Evidence of Restricted Rotation about the N—C Bond in 2:6-Disubstituted Acetanilides

THE failure¹ to effect optical resolution of substituted anilines having two large *ortho* groups has left unconfirmed the theoretical possibility of restricted rotation about the nitrogen-nuclear single bond in such compounds. That such steric effects are indeed present in suitably constituted molecules is now proved by a method entirely independent of optical activity.

It has been shown² that the molecular association of amides is due to the bonding effect of the amide-hydrogen atoms, the complete replacement of which effectively checks association. Subsequent work has shown that, in the case of anilides, certain *ortho* substituents are effective in preventing association, and it is significant that such substituents are invariably hydrogen-acceptor groups such as $-\text{NO}_2$, $-\text{N}:\text{N}-$, $-\text{COOEt}$. In such compounds it is evident that the hydrogen atom responsible for association is no longer available for this purpose, it being engaged in chelate ring-formation, such as that depicted in *o*-nitroacetanilide (I). During these experiments an unexpected difference was revealed between the behaviour of 1-nitro-2-acetnaphthalide (II) and the isomeric 2-nitro-1-acetnaphthalide (III). The former is unimolecular, having a lower melting point and greater solubility in hydrocarbon solvents than the latter, which is associated. This led us to suspect steric influences, and to investigate other substances in which similar steric effects might be expected.

The results showed with surprising regularity that although *o*-nitroacetanilide (I) is unimolecular, the substitution of a second *o*-substituent in this compound (such as in IV, V and VI) restores the tendency to associate. The inevitable conclusion is that the amide-hydrogen atom in III, IV, V and VI is deflected by steric interference between the acetyl group and the methyl group (or the bromine atom) too far away from the neighbouring nitro-group to permit of chelate ring-formation, thus leaving the hydrogen atom free to exert its intermolecular bonding effect.

The sensitiveness of this method of detecting restricted rotation as compared with the classical method of optical resolution can best be explained by considering the example of 3-nitro-2-acet-toluidide (IV). A plan of this molecule as seen from a point above the nitrogen atom and remote from the benzene nucleus is shown in VII, the single line connecting the two *ortho* substituents ($-\text{NO}_2$ and $-\text{CH}_3$) representing the plane of the benzene nucleus. The size of the two *ortho* groups may be such as to limit, but not absolutely prevent, the rotation of the H—N—Ac axis from the position shown in VII a to that shown in the enantiomorph VII b. Any such rotation will

bring about a more or less rapid racemization. Nevertheless, only in a very small proportion of molecules intermediate between (a) and (b) is chelation between H and NO_2 possible, with the result that the majority of the molecules show association.

In other words, whereas the chance of resolving such a compound depends upon the non-conversion, or at least the slow rate of conversion, of molecules of type (a) into those of type (b), the test now applied is completely independent of such conversions, and depends solely on the inclination (in whatever direction) of the H—N—Ac axis to the plane of the benzene nucleus.

The degree of association of these compounds was measured cryoscopically in naphthalene, and the relevant figures will be published elsewhere.

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¹ Tuan, Hsü, and Hsü, *J. Chinese Chem. Soc.*, **4**, 131 (1936).

² Chaplin and Hunter, *J. Chem. Soc.*, 1114 (1937).

Liver Extract and Hæmoglobin in Rats

RECENTLY Tschesche and Wolf¹ have stated that rats, made anæmic on a diet consisting wholly of milk, respond differently to iron and copper and to liver extracts known to be clinically active in the treatment of pernicious anæmia. According to these authors, erythrocyte and leucocyte counts and hæmoglobin are all increased by the metals, while cell counts but not hæmoglobin are increased by the liver extract.

Preliminary attempts in these laboratories to confirm the results of Tschesche and Wolf have led to the surprising result that liver extract produces an apparently significant increase in the hæmoglobin of rats with milk anæmia, while leaving the cell count as low as in untreated animals. It is proposed to publish fuller details of this investigation elsewhere.

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¹ Tschesche, R., and Wolf, H. J., *Z. physiol. Chem.*, **243**, 21 (1937).

Crystal Structure and the Magnetic Anisotropy of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

FROM a discussion of the magnetic susceptibilities of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ powder at different temperatures, Jordahl¹ concluded that the crystalline electric field acting on the Cu^{++} ion in the crystal should be predominantly cubic in symmetry, and further, from