TABLE IV

COMPARISON OF ASSIGNMENT OF FUNDAMENTAL FREQUENCIES: C_3H_6, C_2H_4O, C_2H_4NH AND $C_2H_4{\cdot}NCH_3$; REF. 4

Description	C_3H_6	C_2H_4O	C_2H_4NH[a]	$C_2H_4{\cdot}NCH_3$[b]
CH valency	A_1' 3029	A_1 3007	A′ 3015 I g.	
	E′ 3024	B_1 3007	A′ 2940 I g.	2978
	E″ 3080	A_2 3061	A″ 3079 I g.	3199
	A_2'' 3103	B_2 3061	A″ 3035 I g.	3066
				2900
				2855
				2793
CH_2 deformation	A_1' 1504	A_1 1487	A′ 1486 I g.	1466
	E′ 1435	B_1 1469	A″ 1446 I g.	1444
CH_2 bending		A_1 1120	A′ 1103 I g.	
	E′ 1022	B_1 1153	A′ 1157 R l.	
CH_2 rocking	A_2'' 872	B_2 1153	A′ 918 I l.	1080
	E″ 1120	A_2 1379	A″ 1237 I g.	1292
CH_2 twist	E′ 740	B_2 704	A′ 777 I g.	750
	A_1'' 1000			
	E″ 740	A_2 1023	A″ 1001 I g.	1102
Ring deformation	A_1' 1189	A_1 1267	A′ 1215 I g.	1201
	E′ 866	A_1 863	A′ 855 R l.	818
	E′ 866	B_1 806	A″ 838 I g.	740
NH stretch			A′ 3341 I g.	
NH deformation			A′ 1209 I g.	
NH bending			A″ 1654 I g.	
$N-CH_3$ stretch				1007
$N-CH_3$ deformation				1266
$N-CH_3$ bending				1276

[a] l. = liquid, g. = gas, R = Raman Effect, I = Infrared. [b] All infrared of the gas.

1b. In general, the band envelopes are not as well resolved as in the case of ethylenimine. The observed values of the frequencies of the infrared bands are shown in Table III. A partial assignment is given in the last column of Table IV following the assignments for cyclopropane, ethylene oxide and ethylenimine.

Although the assignments for ethylenimine and N-methylethylenimine are not quite complete, in the sense that certain frequencies have not been established definitely as combinations or overtones, still the picture presented here fits the general ideas of the chemist regarding the related structure of all of these molecules.

One of us (H.T.H.) wishes to express his thanks and appreciation to the Allied Chemical and Dye Corporation for a fellowship grant under which a portion of this research was carried out.

RECEIVED AUGUST 31, 1950

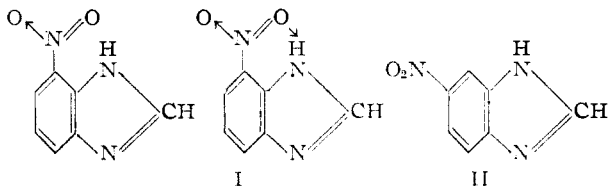
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Restriction of Tautomerism in the Amidine System by Hydrogen Bonding. The Case of 4(7)-Nitrobenzimidazole[1]

BY JOSEPH L. RABINOWITZ[2] AND E. C. WAGNER

Comparisons of 5(6)-nitrobenzimidazole and 4(7)-nitrobenzimidazole directed toward the recognition of possible chelation in the latter resulted as follows. The 4(7)-isomer is the more rapidly reduced polarographically and the more easily reduced catalytically suggesting an intramolecular influence that makes the nitro group more susceptible to reduction. The 4(7)-isomer is the weaker acid, suggesting presence of an obstruction to removal of the essential proton. The 4(7)-isomer is the less associated in solution, suggesting that the hydrogen atoms required for mesohydric linkages are otherwise involved. The 4(7)-isomer is conspicuously the more volatile, being readily sublimed or codistilled with effluent vapors. It is concluded that chelation in 7-nitrobenzimidazole offers a demonstrable impediment to its isomerization to the 4-nitro tautomer by immobilization of the hydrogen involved in the prototropy of this amidine system.

This paper extends to the isomeric nitrobenzimidazoles the methods of investigation of the influence of chelation upon the tautomerism (internal and mesohydric) of the amidine system applied by Runner, Kilpatrick and Wagner[3] to the isomeric N-phenyl-N′-nitrophenyl acetamidines. Of the two nitrobenzimidazoles the structure of the 4(7)-isomer (I) permits chelation and to whatever extent the hydrogen bond is stable to competitive influences (association, solvation, acid or alkaline environment) the tautomeric form so involved is fixed. It is to be expected that this difference will be reflected in certain differences in properties when the two isomers are compared by suitable procedures. The comparison of the nitrobenzimidazoles is somewhat simpler than that of the N-phenyl-N′-nitrophenyl acetamidines: the 4(7)-isomer can chelate in only one way[4]; only two isomers need be compared; the somewhat problematic effects of environment upon the ortho, meta and para nitro group, especially in alkaline medium, are here less complicated, for the 4(7)-nitro and the 5(6)-nitro compounds both have the nitro group ortho or para with respect to one of the nitrogen atoms so that both isomers are capable of quinonoid–nitronic acid tautomerism. The differences between the two isomers due to causes other than chelation should therefore be less obtrusive than with the N-phenyl-N′-nitrophenyl acetamidines.



I II

The experimental means employed included

(1) Paper constructed from the Ph.D. dissertation of Joseph L. Rabinowitz, University of Pennsylvania, 1950.

(2) The School of Medicine, Department of Physiological Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania.

(3) M. E. Runner, Mary Kilpatrick and E. C. Wagner, THIS JOURNAL, **69**, 1406 (1947).

(4) Reference 1, p. 1407, footnote 15.

those applied previously, *viz.*, comparative studies of volatility, association and of the reducibility of the nitro group both polarographically and catalytically. Two additional experimental procedures were applied, *viz.*, potentiometric titrations with acid and base, and ultraviolet spectral comparison of the isomers, to ascertain whether or not there is any observable difference in the acid–base relationships attributable to chelation, and in the ultraviolet adsorption assignable to the change in structure and electronic character due to involvement of the nitro group in chelation. Results of the six experimental approaches are discussed below. It may be said at once that the evidence supports the conclusion that chelation exists in 4(7)-nitrobenzimidazole, in which therefore some stabilization of 7-nitrobenzimidazole occurs.

1. **Volatility.**—The difference between 4(7)-nitrobenzimidazole (I) and 5(6)-nitrobenzimidazole (II) with respect to volatility is striking. The former is conspicuously volatile on warming, sublimes readily (and may be so purified), and is volatile from hot concentrated solutions in alcohol or ethyl acetate; the latter shows no tendency to volatilize. Similar differences were observed for the 2-methyl, 2-ethyl and 2-phenyl derivatives of the two nitrobenzimidazoles. It is generally accepted that when the volatility of a compound apparently capable of chelation is unexpectedly high or much higher than that of an isomeric and structurally similar compound not so capable, this fact may be considered to be inferential evidence that chelation is present.[5]

2. **Polarographic Reduction.**—Values for the half-wave potentials of I and II were determined polarographically in alcohol and at various points in the pK range 1 to 17[6,7] with parallel control determinations on nitrobenzene (III). The amphoteric amidine system in the nitrobenzimidazoles is responsive to the nature of the environment which through the pK range stated, may determine a series of molecular and ionic states analogous to those represented for the N-phenyl-N′-nitrophenyl acetamidines.[3] Results of the polarographic measurements appear in Table I.

The differences in half-wave potentials for I, II and III are shown graphically in Fig. 1. It is shown that 4(7)-nitrobenzimidazole (I) is reduced at lower potential than 5(6)-nitrobenzimidazole (II) and nitrobenzene (III). This is true throughout the pK range, but the differences between I and II are least in strongly acid solution (pK 1) and reach a maximum at pK 17, with a plateau at and near the neutral point. Under strongly acid conditions, with chelation in I presumably excluded, the difference in reducibility for I and II becomes almost zero, while the differences for I and III increase up to pK 3, reflecting the increased reducibility of the nitro group in acid environment.

(5) W. Baker, *J. Chem. Soc.*, 1684 (1934); L. Pauling, "The Nature of the Chemical Bond." Cornell University Press, Ithaca, N. Y., 1948, p. 332.

(6) M. E. Runner, dissertation, University of Pennsylvania, 1950.

(7) The buffers used were those developed by Runner[6] for examination of nitroacetanilides, nitrophenols, etc., in absolute ethanol. Since pK values are used only comparatively and not numerically (in which respect they are not precise) the resulting pK system is consistent and serves the purpose of this study.

TABLE I

POLAROGRAPHIC REDUCTION OF 5(6)-NITROBENZIMIDAZOLE (II), 4(7)-NITROBENZIMIDAZOLE (I) AND NITROBENZENE (III) IN ETHANOL. VALUES OF $E_{1/2}$ AND VARIATIONS OF $\Delta E_{1/2}$ AND DIFFUSION CURRENT WITH pK

pK	Compd.	Diffusion current[a]	$E_{1/2}$ at 25°, v.	$E_{1/2}$(II) − $E_{1/2}$(I)	$E_{1/2}$(III) − $E_{1/2}$(I)
	II	1.9	−1.12		
17	I	2.0	−0.96	0.16	0.02
	III	3.4	− .98		
	II	2.2	− .90		
13	I	2.2	− .90	.13	.03
	III	3.4	− .93		
	II	2.2	− .70		
10	I	2.1	− .59	.11	.09
	III	3.3	− .68		
	II	2.0	− .73		
9	I	2.2	− .62	.11	.11
	III	3.3	− .73		
	II	2.1	− .65		
8	I	2.2	− .54	.11	.12
	III	3.3	− .66		
	II	2.4	− .63		
6	I	2.4	− .52	.11	.13
	III	3.3	− .65		
	II	2.4	− .42		
5	I	2.4	− .34	.08	.14
	III	3.3	− .48		
	II	1.9	− .17		
3	I	1.9	− .12	.05	.24
	III	3.3	− .36		
	II	2.0	− .03		
1	I	2.1	− .01	.02	.19
	III	3.3	− .20		

[a] For 2×10^{-4} M solutions.

As alkalinity increases, chelation in I must be progressively excluded by withdrawal of the essential hydrogen, and the situation is then com-

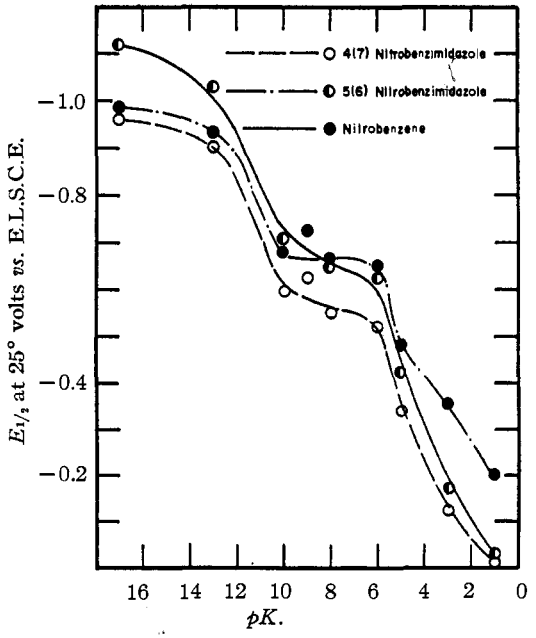


Fig. 1.—Half-wave potentials at 5(6)- and 4(7)-nitrobenzimidazoles and of nitrobenzene.

plicated by the tendencies of both I and II to assume the quinonoid–nitronic acid forms. The vicinal isomer I was observed to be the more prone to such isomerization, for strongly alkaline solutions of I are deep yellow in color, and contact of I with solid sodium ethoxide produces a deep red color; under the same conditions II shows much weaker colors. While this is consistent with the easier reducibility of I in strongly alkaline solution it has no relevancy with respect to chelation. Attention will therefore be centered upon results at and near neutrality,[8] since these are comparable with the results of other and independent procedures, *viz.*, catalytic hydrogenation, volatility, association and spectral examination.

Under approximately "neutral" conditions (pK 6–10) compound I is reduced more readily than II or III, the differences being almost the same, *viz.*, 0.11 ± 0.02 volt and 0.12 ± 0.02 volt, respectively. The virtually equal reducibilities of II and III and the easier reducibility of I suggest that in II, as in III of necessity, the nitro group is in normal

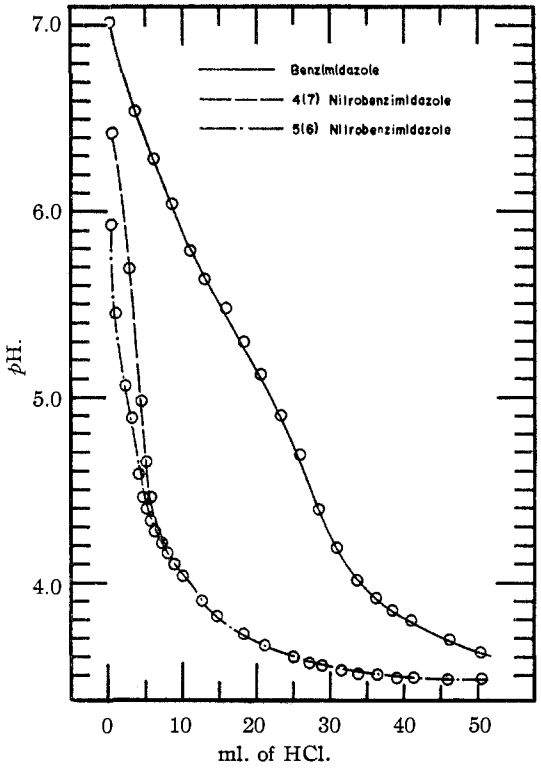


Fig. 2.—Potentiometric titrations of 5(6)- and 4(7)-nitrobenzimidazoles and of benzimidazole with 0.001 *N* hydrochloric acid.

(8) It is appreciated that the easier reducibility of I than of II at all pK values applied (at some of which chelation is presumably excluded) diminishes the significance and specificity of the polarographic evidence with respect to chelation, and that indeterminate factors other than chelation (*e.g.*, quinonization, induced positional effects of the nitro group) may be involved, especially under conditions sufficiently acid or alkaline to induce structural or ionic changes. It is believed that results for extended pK ranges add to those representing substantially neutral conditions little that is relevant with regard to restriction of amidine tautomerism by chelation. Polarographic data for extended pK ranges permit inferences as to the responses of molecules to change in environment, and estimation of the extent of reduction at each pK value, and are therefore retained as of possible interest in filling out a picture of the polarographic behaviors of the compounds.

state, but that in I the nitro group is subject to influence that renders it more susceptible to reduction. It is assumed that this influence is chelation, by which are destroyed the equivalence of the oxygen atoms, and therefore the resonance of the nitro group, which as a result of hydrogen bonding is in a state of "incipient hydrogenation." Calculations by means of the Ilkovic equation,[9] using the approximate values obtainable for the diffusion coefficients, indicate a four-electron reduction for both I and II and a six-electron reduction for III.

3. Catalytic Hydrogenation.—Comparative hydrogenations of I and II in ethanol, using palladium–charcoal catalyst and pressure of hydrogen 10 mm. above atmospheric pressure, yielded the results in Table II. It is shown that I

TABLE II

		Quantity Cmpd. Mole	g.	Catalyst g.	%	Relative rates Cmpd. II	Cmpd. I	Reproducibility
Temperature effect (equal catalyst)	30°	0.001	0.1631	0.050	3	1.0	2.0	Good
	75°	.001	.1631	.050	3	1.0	1.5	Poor
Catalyst effect at 25°		.0005	.0815	.0250	5	1.0	1.75	Good
		.0005	.0815	.0500	5	1.0	1.37	Good
		.0005	.0815	.1000	5	1.0	1.25	Fair

is reduced more rapidly than II; the relative rates are 3:2 at 25° and 2:1 at 30 and 75°. Increase in the amount of catalyst increased the rates of hydrogenation for both isomers, the increase for II being the more rapid, but in all cases I was more rapidly reduced.[10]

4. Acid-Base Strengths by Potentiometric Titration. (a) **Base Strengths.**—Consideration of the probable effects of acids upon the amphoteric amidine system,[3] and of the observation by Pyman[11] that methylation of amidines affects the tertiary nitrogen, leads to the supposition that the basic characters of I and II may be not dissimilar and that chelation in I may not greatly affect the ability of a nitrogen atom to take on a proton. Potentiometric titrations of I and II with hydrochloric acid in water yielded results (Fig. 2) that show the base strengths of the two isomers to be virtually identical, with half-equivalence at pH 3.80 and equivalence at pH 3.60 for both compounds. Similar titration of benzimidazole (IV) showed it to be a stronger base than I and II, with half- and full-equivalence points at pH 5.60 and 4.65.

(b) **Acid Strengths.**—The nitro groups of I and II may be expected to increase the acid strengths to extents that vary with the position of the proton (of the =NH of the imidazole ring) with respect to the nitro group in each case. Because

(9) D. Ilkovic, *Collection Czechoslov. Chem. Commun.*, **6**, 494 (1934); D. MacGillavry and E. K. Rideal, *Rec. trav. chim.*, **56**, 1013 (1937); J. J. Lingane and B. A. Loveridge, THIS JOURNAL, **72**, 438 (1950).

(10) No attempt to explain the tendency of increase in the amount of catalyst toward equalization of the rates of reduction of the isomers seems advisable, as the adsorption–desorption characteristics of the compounds involved are undetermined. The hydrogenations initially (to about 50% completion) appear to be of zero order, permitting the conclusion that the observed rate-differences are due to property differences. The experimental activation energies for I and II are calculated to be about 23 and 25 kcal.; the difference is close to the experimental error.

(11) F. L. Pyman, *J. Chem. Soc.*, 3359 (1923).

of relatively free tautomerism in II its acid character is an over-all value to which both tautomers may contribute, but in I chelation may impair the lability of the acid hydrogen and thus weaken the acid character of the compound. Potentiometric titrations of I, II and benzimidazole (IV) with sodium hydroxide in water solution yielded results (Fig. 3) which show the acid strengths to be in the order II > IV ≅ I. Values for IV and I are nearly identical, the *p*H values for half-neutralization and equivalence for II and I ≅ IV being 9.4 and 9.5, and 9.9 and 10.0. The fact that I is weaker than II by 0.5 *p*H unit cannot well be attributed to unlike activating effects by the nitro groups (exerted in I from the ortho and meta positions, and in II from the para and meta positions), but appears to be accounted for more satisfactorily by assumption of chelation in I, which not only binds the essential hydrogen and opposes its withdrawal as proton, but modifies the character and therefore the influence of the nitro group.

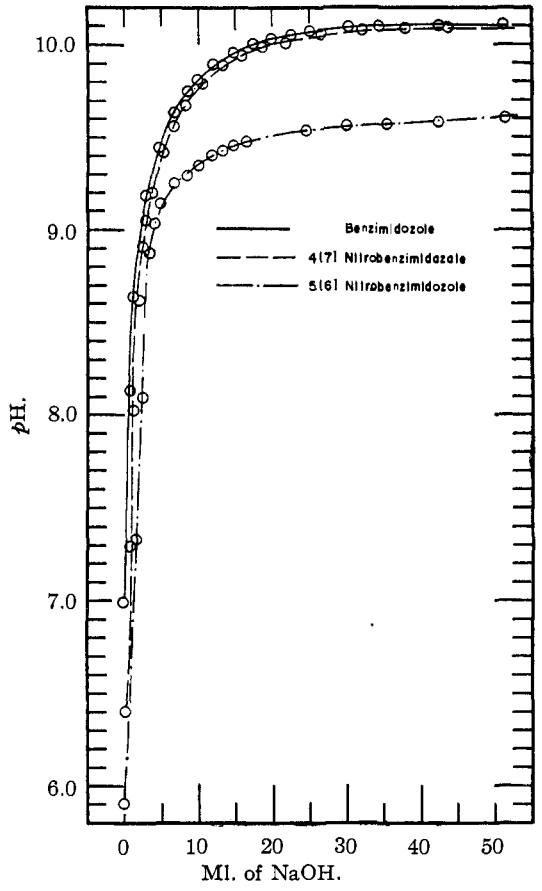


Fig. 3.—Potentiometric titrations of 5(6)- and 4(7)-nitrobenzimidazoles and of benzimidazole with 0.0008 *N* sodium hydroxide.

5. Ultraviolet Absorption.—The absorptions of 4(7)-nitrobenzimidazole (I) and 5(6)-nitrobenzimidazole (II) were determined in ethanol under neutral, acid (0.01 *N* hydrochloric acid) and alkaline (0.1 *N* sodium ethoxide) conditions. The resulting curves, all somewhat resembling the curve of nitrobenzene, appear in Figs. 4, 5 and 6.

Two principal maxima appear in all cases and,

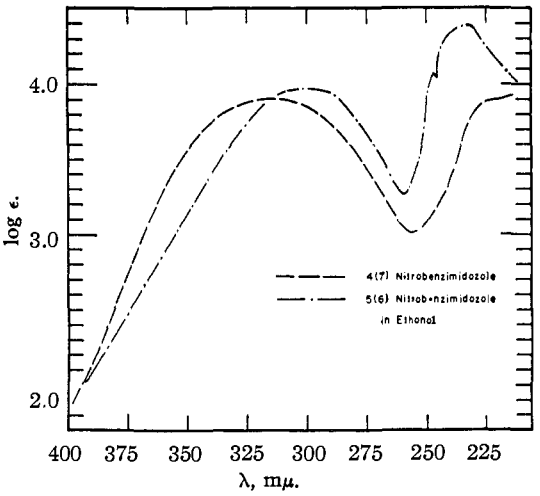


Fig. 4.—Ultraviolet absorptions of 5(6)- and 4(7)-nitrobenzimidazoles in neutral ethanol solutions.

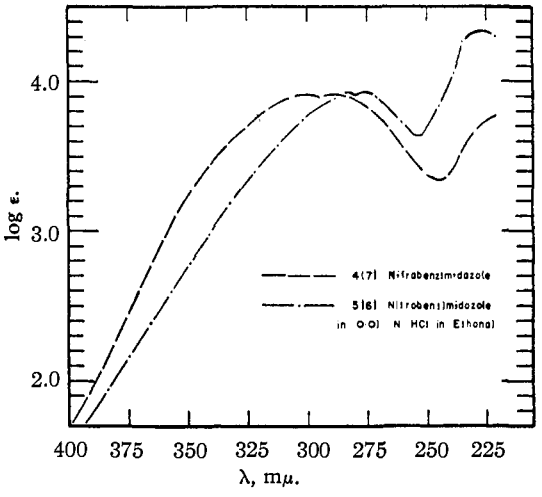


Fig. 5.—Ultraviolet absorptions of 5(6)- and 4(7)-nitrobenzimidazoles in acidified ethanol solutions.

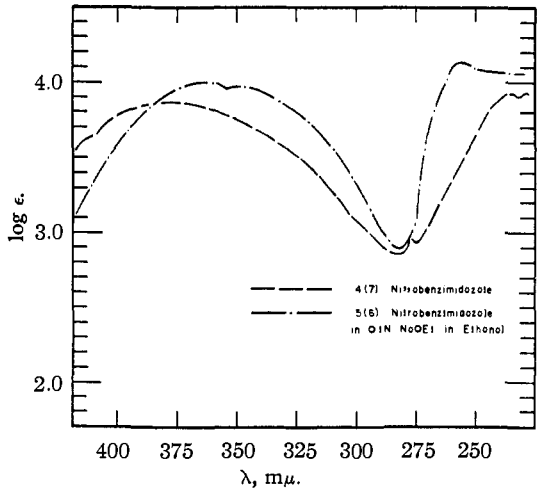


Fig. 6.—Ultraviolet absorptions of 5(6)- and 4(7)-nitrobenzimidazoles in ethanol-sodium ethoxide solutions.

without substantial change in general form, there is a hypsochromic displacement in acid solutions and a bathochromic displacement in alkaline solu-

tions. The results under neutral conditions (Fig. 4), and specifically the absorption of longer wave lengths by I (maxima at about 315 mμ) than by II (maxima at about 300 mμ), appear to be consistent with the view that in I there is indicated some stabilization of polarities, perhaps attributable to chelation. A conclusion to this effect seems to be excluded by the fact that analogous displacements are shown (Figs. 5 and 6) for the isomers in acid and alkaline solutions, under which conditions chelation in I seems improbable or impossible. In a not too strongly acid solution chelation might persist, but under alkaline conditions the absorptions extend into the visible region, and appear to indicate conversion of the nitrobenzimidazole structure with that of the anion of the quinonoid nitronic acid; this effect is more pronounced for I, as is the case also with respect to the visible colors produced by action of alkali on the two isomers. The location of the maxima in the region of shorter wave lengths shows I to absorb farther toward the ultraviolet than II, but this fairly consistent difference likewise cannot be held significant with respect to chelation in I. It appears that the two nitrobenzimidazoles show no differences in ultraviolet absorption which at present can fairly be associated with chelation in isomer I.

6. **Association.**—Benzimidazoles, like open-chain amidines, associate through intermolecular hydrogen bonds,[12] but as association is decreased or excluded if the labile hydrogens are involved in chelation, the comparative determination of molecular weights and of association factors for isomeric compounds of which only one is capable of chelation provides a basis for judging whether or not chelation is present.[12,13,14,15] It is desirable to use a cryoscopic rather than an ebullioscopic method, since association is decreased by increase in temperature and since both association and chelation may be statistically not more than partial, the joint effect of these influences being to decrease toward the point of uncertainty the differences due to chelation.

Phenanthrene was found to be a satisfactory cryoscopic solvent for the nitrobenzimidazoles. The results of comparative molecular weight determinations at increasing concentrations of I and II up to saturation are plotted in Fig. 7.

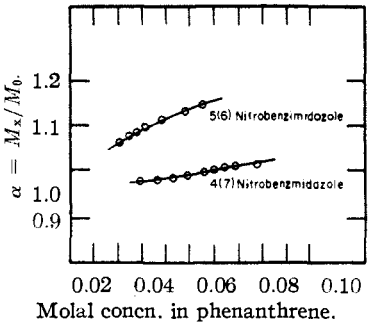


Fig. 7.—Association factors of 5(6)- and 4(7)-nitrobenzimidazoles in phenanthrene.

At and near 98° the association of II is considerable, the association factor M_x/M_0 changing with concentration from 1.09 to 1.13. The association factor for I is near unity, the slope of the curve M_x/M_0 *vs.* concentration being slight. The difference in the indicated associations of I and II is about 10%; the error of observation does not exceed 3%. The fact that association of I is less than that of II is interpreted to mean that in I internal hydrogen bonding makes the hydrogen atom unavailable for associative hydrogen bonding.

The comparisons of 4(7)-nitrobenzimidazole and 5(6)-nitrobenzimidazole made as outlined above thus yielded results all of which, excepting those by ultraviolet absorption, are interpretable as indicative of the existence of 4(7)-nitrobenzimidazole to a significant extent in chelated form, representing an interference with free tautomerism and a stabilization of 7-nitrobenzimidazole.

Experimental

New compounds are indicated by asterisks. Analyses were performed by Sarah M. Woods.

Preparations: 1. **4(7)-Nitrobenzimidazole** (I) was prepared in six steps starting with *o*-nitrochlorobenzene. The entire process is outlined here, because available procedures were found to require considerable study and modification. The over-all yield is about 37%.

Potassium 3,5-Dinitro-4-chlorobenzene Sulfonate.[16,17]—To 157.5 g. (1 mole) of *o*-nitrochlorobenzene (Eastman Kodak Co. No. 184) in a 3-liter beaker in an ice-bath was added gradually 600 g. (307 ml.) of fuming sulfuric acid (25% SO_3). The mixture was withdrawn from the ice-bath, and after about 20 minutes at room temperature was heated on a steam-cone for 2 hours. It was then chilled and treated slowly with a previously prepared and chilled mixture of 120 ml. of red fuming nitric acid (sp. gr. 1.59) and 120 ml. of fuming sulfuric acid, followed by an additional 110 ml. of fuming sulfuric acid. After an hour at room temperature the mixture was heated on a steam-cone for 16 hours, and was then chilled in ice and poured into a 3-liter beaker filled with chipped ice. After filtration the liquid was treated with a solution of 90 g. of potassium chloride in 300 ml. of water. The precipitated sulfonate was collected in a sintered-glass funnel, washed with cold saturated potassium chloride solution, and dried at 70° or in a desiccator over calcium chloride. Yields ranged from 200 to 225 g. (65 to 70%). The crude material (m.p. 300° with effervescence) is colorless; it can be crystallized from hot water, but was generally used as obtained.

Potassium 3,5-dinitro-4-aminobenzene sulfonate[17,18] was prepared from the preceding by adding it in small portions and with stirring to five times as much concd. ammonia water in a large beaker (hood), then warming for 30 minutes on a steam-bath and chilling. The separated salt, washed with concd. ammonia water and dried in the air, showed no m.p. but decomposed rather violently on heating. The yield was 97%.

2,6-Dinitroaniline.[17,18]—To a mixture of 2 liters of a chilled mixture of 3 parts of water and 66 parts (both by volume) of concd. sulfuric acid in a 5-liter flask was added 200 g. of potassium 3,5-dinitro-4-aminobenzene sulfonate. An air condenser was attached, and the mixture was heated on a steam-cone for 12 days. The deep red liquid was chilled, and was poured into crushed ice in a beaker surrounded by cracked ice. The precipitated product was dried at 50° (it sublimes readily). Yields ranged from 75 to 85%. Crystallization from 95% ethanol yielded the pure compound of m.p. 137–139°; recovery was 80%.

1,2-Diamino-3-nitrobenzene.[19,20]—To 4.6 g. (0.025 mole) of 2,6-dinitroaniline in 75 ml. of ethanol (solution may not be complete) was added slowly and with stirring a warm

(12) L. Hunter and J. A. Marriott, *J. Chem. Soc.*, 777 (1941).
(13) L. Hunter, *et al.*, *ibid.*, 806 (1945).
(14) L. Hunter, *Ann. Reports Chem. Soc.*, **43**, 141 (1947).
(15) L. Hunter, *J. Chem. Soc.*, 615 (1945).
(16) German Patent 116,759 (1899); *Frdl.*, **5**, 931 (1899).
(17) F. Ulmann, *Ann.*, **366**, 105 (1909).
(18) C. H. Welsh, THIS JOURNAL, **63**, 3276 (1941).
(19) W. Borsche and D. Rantscheff, *Ann.*, **379**, 164 (1911).
(20) G. M. Van der Want, *Rec. trav. chim.*, **67**, 45 (1948).

solution of 20 g. of crystallized sodium sulfide and 7 g. of sodium bicarbonate in 40 ml. of water. The mixture was warmed at 60° for an hour, then was cooled and filtered. The residue was washed with a few drops of ethanol, and the entire filtrate was diluted with cold water. The crude precipitated diamine was pure enough for the final operation; after crystallization from hot ethanol the yield was 2.7 to 3.0 g. (70–80%). The compound is deep red in color and melts at 159° (cor.).

4(7)-Nitrobenzimidazole.—To 3.0 g. (0.02 mole) of 1,2-diamino-3-nitrobenzene in a small flask fitted with vertical condenser was added 6 g. (4.4 ml., 0.12 mole) of 98% formic acid previously diluted with 4 ml. of water. The solution was heated at reflux for 2 hours, cooled, poured into 30 ml. of cold water, and made alkaline with concd. ammonia water. The pale yellow product, washed with cold water and air-dried, was purified by sublimation at 100° effected as follows. The dry material, in a petri dish, was placed in an oven at 100°, and a beaker filled with chipped ice was placed on top of the dish. The sublimate was removed at intervals, with renewal of the ice as needed. The product (2.6 g., 80%) melted at 240–241° cor. It was dissolved in nearly minimal hot ethanol and caused to crystallize by judicious addition of water, and then melted at 242° cor.; Van der Want[20] reported the m.p. to be 238–239°. As this work was completed before Van der Want's results appeared in print the compound was analyzed; the values 51.32, 2.91 and 25.55 for carbon, hydrogen and nitrogen are consistent with the formula $C_7H_5O_2N_3$.

2. **5(6)-Nitrobenzimidazole** (II).—To a solution of 92 g. (0.5 mole) of 2,4-dinitroaniline (Eastman Kodak Co. No. 1843) in 1800 ml. of methanol was added slowly a solution of 318 g. of crystallized sodium sulfide and 112 g. of sodium bicarbonate in 530 ml. of water. The mixture kept at 60° was stirred for 4 hours, chilled and filtered, and the filtrate was diluted with water to turbidity. After about 24 hours the separated product was removed and crystallized from ethanol. The yield of 1,2-diamino-4-nitrobenzene of m.p. 199° (cor.) was 38–42 g. (50–55%).

To prepare II, 15.3 g. (0.1 mole) of diaminonitrobenzene was heated with 28 g. (20.5 ml., about 0.6 mole) of 98% formic acid under reflux for 3 hours. The cooled solution was poured into 200 ml. of cold water and the mixture was made alkaline with ammonium hydroxide. The precipitate was washed with water, dissolved in water with the aid of hydrochloric acid, and the solution was digested with Norite. The filtrate was made alkaline with ammonium hydroxide and was concentrated by evaporation until chilling caused a copious separation of product, which was removed and dried at 125°. The yield of II was 13 g. (80%) and the m.p. 203–205° (cor.).[21] Material for polarographic testing, recrystallized twice from water and then from aqueous ethanol, was colorless and melted at 204–205° (cor.).

3. **Other Compounds*, 2-Phenyl-4(7)-nitrobenzimidazole.**—To a mixture of 1.5 g. (0.01 mole) of 1,2-diamino-3-nitrobenzene and 4–5 ml. of 10% aqueous sodium hydroxide was added 1.5 g. (1 ml., a slight excess) of benzoyl chloride. After brief heating, during which a yellow precipitate appeared and melted, the mixture was chilled. Addition of more alkali increased the precipitate, which was separated and washed with concd. ammonium hydroxide. The product was dried and sublimed as outlined for 4(7)-nitrobenzimidazole. The canary-yellow phenylnitrobenzimidazole weighed 0.36 g. (15%) and melted at 175° (cor.).

Anal. Calcd. for $C_{13}H_9O_2N_3$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.41; H, 3.94; N, 17.58.

2-Methyl-4(7)-nitrobenzimidazole.[19]—A mixture of 1.5 g. (0.01 mole) of 1,2-diamino-3-nitrobenzene, 6 ml. (0.06 mole) of acetic anhydride and 0.5 ml. of concd. hydrochloric acid[22] was heated under reflux for 2 hours, cooled, and poured into 20 ml. of water. The product, isolated and purified as outlined above for 4(7)-nitrobenzimidazole, was obtained as yellow needles (1.3 g., 75%) melting at 217–218° (cor.).

2-Ethyl-4(7)-nitrobenzimidazole*.—A similar procedure, using 7.8 g. (7.6 ml., 0.06 mole) of propionic anhydride, yielded the product in impure condition. It was chromatographed using benzene as solvent, a 10-cm. column of alumina, and a 9:1 benzene–ethanol mixture as displacer. The material recovered by evaporation of the solvent was sublimed as described above: colorless needles (0.53 g., 28%), melting at 160–161° (cor.).

Anal. Calcd. for $C_9H_9O_2N_3$: C, 56.53; H, 4.74; N, 21.98. Found: C, 56.43; H, 4.76; N, 21.81.

2-Methyl-5(6)-nitrobenzimidazole was similarly prepared from 15.3 g. (0.1 mole) of 1,2-diamino-4-nitrobenzene, 64.8 g. (60 ml., 0.6 mole) of acetic anhydride and 5 ml. of concd. hydrochloric acid,[22] refluxed for 3 hours and then isolated as outlined for 2-methyl-4(7)-nitrobenzimidazole. The product was dissolved in water with aid of some hydrochloric acid, treated with Norite, and recovered from the filtrate by making alkaline with ammonia water, concentrating by evaporation, and chilling. The colorless methylnitrobenzimidazole dried at 120° (11.5 g., 65%), melted at 220–221° (cor.).[23]

Comparative Tests of 4(7)- and 5(6)-nitrobenzimidazoles 1. **Volatility Tests.**—In a sublimation apparatus comprising an obliquely supported tube with ventral indented ridge, electrically heated lower chamber and water-cooled upper chamber, and partially evacuated by means of a water aspirator, the following compounds sublimed readily and were almost quantitatively recovered: 4(7)-nitrobenzimidazole, 2-methyl-4(7)-nitrobenzimidazole, 2-ethyl-4(7)-nitrobenzimidazole and 2-phenyl-4(7)-nitrobenzimidazole. Both 5(6)-nitrobenzimidazole and 2-methyl-5(6)-nitrobenzimidazole failed to sublime.

Steam distillation tests of I and II in a conventional outfit showed the former to distil in steam very readily, and the latter apparently not at all.

2. **Polarographic Reduction.**—Solutions were prepared, stored and handled under nitrogen, and were transferred to storage reservoirs, burets, etc., by pressure of nitrogen, with a mercury trap in the nitrogen line. The gas (water-pumped "Airco" nitrogen) was purified by the method of Meites and Meites.[24] Before entering the system the nitrogen was passed through towers charged with ascarite and dehydrite. Before entering the electrolysis cell it was bubbled through a solution with the composition of the solution in the cell. Absolute ethanol, used as solvent in this work, was purified by the method of Lund and Bjerrum,[25] then distilled in an all-glass system with moisture excluded and forced by pressure of nitrogen into a reservoir previously evacuated and then filled with nitrogen.

Lithium Chloride in Ethanol.[6]—Lithium chloride was prepared by evaporating to dryness a filtered solution of freshly precipitated lithium carbonate (addition of ammonium carbonate to reagent grade lithium chloride) in hydrochloric acid. To prepare a 0.15 *M* solution 6.359 g. was weighed under nitrogen in a weighing bottle, and was transferred under nitrogen to a special volumetric flask provided also with an inlet tube, extending to the bottom of the flask, for introduction of nitrogen; the volume mark on the flask was adjusted for the displacement of this tube. The lithium chloride was transferred by dumping, and the weighing bottle was washed out with ethanol forced from the reservoir by pressure of nitrogen. The solution was made up to 1 liter by introduction of ethanol, and nitrogen was bubbled through the liquid until the lithium chloride was dissolved and for some minutes thereafter. The solution was then transferred by pressure of nitrogen into the storage reservoir.

Lithium Ethoxide in Ethanol.[6]—Pure lithium (soluble without residue in ethanol) was cut into small blocks, washed with ether, and slightly more than the quantity required for 2 liters of 0.10 *M* solution (1.388 g.) was weighed under nitrogen after allowing the ether to evaporate. The lithium was added to about 200 ml. of ethanol in a modified 2-liter volumetric flask (with fittings such as those outlined above), with a stream of nitrogen passing. When the metal was in solution, ethanol was added to the mark, and a 5-ml. sample was withdrawn and titrated with 0.1 *N* hydrochloric acid. The calculated small amount of ethanol required to make the solution 0.1 *M* was added, and the solution was forced into the storage reservoir.

Solutions of the nitrobenzimidazoles (0.001 *M*) were similarly prepared, using 0.0408 g. per 250 ml. of ethanol. Nitrobenzene (1.231 g.) was weighed into a modified 50-ml.

(21) K. Fries, *Ann.*, **454**, 227 (1927).

(22) M. A. Phillips, *J. Chem. Soc.*, 172, 2393 (1928).

(23) O. Fischer and W. Hess, *Ber.*, **36**, 3970 (1903).

(24) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

(25) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931); L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 359.

volumetric flask and dissolved in ethanol, and a 5-ml. aliquot was diluted to 1 liter.

Equipment.[6]—Measurements were made with a Leeds and Northrup electrochemograph operating at the 10 microampere range of the Micromax recorder. The half-wave potential point was determined (to allow for lag in the recorder), after which half-wave potentials were obtained by manual operation, with a 50,000 ohm shunt resistance in circuit. The value of $m^{2/3}t^{1/6}$ for the dropping mercury electrode (8-cm. Corning marine barometer glass) was 1.68 mg.$^{2/3}$ sec.$^{-1/2}$ at 25 ± 0.1° and with no potential applied; the drop time was 4.6 seconds.

Electrolysis Cells.—The H-cells were of the familiar Lingane and Laitinen type[26] with two parallel nitrogen lines on the electrolysis chamber emerging, respectively, above and below the liquid level of the cell. For some, the half-cell part was a saturated calomel electrode in water with agar plug (S.C.E.), while others had a saturated lithium chloride calomel electrode in absolute ethanol with a calomel–mercury–lithium chloride plug (E.L.S.C.E.).[6] In both types the usual platinum electrode was used. The potential of the E.L.S.C.E. against the S.C.E. was determined using a salt-bridge[27] and a potentiometer. The potential remained constant at −0.05 ± 0.002 volt for 25°.

Buffers.[27a]—The compounds used as buffers were commercial materials purified to correct constants, in most cases by recrystallization from ethanol; some from acetone. Amine salts were purified by crystallization from water containing hydrochloric acid, after treatment with Norite. The buffers are listed below with the amounts taken for the 25 ml. volumes prepared for the polarographic reductions

Buffer	Amt. for 0.001 equiv. of acid in 25 ml. solution	pK^a
Guanidine hydrochloride[28]	0.0955	13[b]
o-Chlorobenzylamine hydrochloride[29]	.1781	10
Benzoic acid[30]	.1221	9
m-Bromobenzoic acid[30]	.2010	8
Chloroacetic acid[31]	.0945	6
β-Naphthylamine hydrochloride[32]	.1796	5
o-Bromoaniline hydrochloride[32]	.2085	3

[a] These pK values for ethanol solutions were calculated from dissociation constants of the acids in ethanol (29–32 incl.). After applying corrections for the ionic strength (0.05) each value was rounded off to the nearest whole number since this value is used only to identify the acidity of the medium. In the half-neutralized solutions the concentration of the buffer acid and of its salt was 0.02 *M*. [b] Determined in water solution.

and with the approximate pK of each solution. For pK 17 lithium ethoxide 0.02 *M* in 0.03 *M* lithium chloride was used. Perchloric acid at a final concentration of 0.05 *M* in the solution was used for a pK of about 1. It was obtained by adding the requisite amount of standardized 72% perchloric acid to the alcoholic solution of the compound to be examined; the water thus unavoidably introduced is believed to have had no pronounced effect.

Solutions for the polarograph were prepared under nitrogen in a 50-ml. erlenmeyer flask using manipulations similar to those outlined for preparation of lithium chloride solution. The buffer was weighed into the flask and 5 ml. of the 0.001 *M* stock solution of the nitro compound was introduced, followed by 5 ml. of 0.10 *M* lithium ethoxide solution, 10 ml. of ethanol and 5 ml. of 0.15 *M* lithium chloride solution (or, when the solid buffer was an amine salt, 1.66 ml. of 0.15 *M* lithium chloride and 3.33 ml. of ethanol). The resulting solution was 2×10^{-4} *M* with respect to nitro compounds and 0.05 *M* with respect to total electrolyte. The buffer concentration of 100 times that of the nitro compound sufficed to ensure no irregularities due to buffer changes.[33] The solution in each case was prepared just before the polarographic measurement was started.

Reduction Procedure.—The H-type electrolysis cell was emptied of the saturated solution of lithium chloride with which it was kept filled when not in use, and the cell was rinsed twice with the buffered solution to be examined. With a stream of nitrogen passing, 10 ml. of the buffered solution was pipetted into the cell. For determination of *residual current* the solution contained all the components designated excepting the 5 ml. of nitro-compound solution, which was replaced by 5 ml. of ethanol. Measurements were made with the tip of the capillary about 3 mm. below the surface of the liquid, and were started after preliminary passage of a stream of nitrogen to ensure removal of oxygen. Values for the diffusion currents in reductions of nitrobenzene, 5(6)-nitrobenzimidazole and 4(7)-nitrobenzimidazole are given in Table I, together with values for $E_{1/2}$. The half-wave potentials are averages of at least five observations differing by not more than ±0.01 volt, except at pK 1, where variations reached ±0.02 volt, probably due to hydrogen ion discharge.

Diffusion Coefficients and Extent of Reduction.—The cell used was of the type described by McBain and Liu.[34] Calculations were based on King and Cathcart's equation.[35] Diffusion gradients were confined to the membrane of the cell.[36] The volume of concentrated solution in the cell was near 100 ml.; that of the receiving solution was 15 ±0.1 ml. Determinations of concentrations in both compartments were made polarographically.[6] Measurements were made at room temperature (25 ± 2°) and after a period of 6 to 12 hours for establishment of equilibrium conditions. The cell constant, determined by use of nitrobenzene, the diffusion value of which was found by Runner,[6] was approximately 0.5.

3. Catalytic Hydrogenations.—The reaction vessel was a 50-ml. erlenmeyer flask seated on a liquid-tight elevation of the bottom of the constant-temperature bath; within the chamber thus formed was placed the impelling mechanism of a magnetic stirrer. The bath was operated within ±0.1° of the temperature recorded (25°, 30°, 75°). The flask was connected to the measuring system, which comprised a U-shaped manometer and an air-jacketed gas buret (50 ml. in 0.1 ml.) with leveling tube; manometer and leveling system contained mercury. The end of the train was provided with a stopcock-controlled attachment to the source of hydrogen, and one to a vacuum pump.

The sample for hydrogen was transferred to the flask containing the magnetized stirring bar and was dissolved in 25 ml. of ethanol. The weighed palladium–charcoal catalyst[37] was introduced, and the mixture was stirred for several minutes to ensure complete solution of sample, maximum adsorption on the catalyst, and thermal equilibrium of the suspension. With the stirrer at rest the flask was connected, and was several times flushed with hydrogen and then evacuated, then filled with hydrogen under 10 mm. pressure. Time was recorded at the moment the stirrer was started. Pressure was maintained at 10 mm. by frequent adjustments, and readings of time and hydrogen consumed were recorded at intervals until absorption ceased. Essential experimental data, and calculated relative rates of hydrogenation, are shown in Table II. Results are averages of several runs. Reduction of the nitro group was complete; in separate experiments on a larger scale the products were identified as the aminobenzimidazoles.[20] No hydrogenation of the benzimidazole system occurred, as was shown by the negative result of an attempt to hydrogenate benzimidazole itself under the same conditions. No hydrogen was absorbed in an hour, after which the benzimidazole recovered, after two crystallizations from hot water, was 90% of that taken; it was identified by m.p. and mixed m.p.

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(27) H. A. Laitinen, *ibid.*, **13**, 393 (1941).

(27a) The buffered electrolyte systems with ethanol as solvent were selected and used in similar studies by M. E. Runner[6] before the work here reported was done, and will be described in a forthcoming paper.

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(29) L. D. Goodhue and R. M. Hixon, *ibid.*, **57**, 1688 (1935).

(30) J. H. Elliott and M. Kilpatrick, *J. Phys. Chem.*, **45**, 466 (1941).

(31) A. J. Deyrup, THIS JOURNAL, **56**, 60 (1934).

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(33) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1946, p. 344; O. H. Müller, "The Polarographic Method of Analysis," Mack Printing Co., Easton, Pa., 1946, p. 344.

(34) J. W. McBain and T. H. Liu, THIS JOURNAL, **53**, 59 (1931).

(35) C. V. King and W. H. Cathcart, *ibid.*, **58**, 1639 (1936).

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

(37) R. Mozingo, *Org. Syntheses*, **26**, 78 (1946), method D.

4. **Determination of Acid-Base Strengths.**—Potentiometric titrations were followed with a Leeds and Northrup N. 7662 *p*H indicator with calomel half-cell and glass electrode. The materials examined (I, II and IV) were taken as 25-ml. aliquots of 0.001 *M* solutions in water (0.0408 g. of I or II, or 0.0296 g. of IV, in 250 ml.), and were titrated with 0.001 *N* hydrochloric acid, made by dilution of standard 0.02 *N* acid or with sodium hydroxide solution standardized against the acid by potentiometric titration and found to be 0.0008 *N*. The averaged results of several titrations of each kind are plotted (*p*H *vs.* ml. of reagent) in Figs. 2 and 3.

5. **Ultraviolet Absorption Spectra.**—Absorptions were determined using a Beckmann quartz ultraviolet spectrophotometer with matched quartz cells. Results for the two nitrobenzimidazoles in ethanol under "neutral," acid (0.01 hydrochloric acid) and alkaline (0.10 *N* sodium ethoxide) conditions are shown in Figs. 4, 5 and 6.

6. **Association Factors from Molecular Weight Determinations.**—The Beckman apparatus[38] was somewhat modified to permit operation near 100°. Equipment included a cooling-bath and a heating-bath containing glycerol; the former was kept 1–1.5° below the crystallization temperature and the latter at 100°, *i.e.*, respectively, slightly below and slightly above the melting point of the phenanthrene (Eastman Kodak Co. No. 599, m.p. 98.5°) used as solvent. Samples of the nitrobenzimidazoles were compressed into tablets weighing 30 to 100 mg.; each tablet was brushed free of powder and was stored in a small stoppered vial. The rotary magnetic stirrer used was of new design.[39] To dissolve the pellet of sample the freezing-point tube containing the phenanthrene was withdrawn from the bath and was heated with a very small flame. During this operation it was necessary to raise the Beckman thermometer so that the bulb was about 7 cm. above the surface of the heated liquid. It was supported in this position by affixing one above the other three large-bore rubber stoppers slit through to the bore, with the lowermost resting on the rim of the tube. When the sample was in solution the liquid was allowed to cool to about 100°, the thermometer was lowered into the normal position and the freezing-point tube was introduced into the 100° bath. When equilibrium was attained, the tube was transferred to the cooling-bath, and two readings of the freezing point were taken. An additional pellet of sample was introduced and dissolved as described, and the process was repeated as many times as the solubilities of the nitrobenzimidazoles permitted. For 5(6)-nitrobenzimidazole the limit was 0.06 *M*, at which concentration mixed crystal formation occurred; for 4(7)-nitrobenzimidazole the limit was 0.08 *M*, at which concentration an appreciable color change made addition of further increments seem inadvisable. The freezing-point constant of the phenanthrene was determined empirically by use of triphenylmethane. Six trials, each in duplicate, yielded the averaged value 11.8; the reported value[40] is 12.0. Curves for the association factors plotted against concentration are shown in Fig. 7.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, BAYLOR UNIVERSITY COLLEGE OF MEDICINE]

A Study of the Solubility of Triethylenediaminenickel Thiosulfate[1,2]

BY JOSEPH H. GAST AND FRANK L. ALDRICH

Solubility studies on triethylenediaminenickel thiosulfate (Ni $en_3S_2O_3$) have been carried out over a range from 15 to 50° and at 100° in water and at 20° in ethanol–water mixtures. The concentration of the complex was determined by iodometric titration and spectrophotometric measurements in the ultraviolet. Spectral absorption data are presented for both the thiosulfate and nitrate salts. The thiosulfate is soluble to the extent of 1.5 mg. per ml. at room temperature and shows an appreciable temperature coefficient of solubility. When equilibrium is approached from a higher temperature there is a definite tendency to supersaturation. The data on solubility in ethanol–water mixtures show that addition of an equal volume of redistilled ethanol to a water solution of the salt reduces its solubility to approximately one-tenth that of a water solution. Further depression of the solubility in water and ethanol–water mixtures can be obtained by the presence of excess triethylenediaminenickel ions.

While many of the coördination complexes of nickel have been studied by various investigators since Werner's original work[3] and the ethylenediamine complex has been recommended in the qualitative analysis and separation of thiosulfate from some inorganic sulfur compounds,[4,5] solubility measurements have not been reported.

In order to determine the conditions for more precise analytical use of triethylenediaminenickel(II) thiosulfate, Ni $en_3S_2O_3$, further information concerning its solubility was essential.

In pure solutions, accurate measurements of the thiosulfate salt can be obtained readily by iodometric titrations, nickel analyses[6] and by optical density measurements (discussed below). Solubility determinations in water solutions were carried out using all three analytical procedures. However, in ethanol–water mixtures, iodometric titrations in dilute solutions can only be used after the removal of alcohol by evaporation.

None of these analytical procedures are satisfactory in the presence of an excess of the triethylenediaminenickel(II) ion, which must be used to obtain maximum precipitation of the thiosulfate.[7]

Experimental

The thiosulfate salt was formed by the addition of an excess of four times recrystallized triethylenediaminenickel(II) nitrate to a solution of sodium thiosulfate (Baker C.P). The Ni $en_3S_2O_3$ thus precipitated was purified by fourfold recrystallization from water and its purity ascertained by solubility measurements in the presence of an excess of variable amounts of the solid salt, and by thiosulfate, nickel[6] and nitrogen analyses.[8]

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(8) We are indebted to Miss Kazko Arai for the micro-Dumas and micro-Kjeldahl analyses and to Mr. C. E. Williams of the University of Houston for making the facilities available to us.