

The Dipole Moments and the Ultraviolet Absorption Spectra of Xylocaine and Two Related Compounds

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During the course of a systematic study by Löfgren and Collaborators¹ of the chemical and physical properties of local anesthetics of the type amino-acyl amide, the dipole moments of some of these anesthetics, *viz.* ω -diethylamino-acetanilide (*A*), ω -diethylamino-*N*-methylacetanilide (*M*) and ω -diethylamino-2,6-dimethylacetanilide (xylocaine) (*X*), have been measured. A qualitative investigation of the absorption spectra of these molecules has been made previously by Löfgren¹, who estimated the position of the absorption bands without measuring the extinctions quantitatively. In order to extend our knowledge of the molecules we have now made a more detailed study of the spectra. The results of the measurements of dipole moments and spectra are reported in this paper and the distribution of electrons within the molecules is discussed.

EXPERIMENTAL

Benzene. A thiophene-free product from Baker's Ltd. was stored over sodium wire for several weeks. It was distilled in an atmosphere of dry nitrogen immediately before use.

ω -Diethylamino-acetanilide, $C_{12}H_{16}N_2O$ (206.28), prepared according to Erdtman and Löfgren², freshly redistilled in N_2 -atm., b. p. 160–161° (7 mm).

ω -Diethylamino-*N*-methylacetanilide, $C_{13}H_{20}N_2O$ (220.31), prepared by Löfgren³, freshly redistilled in N_2 -atm., b. p. 157° (9 mm).

ω -Diethylamino-2,6-dimethylacetanilide (xylocaine), $C_{14}H_{22}N_2O$ (234.33), prepared by Löfgren³, six times recrystallized from petroleum ether, m. p. 67°.

The dipole moments were measured in dilute benzene solutions at 25° C with the apparatus recently described by one of us⁴. From the values obtained for the dielectric constants of the solutions, ϵ , and for the specific volumes, v , the moments were computed according to Halverstadt and Kumler⁵; for details of the calculations, see Fischer⁴. The results of the measurements are listed in Table I, where f_2 is the mole fraction of the solute, P_2^0 the molar polarization at infinite dilution, and μ the dipole moment measured in Debye (D) = 10^{-18} e. s. u.

Table 1. Measurements on benzene solutions at 25°C. The values for the pure solvent are extrapolated.

f_2	ϵ	v cm ³ /g.
ω-Diethylamino-acetanilide		
0.00000	2.2842	1.1435
0.01272	2.5586	1.1392
0.01971	2.6851	1.1364
0.02807	2.8635	1.1328
0.03680	3.0596	1.1297
0.05648	3.4995	1.1225
$\partial\epsilon/\partial f_2 = 21.1 \pm 0.3$; $\partial v/\partial f_2 = -0.370 \pm 0.002$; $P_2^0 = 370 \pm 6$ cm ³ ; $MR_D^1 = 62.68$ cm ³ ; $\mu = 3.88 \pm 0.04 D$		
ω-Diethylamino-N-methylacetanilide		
0.00000	2.2866	1.1438
0.00864	2.4202	1.1409
0.01465	2.5254	1.1386
0.01803	2.5761	1.1369
0.02050	2.6270	1.1363
0.04846	3.1049	1.1260
0.07721	3.5373	1.1156
$\partial\epsilon/\partial f_2 = 16.4 \pm 0.3$; $\partial v/\partial f_2 = -0.367 \pm 0.002$; $P_2^0 = 306 \pm 6$ cm ³ ; $MR_D^1 = 66.52$ cm ³ ; $\mu = 3.42 \pm 0.05 D$		
ω-Diethylamino-2,6-dimethylacetanilide		
0.00000	2.2576	1.1441
0.00188	2.3018	1.1438
0.00389	2.3538	1.1427
0.00419	2.3558	1.1426
0.00488	2.3789	1.1422
0.00971	2.4768	1.1402
0.01133	2.5276	1.1396
0.01729	2.6973	1.1370
0.01875	2.6963	1.1362
0.02686	2.8907	1.1352
0.02776	2.9285	1.1328
$\partial\epsilon/\partial f_2 = 24.0 \pm 0.3$; $\partial v/\partial f_2 = -0.385 \pm 0.014$; $P_2^0 = 425 \pm 5$ cm ³ ; $MR_D^1 = 71.25$ cm ³ ; $\mu = 4.16 \pm 0.03 D$		

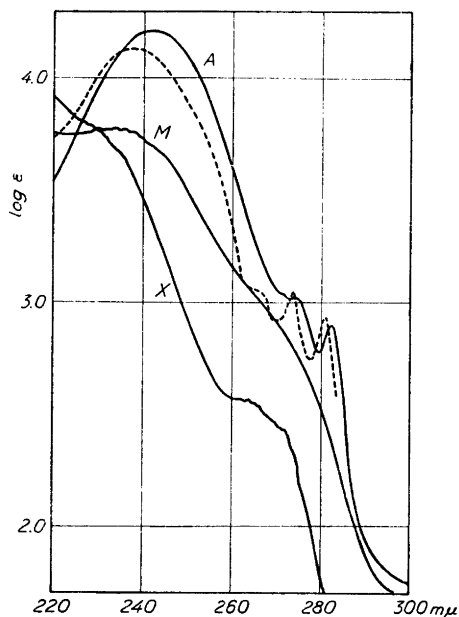


Fig. 1. Ultraviolet absorption spectra measured in hexane solutions.

— The present investigation of A, M and X.
 - - - Acetanilide according to Klingstedt⁶.

The ultraviolet absorption spectra were measured on a Beckman quartz spectrophotometer with a hydrogen lamp as a light source. The solvent was spectroscopically pure hexane and the concentrations were about 10^{-5} mole/l. The interval between two readings was $1 \text{ m}\mu$ except in the more interesting regions where the interval was $1/4 \text{ m}\mu$. The spectra were studied between $\lambda = 220 \text{ m}\mu$ and $\lambda = 300 \text{ m}\mu$, as the earlier measurements showed that none of the molecules has any absorption band at longer wave lengths than $300 \text{ m}\mu$. In Fig. 1 the values obtained for $\log \epsilon^*$ are plotted against the wave length λ .

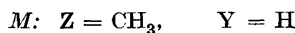
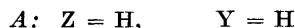
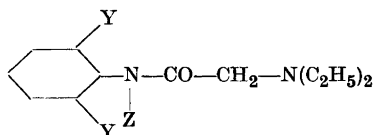
DISCUSSION

Our spectroscopic measurements confirm the earlier, qualitative results obtained by Löfgren¹; as might be expected, the new measurements disclose more details of the bands and indicate the positions with greater accuracy. A has two bands. The one nearest the visible end of the spectrum has three distinct maxima which, however, overlap appreciably: $\lambda = 282.2 \text{ m}\mu$, $\log \epsilon = 2.90$; $\lambda = 275.2 \text{ m}\mu$, $\log \epsilon = 3.01$; $\lambda = 271.8 \text{ m}\mu$, $\log \epsilon = 3.03$. The last maximum is, moreover, strongly overlapped by the second and broader band, with the maximum at $\lambda = 242.0 \text{ m}\mu$, $\log \epsilon = 4.21$. Both these bands are recognizable, although they are distorted and displaced, in the spectra of

* In this connexion ϵ is the extinction coefficient; as confusion is unlikely to occur we have adopted the notation most commonly employed although it is the same both for the dielectric constant and the extinction coefficient.

M and *X*. In *M* the first band lies between 265 and 280 $m\mu$, but the intensity is so low and the band is so strongly overlapped by the second band that no maximum can be distinguished. The second band, $\lambda = 233 m\mu$, $\log \epsilon = 3.78$, has a faint fine structure. In *X* the first band is somewhat more intense than in *M*, but it is still difficult to analyze. It contains several maxima: $\lambda = 261 m\mu$, $\log \epsilon = 2.57$; $\lambda = 265 m\mu$, $\log \epsilon = 2.56$; $\lambda = 272 m\mu$, $\log \epsilon = 2.43$. There appear to be still further maxima in the region $\lambda = 260 - 274 m\mu$, but they are too faint to be localized with precision. The broad band at $\lambda = 230 m\mu$, $\log \epsilon = 3.77$, is still less sharp than in *M* and is overlapped by absorption bands at still shorter wave lengths, which cannot be measured on the available photometer. As in the case of *M*, a fine structure can be traced.

The absorption spectrum of *A*



is closely similar to that of acetanilide, $\langle \text{benzene ring} \rangle - NH - CO - CH_3$, published by Klingstedt ⁶, *cf.* Fig. 1. The band at 270—290 $m\mu$ has a less distinct structure, but all the three maxima observed by Klingstedt in the band of acetanilide can also be distinguished in the spectrum of *A*. Consequently, the $-CH_2N(C_2H_5)_2$ group does not seem to influence the conjugating system $\varphi - N - C = O$ to any greater extent than does a CH_3 -group. In *M* and *X* the bands are displaced towards shorter wave lengths and their intensities are lowered appreciably. This change of the spectrum is analogous to the change of the spectrum of an aromatic amine when transformed into a positive ion, see *e. g.* Wohl ⁷, though the change is more pronounced in the latter case. This similarity suggests that the conjugation between the amide nitrogen and the phenyl group is weakened in *M* and *X*, presumably due to steric hindrance. The hindrance is less obvious in *M* than in *X*, as *M* does not contain any *o*-substituents. However, as pointed out by Klingstedt ⁶, the φ -N conjugation is considerably weaker in acetanilide than in aniline. Therefore, it is not unreasonable to assume that in acetanilide two substituents in the proximity of the amide nitrogen, that is, substituted either at the nitrogen or in *o*-position, will cause a steric repulsion strong enough to overcome the conjugation energy, as three substituents have this effect in aniline ⁴.

The values found for the dipole moments are consistent with a weak φ -N conjugation, which implies that the part of the φ -N dipole moment due to the π -electrons is small. The main part of the total dipole moment of all the

three molecules is certainly due to the $\overset{+}{\text{N}} - \text{C} = \overset{-}{\text{O}}$ group with the indicated polarity. The consequence of the inhibited resonance in *M* and *X* will be that the moments of these molecules would be lower than the moment of *A*. Now, the moment of *M* is 0.46 *D* lower, but the moment of *X* is 0.28 *D* higher than that of *A*. This may be explained if we assume that the π -electron moment of φ -N is only a small fraction of 0.46 *D*. The rest of this difference may be due to the decrease in the positive charge on the nitrogen due to the electron-donating power of the methyl group attached to it. The high moment of *X* partly depends on the moment of the methyl groups in the *o*-positions and it may be due in part to configurational changes within the rest of the molecule. Owing to the complexity of the molecule the total dipole moment cannot be accurately accounted for. However, Löfgren's ¹ suggestion, based on measurements of ionization constants, that the amino nitrogen of *A* and *X* has a resultant positive charge due to the electron-attracting power of the oxygen, is consistent with the relatively high value of the dipole moments. It is not to be expected that such an induction effect will influence the spectrum of the molecule, as the intensity of the absorption is very insensitive to such effects ⁸.

SUMMARY

The dipole moments and the ultraviolet absorption spectra of ω -diethylamino-acetanilide (*A*), ω -diethylamino-*N*-methylacetanilide (*M*) and ω -diethylamino-2,6-dimethylacetanilide, *i. e.* xylocaine (*X*) have been determined. The results suggest that the φ -N conjugation is very weak in *M* and *X*. They are consistent with Löfgren's earlier suggestion that the amino nitrogen of *A* and *X* has a resultant positive charge due to the strong induction effect of the carbonyl group.

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