

TABLE IV

Compound	Structure	Moment	$\Delta\mu$	Electronegativity[a] diff.
Hydrogen cyanide	$H{-}C{\equiv}N$	2.56[b]		
Acetonitrile	 $H_3C{-}C{\equiv}N$	3.33[b]	0.76	0.4
Cyanamide	 $H_2N{-}C{\equiv}N$	3.90[c]	.57	.5
Diisopropylcyanamide	 $(C_3H_7)_2N{-}C{\equiv}N$	4.76	.86[d] .34 (cor.)	.4
Dicyandiamide	 $(H_2N)_2C{=}N{-}C{\equiv}N$	8.16	...	...

[a] Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1942, p. 64. [b] Average of values in *Trans. Faraday Soc.*, 30, Appendix (1934). [c] Average of value in ref. 2 and present work. [d] Not corrected for solvent effect of dioxane.

The assignment of a structure to this particular compound has caused much controversy during the past ninety years. From the present investigation it is concluded that dicyandiamide in dioxane solution is best described by the structures proposed by Hughes.[5]



$$(H_2N^+)(H_2N)C{-}N{=}C{=}N{:}^{(-)} \qquad (H_2N)_2C{=}N{-}C{\equiv}N \qquad (H_2N)(H_2N^+)C{-}N{=}C{=}N{:}^{(-)}$$

It is interesting to note that the same types of resonance structures have to be assumed to account for the large electric moment of urea, wherein the cyanimino group of dicyandiamide is replaced by the carbonyl group.

The electric moment values for the carbodiimide derivatives besides giving considerable aid in determining the structure of cyanamide have proved extremely useful in confirming the structure assigned to carbodiimide. According to Sidgwick,[6] the peculiar arrangement of carbon and nitrogen bonds in this molecule should allow the existence of optically active isomers. The exact stereo relationships are most easily seen from a consideration of Fig. 1. Here, the —N=C=N— chain is assumed to be located along the Y axis. In both isomers, the bond to one substituent group, R_2, is assumed to lie in the $(-Y, -Z)$ plane, whereas, with one enantiomorph, the bond to the other substituent group, R_1, lies in the $(-X, +Y)$ plane and with the other in the $(+X, +Y)$ plane.

The only experimental evidence in support of this asymmetrical structure has been the work of Bergmann and Schütz[7] showing that diphenyl carbodiimide has a finite electrical moment, $1.89D$. However, these investigators did not favor the asymmetrical structure but proposed a linear structure, assuming a finite moment for the N=C=N chain.

The most interesting information obtained from the present work is the observation that *p,p'*-dichlorophenylcarbodiimide has a zero moment. The most plausible explanation of this zero moment is that the aromatic carbon–nitrogen bond moment exactly equals the aromatic carbon–chlorine moment and acts in an opposite direction. An independent value for the carbon–nitrogen moment can be calculated from the observed moment of diphenylcarbodiimide and the proposed structure, assuming that φ, the —C—N=

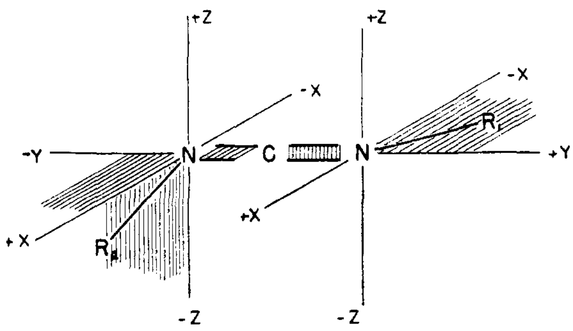


Fig. 1.

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(5) Hughes, THIS JOURNAL, **62**, 1258 (1940).

(6) Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, 1937, pp. 294–295.

(7) Bergmann and Schütz, *Z. physik. Chem.*, **B19**, 389 (1932).

C— bond angle is 121°. Using this value for φ, the angle between the bond moment vectors is calculated to be 105.4°. Substituting the above values in the cosine relation, assuming $\mu_{\text{C-H}} = 0.4D$, one obtains $\mu_{\text{Car.-N}} = 1.17D$.[8] Since the observed moment of chlorobenzene is $1.56D$,[9] then $\mu_{\text{Car.-Cl}} = 1.16D$, which exactly equals $\mu_{\text{Car.-N}}$. Similarly, using the observed moment of diisopropylcarbodiimide, $2.08D$, one obtains $\mu_{\text{C-N}} = 1.28\,D$.

The above analysis clearly indicates that the unsymmetrical structure proposed for carbodiimide, indicated in Fig. 1, is reasonably correct, and given a suitable technique, it should be possible to separate the optical antipodes.

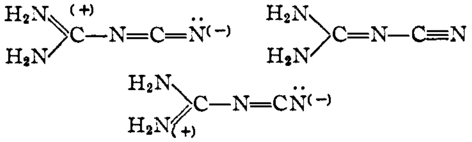
Acknowledgment.—The author wishes to express his indebtedness to the American Cyanamid Company for permission to publish these results and to Drs. D. J. Salley and R. F. Stamm for much helpful discussion.

Summary

1. The dipole moments of cyanamide (4.52D), dicyandiamide (8.16D), diisopropylcyanamide (4.76D), diisopropylcarbodiimide (2.08D) and *p,p'*-dichlorophenylcarbodiimide (0.0D) have been determined at 35° in dioxane solution.

2. The essential identity of the moments of cyanamide and diisopropylcyanamide compared with the moment of diisopropylcarbodiimide precludes any extensive tautomerism between cyanamide and carbodiimide.

3. The observed high moment of dicyandiamide is best explained by assuming resonance among the structures



4. The finite moment of diisopropylcarbodiimide and the observed zero moment of *p,p'*-dichlorophenylcarbodiimide support the asymmetrical structure assumed for carbodiimide.

5. The carbon–nitrogen bond moment in carbodiimide derivatives has been found to be approximately 1.2D compared to 0.6D in such compounds as trimethylamine.

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[8] It can be calculated from the data of Sutton, *Nature*, **128**, 639 (1931), that the carbon–nitrogen linkage in aromatic azides has approximately this value.

[9] Meyer and Buchner, *Physik. Z.*, 390 (1932).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY OF THE UNIVERSITY OF CAMBRIDGE]

An Improved Diaphragm-cell for Diffusion Studies, and Some Tests of the Method

By R. H. STOKES[1]

Recent very precise measurements by Harned and Nuttall[2,3] of the diffusion coefficients of potassium chloride in solutions up to half normal concentration provide a valuable standard by which to test the accuracy of the porous-diaphragm technique due to Northrop and Anson.[4] The development of this method up to 1945 has been reviewed by Gordon[5]; since then there have been modifications designed to give more rapid results,[6] and some applications of tracer techniques,[7] but little new work on electrolytes is reported.

It is clear from Gordon's discussion that the chief points needing further investigation are: the effect of stirring; the extent to which bulk flow occurs, as distinct from diffusion; the choice of a suitable standard for calibration; and the possible disturbing effects of the large surface provided by the diaphragm pores. The present paper deals with these matters, as a preliminary to work on the diffusion coefficients of a number of electrolytes at high concentrations.

I. Design and Operation of a Stirred Diaphragm-cell.—Most users of diaphragm-cells have followed Northrop and Anson[4] in mounting the cell with the diaphragm in a horizontal plane, with the denser solution uppermost, so that the density changes resulting from diffusion lead to the circulation of the liquid in each compartment. One may reasonably doubt whether such circulation is adequate to maintain a really uniform composition, especially if the solutions are very dilute or if the salt studied has only a small density change per unit concentration. There is furthermore the possibility that an appreciable thickness of the liquid near the surface of the diaphragm is held in a stagnant condition. Gordon[5] points out that though such layers have been proved to behave reproducibly, it is by no means certain that they are of equal importance at all concentrations or for different electrolytes. Another disadvantage of this set-up is that the system is inherently unstable with respect to gravity, so that when large concentration differences are used there may well be a certain amount of bulk flow through the diaphragm in addition to diffusion.

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[1] Imperial Chemical Industries Research Fellow, University of Cambridge.

[2] H. S. Harned and R. Nuttall, THIS JOURNAL, **69**, 736 (1947).

[3] H. S. Harned and R. Nuttall, *ibid.*, **71**, 1460 (1949).

[4] J. H. Northrop and M. L. Anson, *J. Gen. Physiol.*, **12**, 543 (1929).

[5] A. R. Gordon, *Ann. N. Y. Acad. Sci.*, **46**, 285 (1945).

[6] A. Aten and J. v. Dreve, *Trans. Faraday Soc.*, **44**, 202 (1948); J. C. Gage, *ibid.*, **44**, 253 (1948).

[7] A. W. Adamson, *J. Chem. Physics*, **15**, 762 (1947); E. B. Robinson and J. B. Drew, *ibid.*, **15**, 417 (1947).