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Basicity of N-Nitrosamines. I. Non-polar Solvents¹

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The ultraviolet spectra of dimethyl-N-nitrosamine, diethyl-N-nitrosamine, diisopropyl-N-nitrosamine and di-n-propyl-N-nitrosamine in cyclohexane solution containing varying amounts of trichloroacetic acid were examined over the range 250–400 m μ . From the changes of spectra as a function of acid content, it was deduced that a nitrosamine reacts with trichloroacetic acid to form a hydrogen-bonded complex containing one equivalent of nitrosamine and one equivalent of trichloroacetic acid, which, in turn, reacts with a second equivalent of trichloroacetic acid. The first and second equilibrium constants are derived for each nitrosamine listed above. The first equilibrium constant is shown to increase with the electron-donating ability of the alkyl substituents, while the second equilibrium constant is shown to decrease with increasing length of the alkyl substituents. The above evidence is interpreted as indicating the structures I and II as the most probable products of the reaction.

Introduction.—In recent years, great interest has developed in the chemistry of hydrazine and its derivatives, at least in part due to their uses in medicine and their potential use as missile propellants. However, the chemistry of nitrogen, and particularly of nitrogen-to-nitrogen bonds, is not nearly as well understood as the chemistry of carbon. In order to shed new light on the behavior of such bonds, we have undertaken a study of the behavior of a series of dialkyl-N-nitrosamines.²

Dialkyl-N-nitrosamines, generally, have been considered to be neutral substances. They do not form salts with acids or bases in dilute aqueous solution, and superficially, show no evidence of reaction. However, the N-nitroso group has four pairs of non-bonded electrons which make it a potential Lewis base, and its basic behavior may be observed in changes of its ultraviolet spectrum and studied through an analysis of these changes.

The ultraviolet spectrum of a dialkyl-N-nitrosamine shows two distinct bands. The stronger usually has a wave length maximum in the vicinity of 220 m μ and a molar extinction coefficient of the order of 7000. This band has been identified with a $\pi \rightarrow \pi^*$ transition.³ The second band generally lies in the vicinity of 360 m μ and has a molar extinction coefficient of about 100. This band has been identified as due to an $n \rightarrow \pi^*$ transition,³ and shows considerable vibrational structure when observed in non-polar solvents, but, with increasing polarity of the solvent, the structure becomes less pronounced and the wave length maximum tends to shift to shorter wave lengths.

If a Lewis acid is added to a nitrosamine, a reaction can occur in which the Lewis acid shares one of the non-bonded electron pairs of the base, making it more difficult for the now bonded electrons to be excited to another orbital. The change of energy to excite these electrons will be reflected in a shift of the wave length to smaller values. Also, by withdrawal of charge from the N-nitroso group, such sharing will tend to stabilize the other lone pair electrons.

Scheibe⁴ unsuccessfully tried to explain the differences in spectra of N-nitrosamines obtained in different solvents in terms of their dielectric constants. Coggeshall and Poyefsky⁵ demonstrated a relationship between spectral shifts and the dielectric constants of solutions, but Brealy and Kasha⁶ showed that this type of shift is not important for some substances which undergo a blue shift in the presence of hydroxylic solvents.

Haszeldine⁷ reviewed some possible reasons for the changes in the ultraviolet spectra and arrived at some tentative conclusions. He suggested that complex formation of the neutral-molecule (Lewis) acid-base type, such as is shown by iodine, could be eliminated as a cause of spectral change. He discussed a number of possible causes, which will be only listed here. These were: (1) rotational isomerism, (2) intermolecular dipolar attractions, (3) hydrogen bonding of a solvent-base type (for CHCl₃ solutions only) and (4) change of dielectric constant. He favored an equilibrium between the monomer and a dimeric species held together by intermolecular dipolar attractions as the most probable explanation. Yet his own data refute this mechanism, as he regards the monomer-dimer ratio to be a function of the dielectric constant of the solvent, and his data indicate that ethanol (dielectric constant 24) produces a greater change than acetonitrile (dielectric constant 39).

McConnell⁸ attempted to explain the blue shift by general solvation effects, but Brealy and Kasha⁶ noted that McConnell's explanation does not account for the spectral changes in solutions of acetophenone, which undergoes an $n \rightarrow \pi^*$ transition.

In the present and a subsequent paper it is shown that hydrogen bonding in a solute-solvent interaction explains the major shifts observed; particularly the amount of shift appears to be of the order of the hydrogen-bonding ability (not acidity) of the solvent and is consistent with the findings of Brealy and Kasha⁶ and Chandra and Basu.⁹

Another type of chemical change which might occur only in the presence of a strong acid is proton transfer. This mode of change would appear to have its widest applicability in strongly acidic solutions of polar solvents; it will be treated in part II of this series.

Experimental

The trichloroacetic acid used was of reagent grade, but contained visible impurities. It was purified by distilling off the benzene-water azeotrope from a solution of the acid in benzene, recrystallizing the trichloroacetic acid from the remaining benzene solution, and drying it under vacuum over concentrated sulfuric acid.¹⁰ The dried material was manipulated under dry nitrogen. The purified material had a melting point range of 59–64°. The highest previously reported melting point of this material is 59.4°.¹⁰

Cyclohexane was chosen as the solvent because it is generally available in a higher degree of purity than other non-polar solvents. All spectra were recorded on a Cary model 11 recording spectrophotometer using 1-cm. quartz window cells unless otherwise noted.

(1) This work was generously supported by the Office of Ordnance Research, U. S. Army.

(2) W. S. Layne, Ph.D. Thesis, University of Cincinnati, 1961.

(3) M. Kasha, *Discussions Faraday Soc.*, **9**, 14 (1950).

(4) G. Scheibe, *Ber.*, **59**, 2619 (1926); G. Scheibe, E. Felgor and G. Rossler, *ibid.*, **60**, 1406 (1927).

(5) N. D. Coggeshall and A. Poyefsky, *J. Chem. Phys.*, **19**, 980 (1951).

(6) G. J. Brealy and M. Kasha, *J. Am. Chem. Soc.*, **77**, 4462 (1955).

(7) R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 691 (1954); R. N. Haszeldine and B. J. H. Mattinson, *ibid.*, 4172 (1955).

(8) H. McConnell, *J. Chem. Phys.*, **20**, 700 (1952).

(9) A. K. Chandra and S. Basu, *Trans. Faraday Soc.*, **56**, 632 (1960).

(10) J. Kandall and P. M. Gross, *J. Am. Chem. Soc.*, **48**, 1426 (1921).

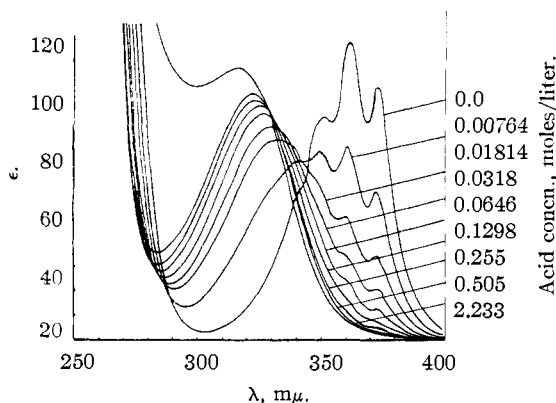


Fig. 1.—Spectra of dimethyl-N-nitrosamine in cyclohexane-trichloroacetic acid solutions.

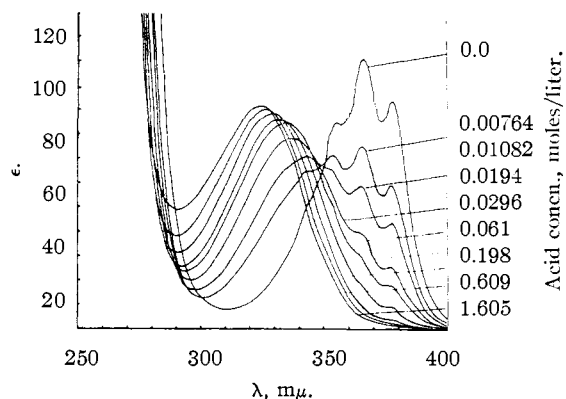


Fig. 3.—Di-n-propyl-N-nitrosamine in trichloroacetic acid-cyclohexane solutions.

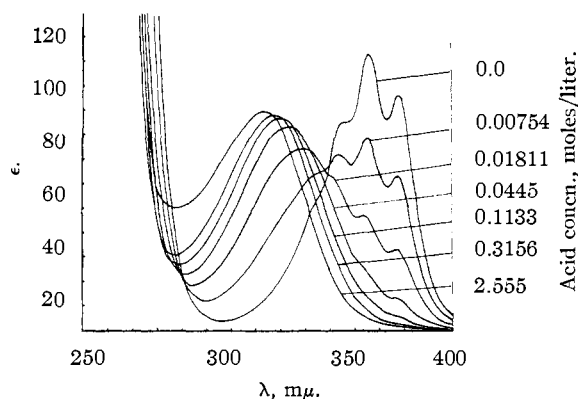


Fig. 2.—Spectra of diethyl-N-nitrosamine in cyclohexane-trichloroacetic acid solutions.

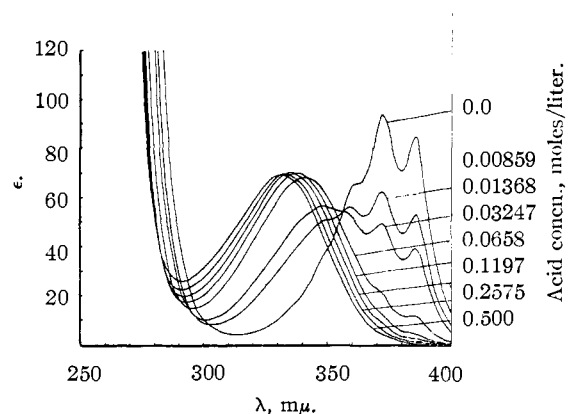


Fig. 4.—Spectra of diisopropyl-N-nitrosamine in cyclohexane-trichloroacetic acid solutions.

The N-nitrosamines were available from previous work by the authors¹¹; they were repurified by vacuum distillation immediately prior to use.

Solutions were prepared by diluting a weighed or pipeted portion of a nitrosamine in a volumetric flask with the approximate quantity desired of a solution of trichloroacetic acid in cyclohexane, and adding cyclohexane up to the desired volume. The exact acid concentration of each acid solution was determined by shaking an aliquot with water, and titrating the aqueous extract with standard aqueous base to the phenolphthalein end-point.

Results

A series of solutions was prepared having a constant concentration of dimethyl-N-nitrosamine and various concentrations of trichloroacetic acid in cyclohexane. The concentrations of dimethyl-N-nitrosamine and trichloroacetic acid are given in Table I. Examination

TABLE I^a
EQUILIBRIUM CONSTANTS OF DIMETHYL-N-NITROSAMINE IN CYCLOHEXANE-TRICHLOROACETIC ACID SOLUTIONS

Acid concn., mole/liter	pK_1	pK_2
0.00764	-2.80	-1.59
.01814	-2.84	-2.08
.0318	-2.83	-2.22
.0646	-2.81	-2.23
.1298	-2.74	-2.26
.255	-2.61	-2.43
.505	-2.35	-2.44
Best values	-2.82	-2.24

^a Concentration of dimethyl-N-nitrosamine was 0.01061 molar.

of the spectra of these solutions (see Fig. 1) showed: (1) a peak with vibrational structure and a maximum absorption at 362 $m\mu$, undoubtedly due to the $n \rightarrow \pi^*$

transition; (2) a progressive decrease in the intensity of this peak as the concentration of acid increased; (3) an absorption minimum at 303 $m\mu$; (4) an apparent isoabsorptive point at 346 $m\mu$ for solutions of zero or low acid concentrations up to about 0.0075 molar; (5) a progressive decrease of absorption at that wave length as acid concentration is increased beyond about 0.0075 molar; (6) an apparent formation of an absorption peak at about 324 $m\mu$; and (7) a shift of this peak to shorter wave lengths and an increase in its intensity with increasing acid concentration. The other N-nitrosamines examined showed similar behavior, with wave lengths of maxima and minima somewhat displaced; see Fig. 2, 3 and 4.

The results of limited experiments indicate that the N-nitrosamine-trichloroacetic acid system obeys Beer's law. A mechanism of spectral change dependent on a monomer-dimer equilibrium is thus ruled out, since an increase of nitrosamine concentration would decrease the monomer-dimer ratio. The results of our experiments indicate the spectra change as a function of acid concentration, but are not a function of N-nitrosamine concentration, provided of course that N-nitrosamine concentration times cell length remains unchanged.

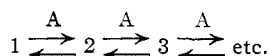
The decrease in the absorption maximum of the base while the vibrational structure remains fixed in wave length, together with the increase of the absorption at another wave length, is indicative of a mechanism in which one species disappears and is replaced by one or more other species. Any mechanism which presupposes formation of a continuum of species must be discarded, for such a mechanism would require a gradual shift of the peak representing the base toward shorter wave lengths, until the limiting case of maximum concentration of trichloroacetic acid is reached. Vibrational structure presumably would shift in wave length

(11) W. S. Layne, M.S. Thesis, University of Cincinnati, 1960; W. S. Layne and H. Zimmer, to be published.

along with the absorption maximum and become less resolved as the shift progressed, finally disappearing when the transition was complete. The fact that this behavior is not observed is an excellent reason to reject the effect of dielectric constant or McConnell's solvation effects as being the causes of spectral change in this system.

As has been noted, an apparent isoabsorptive point is observed for solutions of low acid concentration, but with the absorptivity at this point decreasing with higher acid concentrations (see Fig. 1, 2, 3 and 4). This behavior can be interpreted as representing a system in which two species are present at low acid concentrations, and at least one new species appears in significant proportion at higher acid concentrations. To test whether this hypothesis is correct, a graph was prepared of the spectra at various acid concentrations, in which the calculated contributions of the free base were graphically subtracted from the total spectra by assuming that all absorption at 380 m μ was due to the free base, and the remaining absorption was so adjusted that it represented a constant concentration of the sum of the remaining species. In spite of the graphical and experimental uncertainty (see Fig. 5), it was found that a fairly clean-cut isoabsorptive point is formed at 326 m μ , demonstrating that the N-nitrosamine is present in the solutions studied in three forms, and that no further spectroscopically distinguishable forms make substantial contributions.

When the trichloroacetic acid present in the cyclohexane solution reacts with the nitrosamine under these conditions, the proton remains tightly bound to its anion, and the resulting species can best be described as a base which is hydrogen bonded to undissociated acid. Such a molecule of Lewis base should be capable of forming several hydrogen bonds simultaneously since it has several pairs of non-bonded electrons available. Then, let us define C_1 as the concentration of unreacted free base, C_2 as the concentration of singly hydrogen-bonded base, C_3 as the concentration of doubly hydrogen-bonded base, etc., and A as the concentration of free acid. The reaction between trichloroacetic acid and a nitrosamine can then be expressed as



For the first equilibrium, the equilibrium constant is given by

$$K_1 = C_2/C_1A \quad (1)$$

The acid concentration determined experimentally is related to the concentration of free acid by the expression

$$A = A_0 - C_2 - 2C_3 \quad (2)$$

where A_0 equals the total concentration of acid in all forms. Upon combining eq. 1 and 2 we obtain the equation

$$K_1 = \frac{C_2}{C_1(A_0 - C_2 - 2C_3)} \quad (3)$$

This expression is still inadequate to express the equilibrium, because trichloroacetic acid exists in solution as an equilibrium mixture of monomeric and dimeric forms. If A_1 represents the concentration of monomeric acid and A_2 the concentration of dimeric acid, the equilibrium constant for the dimerization of acid may be expressed as

$$K_D = (A_1)^2/A_2 \quad (4)$$

Considering the acid to be partially dimerized, the expression for total acid concentration in the presence of an N-nitrosamine becomes

$$A_0 = A_1 + 2A_2 + C_2 + 2C_3 \quad (5)$$

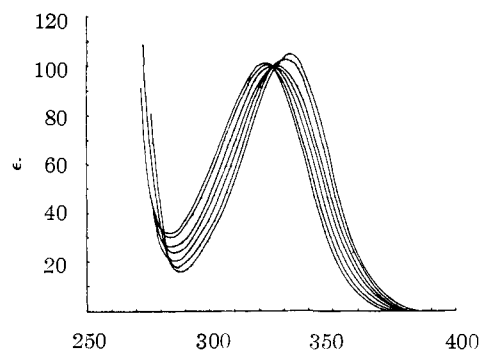


Fig. 5.—Dimethyl-N-nitrosamine in cyclohexane-trichloroacetic acid solutions. Revised to eliminate extinction of base and to adjust spectra of remaining portions to a constant total concentration.

Combining eq. 3, 4 and 5, the first equilibrium constant can be expressed as

$$K_1 = \frac{4C_2}{C_1K_D[-1 + \sqrt{1 + 8/K_D(A_0 - C_2 - 2C_3)}]} \quad (6)$$

and similarly the second equilibrium constant can be expressed as

$$K_2 = \frac{4C_3}{C_2K_D[-1 + \sqrt{1 + 8/K_D(A_0 - C_2 - 2C_3)}]} \quad (7)$$

Letting ϵC equal the absorbance, and ϵ_n equal the molar extinction coefficient of C_n , we may write

$$\epsilon C = \epsilon_1 C_1 + \epsilon_2 C_2 + \epsilon_3 C_3 + \dots \quad (8)$$

Assuming only three species, in this equation of eight unknowns it is necessary to evaluate seven of them in order to solve for the eighth: C can be fixed in the preparation of the solutions, ϵC is determined directly from the spectra, ϵ_1 can be determined by the limiting case where no acid is present and therefore, C_2 and C_3 are zero. Introduction of the mass balance equation of the nitrosamine

$$C = C_1 + C_2 + C_3 \quad (9)$$

determines a fourth variable. By choosing the wave length so that C_1 and C_2 are isoabsorptive, we can set $\epsilon_1 = \epsilon_2$. The absorption on the long wave length slope of the absorption curve is due almost entirely to C_1 , and is an acceptable measure of C_1 at all but the highest acid concentrations. Finally, the absorption at the wave length where $\epsilon_1 = \epsilon_2$ is due almost entirely to C_3 at maximum acid concentration, which gives a measure of ϵ_3 . Consideration of the above relationships makes possible the calculation of the equilibrium constants K_1 and K_2 , assuming a knowledge of the value of K_D .

The ratio of monomer to dimer concentrations for trichloroacetic acid has been studied by Brown and Mathieson¹² in a number of solvents. Cyclohexane is not one of the solvents used, so it is necessary, pending measurement of K_D in cyclohexane, to assume a reasonable value for the dimerization constant. Of those investigated, toluene is the solvent most similar to cyclohexane and the value given for toluene, $K_D = 0.0018$, is assumed in the following calculations.

From the spectra of dimethyl-N-nitrosamine (see Fig. 1) the equilibrium constants were calculated, assuming a slightly lower value of the extinction coefficient of the second neutralization product than is indicated by the above generalizations. This slightly lower assumed value compensates partially for the error introduced by assuming that all of the absorption at the highest acid concentration is due to the third nitrosamine species, and gives better experimental agreement. Examination of the calculated values of K_1

(12) C. P. Brown and A. R. Mathieson, *J. Phys. Chem.*, **58**, 1057 (1954).

