

## IONIZATION CONSTANTS OF SULFANILAMIDE

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At the meeting of Northwest Scientific Association on December 28, 1940, we had an opportunity to propose a partial explanation of the connection between therapeutic activity and chemical structure of sulfanilamide and its derivatives. The facts to be explained were: (1) The importance of the amino group. Substitution of the amino hydrogens regularly destroys the activity and several authors have shown that this group probably is oxidized in the body. (2) Substituents which are far distant from the amino group affect the activity in a way which depends not only on the nature of the substituent, but even on its position. The difficulties of an explanation of this fact have been pointed out by Northey.<sup>1</sup>

There is only one way in which "remote control" is transmitted through a large molecule: by loosely bound electrons, i. e., electrons which are not so tightly attached to a certain atom or bond as electrons usually are. Molecules with loosely bound electrons cannot be represented by the means of the classical valence theory. However, they may be considered as hybrids of two or more classical structures ("quantum mechanical resonance").

As the loosely bound electrons are particularly apt to transmit *electric* influences, we shall expect some relationship between the *electrical* character of remote substituents and the therapeutic activity of the derivatives. Indeed, the results of Roblin and Winnek<sup>2</sup> give striking evidence of a relationship of this sort (cf. Table 1).

In order to characterize the electrical character of a substituent X we can make use of the dipole moment  $\mu$  of Hammett's quantity  $D$  (sigma) or some similar property.<sup>3</sup>

Table 1

Therapeutic activity and electric character of the substituent of 5-sulfanilamido-2-X-pyridines and 2-sulfanilamido-5-X-pyridines.

Substituent	Therapeutic activity $\mu \cdot 10^{18}$		
	2-S-5-X	5-S-2-X	of $C_6H_4X$
NH <sub>2</sub>	+	—	+1.5
OC <sub>2</sub> H <sub>5</sub>		—	+1.2
H	+	+	0
Cl		+	-1.5
Br	—	+	-1.5
I	—	+	-1.3

Shortly after we had presented this suggestion before the 1940 meeting of this Association, Halverstadt and Kumler<sup>4</sup> published a note in which the same basic idea was advocated, though without a discussion of the data assembled in Table 1. Later the same authors<sup>5</sup> tested and confirmed the assumption of resonance by measuring dipole moments.

As pointed out a year ago, several methods could be used to test our assumption and to make predictions later as to the probable activity of unknown compounds. Besides dipole moments, there are atomic distances, ultraviolet absorption spectra, heat of combustion and other properties which give information of resonance.

The most direct and promising way appeared to be the determination of ionization constants. The deviation from the structure given by the usual formula results from resonance with quinoid forms in which the amino and the sulfamido group carry electric charges. These charges counteract ionization so

1. E. H. Northey, Chem. Rev., 27, 85 (1940)
2. R. O. Roblin, Jr. and M. S. Winnek, J. A. C. S. 62, 1389 (1940).
3. L. P. Hammett, "Physical Organic Chemistry" McGraw-Hill Book Co., New York, 1940 (Chapter VII).
4. I. F. Halverstadt, W. D. Kumler, J. A. C. S., 63, 624 (1941).
5. W. D. Kumler, I. F. Halverstadt, J. A. C. S., 63, 2182 (1941).

that the ionization constants should be smaller than in corresponding non-resonating compounds.

The experimental difficulties of determining the ionization constants of slightly soluble, very weak electrolytes are considerable. Only a potentiometric method can be applied. We are using a cell consisting of two hydrogen electrodes, one in hydrochloric acid, the other in a solution of sulfanilamide in acid. The two flasks are connected by a KCl-agar bridge. Using microburettes, we add carbon dioxide-free sodium hydroxide solution first to the first, then to the second flask, determining the electromotive force by means of a precise potentiometer and sensitive mirrorgalvanometer.

From the results of these determinations we find the pairs of acid and acid-sulfanilamide solutions which have equal hydrogen ion concentration. The composition of these solu-

tions furnishes the data from which the ionization constants can be calculated.

This method diminishes and practically eliminates most of the uncertainties and sources of error usually connected with potentiometric titration methods.

So far our measurements on sulfanilamide have been finished. This substance is not only a base (ionization constant  $K_1=1.10^{-12}$ ) but also an acid ( $K_2=2.10^{-11}$ ). It is interesting that the acidic ionization, obviously originating in the amido group, is even appreciably stronger than the basic ionization, to be localized in the amino group. As far as we know, the acidic ionization of a sulfamido group has been previously observed only indirectly, namely by the solubility of primary and secondary (not tertiary) sulfamides in strong bases.

Determinations on related substances are being carried out.