ACTA CHEMICA SCANDINAVICA 12 (1958) 1777—1781

Intra- and Intermolecular Hydrogen Bonds in Nitro- and Nitrosophenols

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Nitro- and nitrosophenols are examined in the infrared part of the spectrum in the solid state as well as in solution in order to gain information on the relationship between molecular structure and intra- and intermolecular hydrogen bond formation.

2-Nitrophenols show intramolecular hydrogen bonding, whereas 3- and 4-nitrophenols show intermolecular hydrogen bonding, which is ruptured by solution. 2-Nitrosophenols (4-nitrosoresorcinol, 1-nitroso-2-naphthol) lack fundamental bands of hydroxyl absorption indicating that these compounds exist exclusively in the condition of a completely chelated system.

Additional evidence of the derivative formed by reacting morphine hydrochloride with nitrous fumes being 2-nitromorphine hydrochloride is given.

There has been some doubt about the derivative prepared when reacting morphine hydrochloride with nitrous fumes was a *nitroso* or a *nitro* compound. By chemical means Baggesgaard Rasmussen and Boll[1] found the compound to be 2-*nitro*morphine. Spectroscopically, in the infrared part of the spectrum a *nitroso* compound $(\text{N}\leftrightarrow\text{O})$ is characterized by only one absorption band whereas a *nitro* compound due to both symmetrical stretching $(\text{—N}\overset{\swarrow\text{O}}{\underset{\nwarrow\text{O}}{\rightarrow}}\ )$ and unsymmetrical stretching $(\text{N}\overset{\nearrow\text{O}}{\underset{\nwarrow\text{O}}{\rightarrow}}\ )$ is characterized by two absorption bands. All these bands have to be strong. The spectrum of the compound considered to be 2-*nitro*morphine hydrochloride has indeed such two bands at 1 525 and 1 530 cm^{-1}. These frequencies correspond closely to the frequencies expected for a *nitro* compound. A *nitroso* compound, on the other hand, should have given one band at 1 525 cm^{-1}.

The present work was planned in order to gain information on the relationship between molecular structure and intra- and intermolecular hydrogen formation in *nitro* and *nitroso*phenols. It was hoped that such information should give conclusive spectroscopic evidence of the aforementioned compound being 2-*nitro*morphine hydrochloride.

Since the infrared spectrum affords a picture of the molecule in its ground state it seemed that the infrared examination of the strength of chelation in *nitro*- and *nitroso*phenols through the hydroxyl band shift might afford the desired information. The hydroxyl bands in the 3 000—3 500 cm^{-1} region have been measured for some *nitro*- and *nitroso*phenols in solid state and in chloroform solution. The high frequency band is due to the free hydroxyl group and the low frequency band is due to the bonded hydroxyl group.

DISCUSSION

It has been known for a long time that 2-*nitro*phenol differs from its 3- and 4-isomers in many of its physical properties. The explanation has been that the former compound is chelated and not associated. The vibration corresponding essentially to the hydroxyl bond stretching for molecules containing this group gives absorption in the 3 000—3 500 cm^{-1} region and its

Table 1. Fundamental bands of hydroxyl and amine absorption in the infrared part of the spectrum.

Compound	Hydroxyl and Amine Band (cm^{-1})			Interpretation
	Solid (KBr)	In CHCl$_3$	Conc.	
2-Nitrophenol	3 200	3 200	0.025 M	intramolecular H-bond
3-Nitrophenol	3 330	3 520	0.025 M	intermolecular H-bond
4-Nitrophenol	3 325	3 530	0.025 M	intermolecular H-bond
4-Nitrosophenol	3 170	3 500	0.025 M	intermolecular H-bond
1-Nitro-2-naphthol	no absorpt.	3 200 (weak)	0.025 M	intramolecular H-bond
1-Nitroso-2-naphthol	no absorpt.	no absorpt.	0.025 M	completely chelated
4-Nitroresorcinol	3 225 3 340	broad band 3 580	saturat.	intramolecular H-bond intermolecular H-bond
4-Nitrosoresorcinol	no absorpt. 3 270	no absorpt. 3 580	0.0125 M	completely chelated intermolecular H-bond
2-Nitromorphine hydrochloride	3 220 3 360 3 450 (NH)	3 220 3 540 3 620 (NH)	0.01 M	intramolecular H-bond intermolecular H-bond intermolecular H-bond
Morphine hydrochloride	3 340 (broad) 3 510 (NH)	3 560 3 620 (NH)	0.01 M	intermolecular H-bond intermolecular H-bond
2,4-Dinitrophenol	3 250	3 250	0.025 M	intramolecular H-bond
2,4,6-Trinitrophenol	broad band	3 190 (weak)	0.025 M	intramolecular H-bond
1-Methyl-4,6-dinitrophenol	3 240	3 240	0.025 M	intramolecular H-bond

first overtone is found at about 7 000 cm^{-1}. Hilbert *et al.*[2] have studied the hydrogen bonding in the 7 000 cm^{-1} region for a large number of compounds containing phenolic hydroxyl groups and found that such a group forms a strong hydrogen bond with an oxygen atom of an adjacent *nitro* group. For example, 2-*nitro*phenol does not absorb radiation in this region indicating that the steric conditions for forming strong hydrogen bonds are satisfied, whereas 3-*nitro*phenol as well as 4-*nitro*phenol present strong absorption indicating absence of intramolecular hydrogen bonding.

The same conclusion can be drawn from Table 1. The position of the hydroxyl band of 2-*nitro*phenol does not shift by dissolving the compound, whereas those of both 3- and 4-*nitro*phenol shift. This observation can only be explained by intramolecular hydrogen bonding in 2-*nitro*phenol. The values recorded for 3-and 4-*nitro*phenol are close to the values given by Ginetti [3] who for both compounds found the hydroxyl band at 3 330 cm^{-1} and 3 520 cm^{-1} in chloroform and in solid state, respectively.

Furthermore, the finding of Amstutz *et al.*[4] that the fundamental band of hydroxyl absorption is lacking for 1-*nitroso*-2-naphthol, whereas 1-*nitro*-2-naphthol has a definite, although weak, band at approximately 3 250 cm^{-1}, has been confirmed. Besides, it was found that 4-*nitroso*-resorcinol only showed one band of hydroxyl absorption at 3 270 cm^{-1} corresponding to an intermolecular type of hydrogen bonding which was ruptured by solution and shifted to 3 580 cm^{-1}. 4-*Nitro*resorcinol, on the other hand, gave two bands of hydroxyl absorption corresponding to intermolecular as well as intramolecular hydrogen bonding. The lack of a fundamental band of hydroxyl absorption for 1-*nitroso*-2-naphthol and the presence of only one band of hydroxyl absorption for 4-*nitroso*resorcinol corresponding to intermolecular hydrogen bonding appears to be conclusive evidence that the phenolic hydroxyl group adjacent to the nitroso group is not free. This lack of hydroxyl absorption indicates that 1-*nitroso*-2-naphthol exists exclusively in the condition of a completely chelated system, whereas 4-*nitroso*resorcinol, besides possessing a completely chelated system, also is di- or polymerized. The existence of a resonance possibility with the corresponding quinone monoxime only tends to stabilize the chelated system:

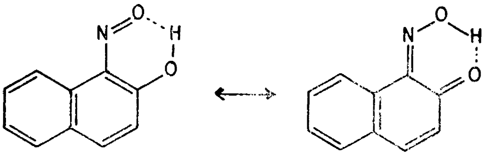
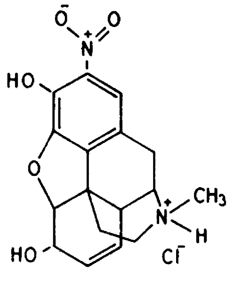


Fig. 1.

From the above mentioned observations it should now be possible to give additional evidence of the derivative prepared by reacting morphine hydrochloride with nitrous fumes being in fact 2-*nitro*morphine hydrochloride. If the compound had been 2-*nitroso*morphine hydrochloride, the infrared spectrum of the compound should only give two bands, namely from the alcoholic hydroxyl group and the substituted amino group, respectively. On the other hand, the infrared spectrum of 2-*nitro*morphine hydrochloride should, besides



2-Nitromorphine hydrochloride

Fig. 2.

showing the two aforementioned absorption bands, give a third band originating from a not completely chelated system consisting of the *ortho*-situated *nitro* and phenolic hydroxyl groups. From Table 1 is clearly seen that the compound which is thought to be 2-*nitro*morphine hydrochloride, indeed gives the three expected absorption bands. At this place it has to be mentioned that this conclusion is only valid if it be assumed that the alcoholic hydroxyl group and the substituted amino group in 2-*nitro*morphine hydrochloride each only gives one band of absorption.

Finally it can be seen from Table 1 that a *para*-substituted *nitroso*phenol gave the same type of intermolecular hydrogen bonding as the *para*-substituted *nitro*phenol, just as three different poly*nitro*phenols with the phenolic hydroxyl group *ortho* to the *nitro* group all showed intramolecular hydrogen bonding.

EXPERIMENTAL

The measurements were carried out with a Perkin-Elmer model 21 double beam spectrophotometer equipped with a rock salt prism.

For the bands due to unassociated molecules, solutions were made up to 0.025 M in chloroform *Merck* grade *pro analysi*. However, in some cases the components were not soluble to this extent and saturated solutions of the compounds in chloroform were used. The solutions were measured in 1 mm cells. In the reference beam chloroform was placed to compensate for the bands originating from the solvent.

Commercially available chemicals recrystallized from ethanol-water mixtures were used with the exception of the following compounds:

1-Nitro-*2-naphthol.* 1-*Nitroso*-2-naphthol was oxidized with nitric acid following the procedure of Fierz-David and Ischer[5]. Subjected to distillation with superheated steam the compound distilled over as orange-yellow crystals, which after recrystallization melted at 100—102°C (Lit. value[5] 102°C).

4-Nitroso*resorcinol.* Resorcinol was reacted with *iso*amyl nitrite in alkaline alcoholic solution according to Henrich[6]. After recrystallization from water the compound began to decompose at 110°C and turned black at 145°C.

4-Nitro*resorcinol.* The potassium salt of 4-*nitroso*resorcinol was oxidized with 3 % hydrogen peroxide according to Gilbert *et al.*[7] The reaction mixture was acidified and extracted with ethyl ether. After evaporation of the ether, the compound was recrystallized from water. Its melting point, after quick dehydration, was 112—115°C (Lit. value[7] 115°C).

2-Nitro*morphine hydrochloride.* Morphine hydrochloride was reacted with nitrous fumes at −2 to −3°C using the modified procedure described by Baggesgaard Rasmussen and Boll[1]. The compound was recrystallized from N hydrochloric acid.

Acknowledgement. My sincere thanks are due to Professor Børge Bak, University of Copenhagen, for valuable advice.

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Received August 14, 1958.