ably pliable and have tensile strengths which average about 38,000 pounds per square inch (Table II).

Acknowledgment.—We wish to express our sincere thanks to Dr. Harold Lundgren, who very generously supplied us with fibers used, and to Dr. C. H. Kunsman for his encouragement and advice during the course of this investigation.

Summary

Fibers which were made from native egg albumin by a process which involves complex formation with detergent and drawing under steam are shown to be composed of parallel bundles of polypeptide chains running parallel to the fiber axis. The peptide chains are shown to have the β-keratin configuration as is evident from the similar appearance of the X-ray patterns obtained from the albumin fibers as compared with those obtained from well oriented β-keratin. The tensile strength of the synthetic pure protein fiber is shown to be dependent upon the degree of molecular orientation and reaches a value of 38,000 pounds per square inch.

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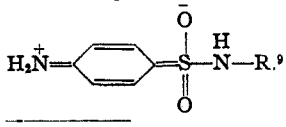
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Relation between Chemical Structure and Bacteriostatic Activity of Sulfanilamide Type Compounds

BY W. D. KUMLER AND T. C. DANIELS

The mechanism of the action of sulfanilamide type compounds[1] as proposed by Woods[2] and Fildes[3] in which the compound competes for the essential metabolite *p*-aminobenzoic acid seems to be well established and generally accepted.[4] The nature of the competitive action between *p*-aminobenzoic acid and the sulfonamides is an important factor in considering the relation between structure and bacteriostatic activity in these compounds. Some investigators[5,6] have correlated the activity of the sulfanilamide derivatives with their acid dissociation constants. Others[7] have suggested that the activity is related to the basic dissociation constants.

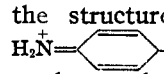
Kumler and Halverstadt[8] have suggested that the activity of sulfanilamide compounds is associated with the contribution of the resonating form with a separation of charge



They showed that this form makes about the same contribution in sulfanilamide as the analogous resonating form with a separation of charge makes in the methyl ester of *p*-aminobenzoic acid. The same thing holds true for free *p*-aminobenzoic acid.

Recently, Bell and Roblin[10] have reported that the bacteriostatic activity of sulfanilamide type compounds can be correlated with the negative character of the SO_2 group and with the acid dissociation constants. They present evidence to show that the more negative the SO_2 group, the more active the compound. They also point out that the more negative the SO_2 group, the more nearly it resembles the CO_2 group in *p*-aminobenzoic acid at *p*H 7. At the *p*H of 7 the carboxyl group in *p*-aminobenzoic acid is over 99% ionized and consequently the CO_2 group carries a negative charge.

In this paper we present evidence, first, that a fundamental factor for activity is the contribution of the resonating form with a coplanar amino group; second, that the negative character of the SO_2 group is a concomitant factor associated with the resonating form; third, that compounds which appear to be exceptions to Bell and Roblin's theory or do not fall within the scope of their theory, can be adequately accounted for on the basis of resonance, and fourth, that these ideas in part apply to certain other bacteriostatic compounds including the mono-aminoacridines.

In aniline some contribution is made to the structure of the molecule by the form  . If a group which has a greater tendency than hydrogen or carbon to accept a negative charge is placed in the para position, the contribution of such a form is greatly in-

(1) In accordance with the suggestions of Green and Bielschowsky, *Brit. J. Exptl. Path.*, XIII, 1, 13 (1942) sulfanilamide type compounds are here considered to be those that are antagonized by *p*-aminobenzoic acid.

(2) Woods, *ibid.*, **21**, 74 (1940).

(3) Fildes, *Lancet*, **238**, 1, 955 (1940).

(4) Rubbo and Gillespie, *Nature*, **146**, 838 (1940); Lampen and Peterson, THIS JOURNAL, **63**, 2283 (1941); Landy and Wyeno, *Proc. Soc. Exptl. Biol. Med.*, **46**, 54 (1941); Wood, *J. Exptl. Med.*, **75**, 369 (1942).

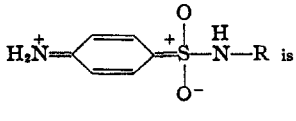
(5) Schmelkes, Wyss, Marks, Ludwig and Strandskov, *Proc. Soc. Exptl. Biol. Med.*, **50**, 145 (1942).

(6) Fox and Rose, *ibid.*, **50**, 142 (1942).

(7) Tolstoouhov, Paper presented at the Buffalo meeting of the American Chemical Society, Sept., 1942.

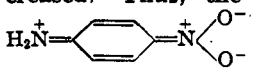
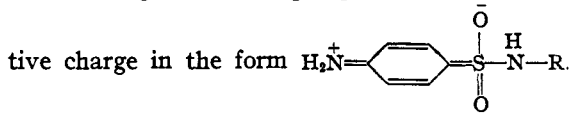
(8) Kumler and Halverstadt, THIS JOURNAL, **63**, 2182 (1941).

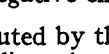
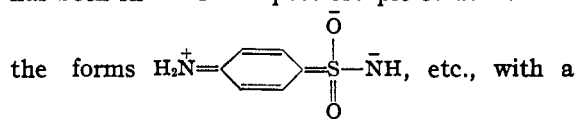
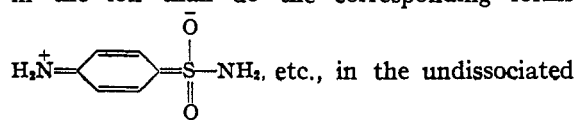
(9) Whether this structure is written as above, or as



is immaterial. The sulfur–oxygen bonds are mainly single, but they have some double-bond character. In this paper we have chosen to use double bonds because the separation of charge associated with the resonance with which we are mainly concerned is then illustrated more clearly.

(10) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

creased. Thus, the contribution of the form  in *p*-nitroaniline greatly exceeds the contribution of the above form in aniline.[11] The contributions made by such a form with a separation of charge in any para substituted aniline will be dependent on the ability of the para group to accept a negative charge. Furthermore, the negative character of the para group in such a compound will be in part a measure of the contribution made by the form with a separation of charge. The SO_2 group takes on the negative charge in the form 

If the negative charge on the SO_2 group came only from the resonance, the contribution made by this resonating form would be directly related to the negative character of the SO_2 group. However, some of the negative charge, or lack of it, on the SO_2 is contributed by the  group. If R is electron repelling the electrons will be shifted toward the SO_2. If R is electron attracting the hydrogen tends to ionize and part of the negative charge left on the nitrogen distributes itself to the oxygens of the SO_2.[10] In the previous paper it has been shown from spectroscopic evidence that the forms  , etc., with a separation of charge make a greater contribution in the ion than do the corresponding forms  , etc., in the undissociated molecule and the reason for this effect has been discussed. This observation indicates that any effect which increases the relative negative charge on the SO_2 group will increase the contribution of this form with a separation of charge. Thus the observation that the bacteriostatic activity is associated with the negative character of the SO_2 group is compatible with the idea that the activity is associated with the resonating form having a separation of charge. The negativity of the SO_2 group and the contribution of the resonating form with a separation of charge are concomitant factors related to one another.

The character of the amino group is also related to these two factors. As the contribution of the resonating form with a separation of charge increases, the amino group is affected in three ways. First, the amino group has a tendency to become coplanar with the ring; second, it takes on a plus charge, and, third, it becomes double-bonded to carbon, resulting in a quinoidal structure. There is reason for believing that it is these properties of the *p*-amino group, in the form with a separation of charge, that is chiefly responsible for the activity of sulfanilamide type compounds and not the negative character of the SO_2 group.

In the first place the SO_2 group in sulfonamides, sulfones, etc., is not an active group chemically. It enters into almost no reactions, while an aromatic amino group, on the other hand, is a very reactive group. Since the reactions of enzyme systems are essentially chemical, these compounds would be more likely to exert their influence through the *p*-amino group rather than through the SO_2 group. It has been stated,[10] and seems to be generally accepted, that no compounds are active *per se* that have a substituted *p*-amino group. This in itself attests to the importance of this group for activity. On the other hand, compounds with various types and sizes of groups substituted on the N^1 nitrogen show activity. These groups are in a position where they might be expected to block the SO_2 group if it were involved in some specific reaction with the enzyme system. Some of the most active compounds, such as sulfathiazole and sulfadiazine, are those that differ the most sterically from *p*-aminobenzoic acid if one considers the environment about the CO_2 and SO_2 groups.

Bradbury and Jordan[12] from a study of the electrokinetic mobility of *B. coli* in dilute water solutions of *p*-aminobenzoic acid, aniline hydrochloride, benzene sulfonamide, metanilamide, sulfanilamide, sulfapyridine, sulfathiazole and related compounds deduce that the sulfonamide group has no effect on the bacterial surface, since with benzenesulfonamide there is no change of mobility with time. The amino group on the other hand has a marked effect, the mobility in the case of aniline hydrochloride falling to 75% of its original value in four hours. Inactive metanilamide behaves like aniline hydrochloride. The active compounds, however, such as sulfanilamide, sulfathiazole, etc., as well as *p*-aminobenzoic acid, show characteristic mobility-time curves with two well defined maxima. This evidence is important in that it demonstrates that the active bacteriostatic compounds differ from the inactive compounds with respect to the mobility of bacteria in an electric field which indicates a difference with respect to the action on the surface of the bacteria. Furthermore, it demon-

(11) Ingold, *Chem. Revs.*, **15**, 225 (1934); Kumler and Porter, THIS JOURNAL, **56**, 2549 (1934); Sutton, *Trans. Faraday Soc.*, **30**, 789 (1934); Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941.

(12) Bradbury and Jordan, *Biochem. J.*, **36**, 287 (1942). These authors incorrectly state, "Kumler and Halverstadt have shown that in *p*-(*p*-aminophenyl)-benzenesulfonamide the contribution of the polar resonance form is twice as great as in sulfanilamide. . . ." Kumler and Halverstadt showed that the contribution of the polar resonance form was about half as great in *p*-(*p*-aminophenyl)-benzenesulfonamide as in sulfanilamide, Hence, this evidence does not warrant the conclusion of Bradbury and Jordan that some other factor besides the contribution of the form with a separation of charge is of major importance in determining the activity of sulfanilamide type compounds.

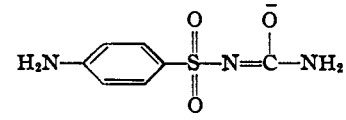
strates that this effect is associated with the amino and not with the sulfonamide group.

The finding of Green and Bielschowsky[1] that the bacteriostatic action of *p*-aminothiophenol, and 4,4′-diaminodiphenylsulfide is antagonized by *p*-aminobenzoic acid is also important evidence that the SO_2 group is not of major importance for the activity of a sulfanilamide type compound. Neither of these compounds contain an SO_2 group, yet they satisfy the criterion for a sulfanilamide type compound, *i. e.*, they are antagonized by *p*-aminobenzoic acid.

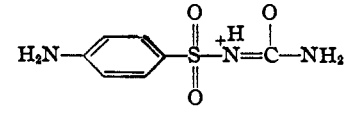
All of the above evidence points strongly to the conclusion that the amino group is the functional part of the molecule for activity and changes in activity brought about by placing different R groups on the sulfonamide group results from the effect the R group has on the amino group through resonance and induction. One or all of the properties associated with the amino group in the resonating forms namely the steric factor of coplanarity with the ring, the positive charge on the nitrogen, the double bond between nitrogen and carbon together with the quinoidal structure, may be essential for activity. The idea that the sulfonamide group is significant for activity only insofar as it affects the amino group has been suggested before[13] but we now have evidence to support this view plus an explanation, in terms of known chemical phenomena, of how the effect comes about.

The theory is supported by the following evidence. Metanilamide cannot have a resonating form of the type considered and, hence, shows no activity. Orthanilamide can have a similar form but the compound is inactive because a hydrogen bond exists between the amino group and the SO_2 group. The amino group is, therefore, substituted, in a sense, and would not be expected to enter into reactions with enzyme or other systems that demand a free amino group. A similar case is present in the amino acridines which we will discuss later. The nuclear substituted sulfonamides are inactive due to steric interference between the substituents and the amino or SO_2 groups which greatly reduces the form with a separation of charge. If the substituents are ortho to the amino group they prevent the amino group from assuming a coplanar configuration which prevents an appreciable contribution from the resonating form. Ingram and Hampson[14] showed that a group as small as methyl gives this effect. The same sort of interference and reduction of resonance would take place with groups ortho to the sulfonamide group. Since nuclear substituents are always ortho to either the amino or sulfonamide group, the presence of substituents in the ring would be expected to reduce greatly the contribution of the resonating form and, hence, such compounds show very little or no activity. Compounds in which the amino or sulfonamide groups are removed from the ring do not have this type of resonance and, hence, are inactive.

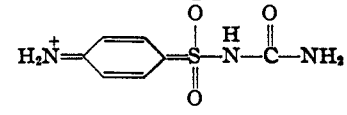
Sulfanilylurea shows considerably less activity at *p*H 7 than is expected by Bell and Roblin's theory. At this *p*H the compound is about 97% ionized so that the ion is the species with which we are mainly concerned. The low activity of the compound results from the fact that the ion has a resonating form in which the negative charge which would normally distribute itself to the SO_2 group goes mainly to the urea oxygen



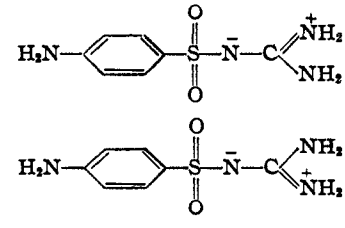
This results in the SO_2 group being less negative than would be expected from the *Ka* value of the compound and consequently the contribution of the resonating form with the coplanar amino group is greatly reduced. Essentially the same conclusion is reached if we consider the un-ionized molecule. Here the form



places a plus charge on the N^1 nitrogen which cuts down the contribution of the form responsible for the activity



Sulfanilylguanidine is also anomalous in Bell and Roblin's theory, its activity being considerably greater than is predicted by its *Ka* value. This compound would normally be expected to have a *Ka* value about the same as sulfadiazine $Ka = 3.3 \times 10^{-7}$, a compound which also has two nitrogen atoms in the substituted group. That sulfanilylguanidine has a *Ka* value so low it cannot be measured in water solution is due to the fact that a monosubstituted guanidine is a fairly strong base because of resonance and an intra-molecular neutralization involving a migration of hydrogen takes place in this molecule resulting in a nearly neutral compound.



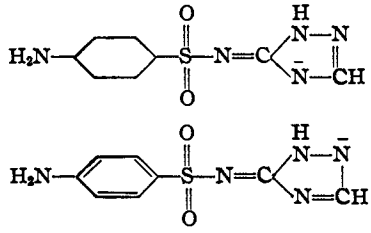
The resulting compound although an extremely weak acid has a negative charge on the N^1 nitro-

(13) Shinn, *J. Am. Med. Assoc.*, **113**, 1714 (1939).
(14) Ingram and Hampson, *J. Chem. Soc.*, 981 (1939).

gen. The net result with respect to the charge on the nitrogen is the same as if the compound were a much stronger acid neutralized at *p*H 7.

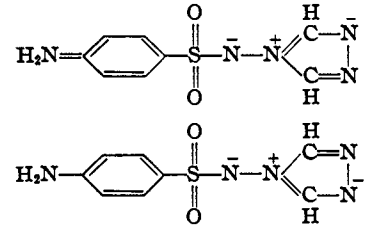
It is evident from the above that a prediction of the bacteriostatic effect of any N^1 substituted sulfanilamide on the basis of the inductive constants of the substituted group or the *Ka* value of the compound will fail whenever the substituent group causes a major contribution from a resonating form of the ion that can accept the negative charge from the N^1 nitrogen (sulfanilylurea) or if the substituent group has a resonating form that places a charge on the N^1 nitrogen (sulfanilylguanidine).

The low activity of 3-sulfanilamide-1,2,4-triazole can also be accounted for by this effect. In this case the contribution of the forms



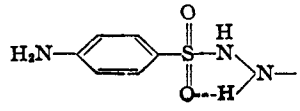
in the ion reduces the negative charge on the SO_2 group decreasing the contribution of the resonating forms with the coplanar amino group.

The abnormally low activity of 4-sulfanilamide 1,2,4-triazole probably results from two effects. The resonating forms



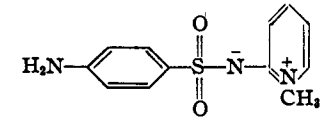
which make an appreciable contribution in this molecule, have a plus charge on the ring nitrogen to which the rest of the molecule is attached. This plus charge, which is partly responsible for the compound being a fairly strong acid, tends to hold the negative charge in the ion on the N^1 nitrogen thus preventing it from migrating to the SO_2 group. It is likely that a weak hydrogen bond exists in this compound between a hydrogen on the ring and an SO_2 oxygen. This bond would decrease the negative charge on the SO_2 and reduce the activity of the compound.

The presence of a much stronger hydrogen bond accounts for the abnormally low activity of sulfanilylhydrazine

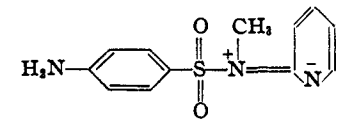


This compound is about as strong an acid as sulfanilamide, but is considerably less active.[14a]

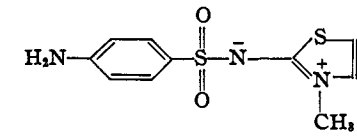
Shepherd, Bratton and Blanchard[15] recently showed that the ring N methyl derivatives of sulfapyridine and sulfathiazole have about the same activity as the parent compounds while the N^1 methyl derivatives are practically inactive. The inductive constants of the substituent groups are totally incapable of accounting for the activity of these compounds. On this basis the N^1 methyl compound would be more active than the ring methyl compound while it actually shows no activity. On the basis of our theory, however, the activity of these compounds can be adequately accounted for. In the ring N methyl compound there is a large contribution from the form



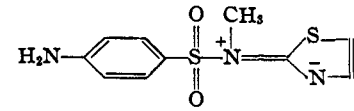
which places a negative charge on the N^1 nitrogen. As we have previously stated, this increases the contribution of the form with the coplanar amino group. On the other hand the N^1 methyl compound has a contribution from the resonating form



which places a plus charge on the N^1 nitrogen reducing the contribution of the form with the coplanar amino group, thus making the compound virtually inactive. The corresponding forms in the case of the sulfathiazole compounds are



and

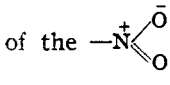
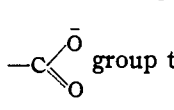
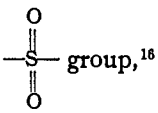


The activity of such non-acidic compounds as the ring N-methylsulfapyridine, the ring N-methylsulfathiazole and sulfanilylguanidine clearly demonstrates that the negative ion is not in itself a prerequisite for activity in sulfanilamide type compounds as has been concluded by some workers.[5,6] It just happens that the negative ion in a number of compounds has more contribution from the resonating form with separation of charge.

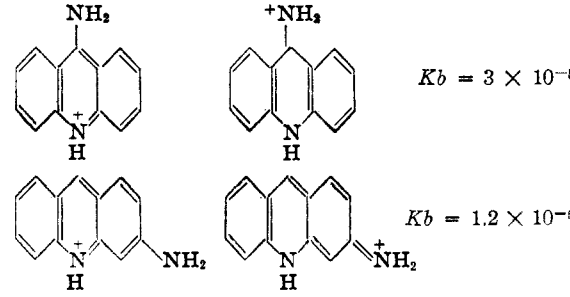
p-Nitroaniline is very similar in structure to the anion of *p*-aminobenzoic acid. The dimensions

(14a) Personal communication, R. O. Roblin, Jr.

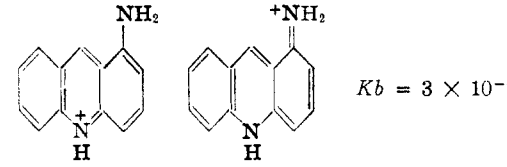
(15) Shepherd, Bratton and Blanchard, THIS JOURNAL, 64, 2532 (1942).

of the  group are closer to those of the  group than are those of the  group,[16] also there is a large amount of resonance in *p*-nitroaniline. In this connection the findings of Gunnison[17] are of much interest. It was found that *p*-nitroaniline was bacteriostatic against *B. coli* in concentrations of 1:4000 and that this activity was reversed by *p*-aminobenzoic acid 1:10,000. *p*-Nitroaniline is then, by the criterion previously set up,[1] a sulfanilamide type compound. That the compound does not show a higher order of activity may be due to the reduction of the nitro group under the conditions of the test.

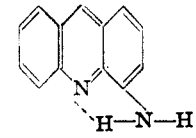
A study of another series of compounds, namely, the monoaminoacridines reveals that their bacteriostatic activity is also correlated with the contribution of the resonating form with a coplanar amino group. The activity of these compounds, however, is not reversed by *p*-aminobenzoic acid.[17] Rubbo, Albert and Maxwell[18] found the 3- and 9-monoaminoacridines had marked antiseptic action, the 1- and 2-mono-aminoacridines had some activity and the 4-aminoacridine had very little activity. These authors suggest two explanations. One is that the basic dissociation constants, which were found to be in the same order, are responsible for the activity; the other that an imino structure which is present in the 3- and 9-compounds confers the marked activity. The 3- and 9- compounds are sufficiently strong bases, $Kb = 1.2 \times 10^{-5}$ and 3×10^{-5}, so they would be almost entirely in the form of the ions at *p*H 7. The ions have resonating forms which account for the strong basic character of the compounds



in each case one of the resonating forms has a coplanar amino group. The 2-aminoacridine, $Kb = 1.2 \times 10^{-9}$ does not have forms of this kind. The 1-aminoacridine, $Kb = 3 \times 10^{-9}$, can have these forms

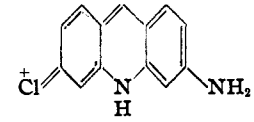


but its low Kb and low bacteriostatic activity are presumably due to the fact that the ortho type quinoid form which is present here is considerably less stable than the paraquinoid forms present in the 3- and 9- compounds. 4-Aminoacridine has the possibility of a hydrogen bond and

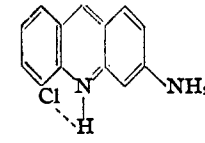


as in the case of orthanilamide this apparently completely inactivates the compound.

Substitution of chlorine in the 5, 6, 7 and 8 positions of 2-aminoacridines has practically no effect on the bacteriostatic activity of the compounds.[19] With the 3-aminoacridines, however, chlorine causes a marked lowering of activity when placed in the 5 or 6 position. When chlorine is in the 6 position the form



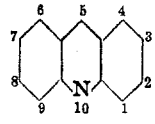
will make some contribution to the structure of the ion, thus cutting down the contribution of the form with the coplanar amino group. When chlorine is in the 5 position a weak hydrogen bond would be formed which would tend to disrupt the resonance



(16) Bell and Roblin[10] on page 2908 give the distance between the oxygen atoms in an SO_2 group as 2.4 Å. and refer to Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd. Ed., 1940. Taking the values given in this reference, namely, an S—O distance of 1.51 Å. and an O—S—O angle of 129°, we calculate an O—O distance of 2.72 Å. which is considerably greater than the O—O distance of about 2.3 in the carboxyl ion. The dimensions taken are C—O 1.27 ±0.01 Å., O—C—O 124° ±4°; N—O 1.21 ±0.02 Å., O—N—O 127° ±3°; S—O 1.51 Å., O—S—O 129°. The S—O distance is from sulfate and would be expected to be nearly the same in a sulfonamide or sulfone. The angle of 129° is from SO_2 and the angle in a sulfonamide or sulfone might be expected to be nearer 125°. Making the calculation, assuming an angle of 125°, gives an O—O distance of 2.68 Å.

(17) Janet B. Gunnison, Unpublished work, Department of Bacteriology, Medical School, University of California.

(18) Rubbo, Albert and Maxwell, *Brit. J. Exptl. Path.*, XXIII, 69 (1942). The British system of numbering the acridine ring differs from the numbering appearing in this paper which is the American system. In the British system of numbering employed by Rubbo, Albert and Maxwell and by Berry,[19] the ring is numbered as follows



(19) Berry, *Quart. J. Pharm. Pharmacol.*, **14**, 363 (1941).

When 3,6-diaminoacridine is acetylated it becomes practically inactive, thus behaving in a similar fashion to the acetylated sulfanilamide derivatives.

It is interesting in the case of the 3- and 9-monoaminoacridines that the active compound is a fairly strong base, $Kb = 10^{-5}$, and the active form is the cation. When the mono N^1 substituted sulfanilamides the most active compounds have Ka's of approximately 10^{-6} and the active form is the anion. The ring N-methylsulfapyridine and sulfathiazole, however, are nearly neutral molecules and have activities about equal to the parent compounds. The one thing that all of these have in common is a large contribution from resonating forms with coplanar amino groups and either a separation of charge or different positions that a charge can occupy. This appears to be the fundamental property responsible for the activity. Whether the active species is acidic, basic or neutral, an anion, cation or neutral molecule appears to be an incidental property as far as the bacteriostatic activity of these compounds is concerned. The important thing is whether the compounds have large contributions from resonating forms with coplanar amino groups. This suggests that in looking for new bacteriostatic agents one should investigate compounds expected to have large amounts of resonance producing coplanar amino groups.

Bell and Roblin[10] have explained the maximum in the curve relating pKa to bacteriostatic activity by attributing the downward trend at low pKa values to the lack of a proportionate increase in the number of ions, for further increases in acid strength, so the added electron attracting power of the R in decreasing the negative character of the SO_2 group, is the predominant effect. This effect as the authors themselves point out is not of sufficient magnitude to account for the observed downward trend at low pKa values. We are inclined to believe that this effect is even less than they have assumed in the theoretical curve given in their Fig. 4. The evidence of Shepherd, Bratton and Blanchard[15] that the ring N-methyl derivatives of sulfapyridine and sulfathiazole have about the same activity as sulfapyridine and sulfathiazole, while the N^1-methyl compounds are practically inactive, also casts serious doubt that the explanation of Bell and Roblin for the decrease in the activity *vs.* pKa curve at high pKa values is adequate.

An alternative explanation for the shape of this curve is as follows. There are at least two reactions involved in the activity of the bacteriostatic agents under discussion. One form of the molecule may be much more suitable for one of these reactions than is the other form and *vice versa*. Such a situation is, of course, sufficient to account for a maximum or minimum in an activity curve. Specifically, in the case of the sulfanilamide derivatives with one R group on the N^1 nitrogen, it might be suggested that the ion is much more effective for one of the reactions while the undissociated molecule is much more effective for the other reaction. Hence, for the maximum activity one must have a particular ratio of ions to undissociated molecules. This need not be a 50-50 ratio but could be almost any ratio depending on the relative rates of the two reactions involved.

There is a large amount of evidence in the literature indicating that with organic molecules it is the undissociated molecule and not the ion that is responsible for the passage of the compound through membranes.[20,21,22,23] Since the sulfonamides apparently act by competing with *p*-aminobenzoic acid for an essential enzyme system and since considerable evidence points to the enzymes in some cases being inside the cells, it seems reasonable that some of the undissociated sulfonamide may have to be present to get the compound to where it can act on the enzyme. After it gets there the ions may be the form that is responsible for activity by competing with the *p*-aminobenzoic acid for the essential enzyme system.

With the ring N-sulfathiazole and sulfapyridine compounds the neutral molecules perform both functions because they not only get to the site of action, but they are active when they get there due to the resonances which place a negative charge on the N^1 nitrogen.

In this connection, the paper by Lwoff, Nitti, Tréfouël and Hamon[24] is of interest for they present evidence that with *p*-aminobenzoic acid itself, it is the undissociated molecule only that goes through cells.

The idea that both the ion and the undissociated molecule must be present for maximum physiological activity of some compounds may very likely be the reason so many physiologically active agents are either weak acids or bases or salts of weak acids or bases. Furthermore, this idea supplies a simple logical explanation for the fact that the physiological activity of different types of agents such as local anesthetics and bacteriostatic compounds, is a function of dissociation constants of the compounds for any given series within each particular class.

Summary

1. A fundamental factor for activity of sulfanilamide type compounds appears to be the contribution of the resonating form with a coplanar amino group.

2. The negative character of the SO_2 group is a concomitant factor associated with this resonating form.

3. The activity of compounds which appear to

(20) Hoskins, *Hilgardia*, **13**, 307 (1940).

(21) Alexandrov, *Biol. Zhur.*, **3**, 490 (1934).

(22) Clowes and Keltch, *Proc. Soc. Expil. Biol. Med.*, **29**, 312 (1931).

(23) Ellison and Richardson, *J. Cell Comp. Physiol.*, **11**, 377 (1938).

(24) Lwoff, Nitti, Tréfouël and Hamon, *Ann. inst. Pasteur*, **67**, 19 (1941); *C. A.*, **36**, 7144 (1942).

be exceptions to Bell and Roblin's theory such as sulfanilylurea, sulfanilylguanidine and sulfanilamido-1,2,4-triazole, or compounds which do not fall within the scope of their theory such as the sulfones and the ring N-methyl and N^1-methylsulfapyridine and sulfathiazole compounds can be adequately accounted for on the basis of this resonance theory.

4. These ideas appear to apply to other bacteriostatic compounds including the monoaminoacridines.

5. Whether the active species is an anion, cation or neutral molecule appears to be an incidental property as far as bacteriostatic activity of these compounds is concerned. The important factor is the contribution of the resonating form.

6. It is proposed that the reason for the maximum in the activity *vs. pKa* curve for the N^1 mono-substituted sulfanilamides is that in these compounds neutral molecules are more effective in getting the agent to the site of action and once it gets there, the ion then interferes with essential metabolic processes resulting in bacteriostasis. It is suggested that this is also the reason the activities of various other types of bacteriostatic agents and local anesthetics are correlated with their acidic or basic dissociation constants.

SAN FRANCISCO, CALIFORNIA RECEIVED JUNE 29, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. VII. The Methoxyl Group

BY S. WINSTEIN AND R. B. HENDERSON

Participation of a neighboring group in replacement reactions of the so-called S_Ni type has been demonstrated in a number of cases.[1] On the qualitative side, we have been studying the generality[2] of this participation with respect to variations in the nature of both the group and the rest of the reacting molecule. Any findings are not only of immediate interest but may prove equally useful in connection with other processes, for example, certain addition reactions. In the course of this work, most of which has been interrupted for the present, we studied the steric result of some reactions in the presence of a neighboring methoxyl group. These reactions involved the action of silver acetate in acetic acid on the *threo-* and *erythro*-2-bromo-3-methoxybutanes II and VII and *trans*-1-bromo-2-methoxycyclohexane XII.

The diastereomeric 2-bromo-3-methoxybutanes were prepared by the addition of the elements of methyl hypobromite to the known *cis-* and *trans*-2-butenes[3] I and VI. Acetbromamide in methyl alcohol[4] was used. It seems safe to assume *trans*-addition[5] to the double bond in assigning configurations to the 2-bromo-3-methoxybutanes.

Diastereomeric 2-acetoxy-3-methoxybutanes III and VIII were prepared by acetylation of the corresponding 3-methoxy-2-butanols IV and IX. The latter were prepared by the reaction of the known[6] *cis-* and *trans*-2,3-epoxybutanes V and X with methyl alcohol. Analogy with the reactions of oxides with water,[6a,7a] acetic acid[7b] and malonic ester[7c] warrants the assumption of *trans*-opening of the oxide ring by methyl alcohol.

The cyclohexene derivatives, *trans*-1-bromo-2-methoxycyclohexane XII and *trans*-2-methoxycyclohexanol XIV (acetate XIII) were prepared from cyclohexene XI and cyclohexene oxide XV, respectively. Configurations were assigned as in the case of the butene derivatives.

Comparison of the reaction products from the methoxybromides with the known compounds is shown in Table I. Except for the preliminary

TABLE I

COMPARISON OF REACTION PRODUCTS WITH KNOWN COMPOUNDS

Compound	B. p. °C.	B. p. Mm.	$n^{25}D$	M. p. of derivative, °C.
3-Methoxy-2-butanol from *erythro*-bromide	131.4–131.5	746	1.4105	108–110[a]
Known *erythro*-3-methoxy-2-butanol	132.3–132.5	748	1.4107	111–112[a]
3-Methoxy-2-butanol from *threo*-bromide	126.5–126.6	746	1.4076	82– 84[a]
Known *threo*-3-methoxy-2-butanol	126,4–126.5	752	1.4074	84– 85[a]
2-Methoxycyclohexyl acetate from bromide	87 – 89	10	1.4437	
Known *trans*-2-methoxycyclohexyl acetate	87.5– 88.0	10	1.4440	
2-Methoxycyclohexanol from bromide	72.8– 73.3	10	1.4586	101–102[b]
Known *trans*-2-methoxycyclohexanol	72.5– 73.2	10	1.4586	101–102[b]

[a] α-Naphthylurethan. [b] 3,5-Dinitrobenzoate.

(1) Winstein, Hess and Buckles, THIS JOURNAL, **64**, 2796 (1942).

(2) Winstein and Buckles, *ibid.*, **64**, 2780 (1942).

(3) Young, Dillon and Lucas, *ibid.*, **51**, 2528 (1929); (b) Brockway and Cross, *ibid.*, **58**, 2407 (1936); (c) Kistiakowsky, *et al.*, *ibid.*, **57**, 876 (1935).

(4) Schmidt, Knilling and Ascherl, *Ber.*, **59B**, 1260 (1926).

(5) (a) Michael, *J. prakt. Chem.* **52**, 344 (1895); (b) Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925); (c) Bartlett and Tarbell, *ibid.*, **58**, 466 (1936); (d) Roberts and Kimball, *ibid.*, **59**, 947 (1937); (e) Winstein and Lucas, *ibid.*, **61**, 1576 (1939); (f) Lucas and Gould, *ibid.*, **64**, 601 (1942).

(6) (a) Wilson and Lucas, *ibid.*, **58**, 2396 (1936); (b) Brockway and Cross, *ibid.*, **59**, 1147 (1937).

(7) (a) Böeseken, *Rec. trav. chim.*, **47**, 683 (1928); (b) Winstein and Lucas, THIS JOURNAL, **61**, 1581 (1939); (c) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2606 (1942).