[Contribution from the College of Pharmacy, University of California]

ACIDIC AND BASIC DISSOCIATION CONSTANTS AND STRUCTURE

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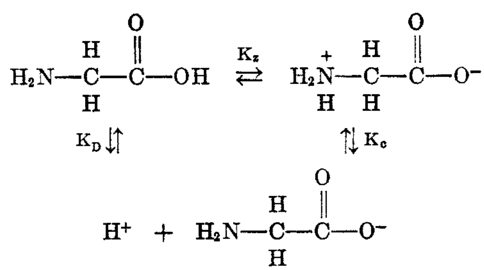
A simple almost self-evident principle is *that acidic and basic groups of appreciable strength will not coexist in the same molecule.* Current chemical literature, however, contains numerous structures which violate this principle and the reason may be either that chemists are unaware of the principle or they do not recognize acidic and basic groups of appreciable strength. Some minimum value for the product of the acidic and basic dissociation constants must be exceeded before one will neutralize the other. The value of that minimum product can be deduced as follows: Taking the specific example of aminoacetic acid, we have the equilibria



or generalizing using Edsall's nomenclature (1)

$$\begin{array}{ccc} R & \overset{K_z}{\rightleftharpoons} & R^{\pm} \\ K_D \downarrow\uparrow & & \uparrow\downarrow K_c \\ H^+ & + & R^- \end{array}$$

$$K_z = \frac{(R^{\pm})}{(R)} \qquad K_D = \frac{(H^+)(R^-)}{(R)} \qquad K_c = \frac{(H^+)(R^-)}{(R^{\pm})} \qquad K_z = \frac{K_D}{K_c}$$

For the compound to be 50% in the dipolar ion form K_z or $\frac{K_D}{K_c}$ must be equal to 1. K_D is the dissociation constant of the acid group and K_c is the acid dissociation of the conjugate acid of the base group. These constants include the effects of the rest of the molecule. Thus in the case of aminoacetic acid, K_D represents the dissociation constant of the carboxyl as affected by the amino group and K_c represents the dissociation of the $-\overset{+}{N}H_3$ group as affected by the carboxyl ion. For ratios of $\frac{K_D}{K_c}$ the per cent in the dipolar ion or other neutralized form would be as follows: (The term "other neutralized form" must be

TABLE I

K_D/K_c	% Dipolar ion or other neutralized form	% Form without separation of charge or other non-neutralized form
1000	99.9	0.1
100	99	1
10	91	9
1	50	50
0.1	9	91
.01	1	99
.001	0.1	99.9

TABLE II

$K_DK_{c\ base}$	% Dipolar ion or other neutralized form	% Form without separation of charge or other non-neutralized form
10^{-19}	0.001	99.999
10^{-18}	.01	99.99
10^{-17}	.1	99.9
10^{-16}	1	99
10^{-15}	9	91
10^{-14}	50	50
10^{-13}	91	9
10^{-12}	99	1
10^{-11}	99.9	0.1
10^{-10}	99.99	.01
10^{-9}	99.999	.001

considered because not all compounds remain in a dipolar or zwitterion form when the acid has neutralized the base. Compounds such as nitroguanidine where the dipolar ion has a resonance form without a separation of charge will be mainly in such an "other neutralized form.")

K_D can be deduced in case of carboxylic acids by applying appropriate inductive constants or it can be calculated from the relation $K_D = \frac{K_1K_2}{K_E}$ as pointed out by Edsall (1), where K_1 and K_2 are the observed dissociation constants of the amino acid and K_E is the dissociation constant of the conjugate acid of the amino ester. K_c can be obtained from the relationship $K_c = \frac{K_1 K_2}{K_1 - K_E}$.

Many chemists prefer to think in terms of the basic dissociation constant. In this case we have the relation $K_c = \frac{10^{-14}}{K_{c\ base}}$ so if $\frac{K_D}{K_c} = 1$ when the groups are 50% neutralized, then $\frac{K_D}{\frac{10^{-14}}{K_{c\ base}}} = 1$ and $K_D\ K_{c\ base} = 10^{-14}$. For other percentages the values of $K_DK_{c\ base}$ will be as given in Table II.

Table II enables one to determine to what extent a compound is a dipolar ion if the strength of the acidic (K_D) and basic ($K_{c\ \mathrm{base}}$) groups can be predicted by analogy or with the use of inductive constants.

In case of aminoacetic acid the value of K_D, the dissociation constant of the carboxyl group in the molecule, $H_2N—CH_2—COOH$ is 5×10^{-5} as calculated from the K_1K_2 and K_E while the estimated value using Branch and Calvin's (2) inductive constants is 4.3×10^{-5}. The value of $K_c = \dfrac{K_1\ K_2}{K_1 - K_E}$ is 1.9×10^{-10}; therefore, $K_{c\ \mathrm{base}}$ is $\dfrac{10^{-14}}{1.9 \times 10^{-10}} = 5.3 \times 10^{-5}$. $K_DK_{c\ \mathrm{base}}$ is then 2.7×10^{-9} and from Table II it can be seen that the compound is more than 99.999% in the dipolar ion form.

Table III gives results on some typical compounds containing acidic and basic groups of different strengths.

A useful generalization which is evident from the above is that if the observed K_a is less than K_D or the observed K_b less than $K_{c\ \mathrm{base}}$ the compound will exist in the zwitterion or other neutralized form roughly to the extent that K_a differs from K_D and K_b differs from $K_{c\ \mathrm{base}}$.

A series of compounds whose structures have been written incorrectly for a number of years are certain derivatives of guanidine. This compound itself is a very strong base. The center of high basicity resides on the doubly bonded nitrogen for when a proton is attached thereto the resulting ion has three equivalent forms which because of the large amount of resonance stabilize the ion and make the base strong. A mono- or di-substituted guanidine will still have appreciable strength as a base. Now if in the $A—\overset{\displaystyle H}{N}—\overset{\displaystyle NH}{\overset{\|}{C}}—NH_2$ or $A—\overset{\displaystyle H}{N}—\overset{\displaystyle NH}{\overset{\|}{C}}—\overset{\displaystyle H}{N}—B$ groups A or B contain an acid group or if they make the H attached to the N to which they are attached an acid with a K_a or 10^{-10} or perhaps even as weak as 10^{-12}, the acid will neutralize the base and the substituted guanidine will not have the structure above, but will have a structure in which the acid has

TABLE III

Compound	K_D	$K_{c\ \mathrm{base}}$	$K_DK_{c\ \mathrm{base}}$	Approx. % dipolar ion or other neutralized form	Obs. K_b	Obs. K_a
m-Aminophenol.......	10^{-10}	10^{-10}	10^{-20}	0.0001		
Morphine............	10^{-9}	10^{-6}	10^{-15}	9	7.5×10^{-7}	
p-Aminobenzoic acid..	10^{-5}	10^{-10}	10^{-15}	9	2.6×10^{-12}	2.1×10^{-5}
m-Aminobenzoic acid..	10^{-4}	10^{-10}	10^{-14}	50		3.2×10^{-5}
Nicotinic acid........	10^{-4}	10^{-10}	10^{-14}	50		1.4×10^{-5}
Sulfanilic acid........	>1	10^{-11}	10^{-11}	99.9		6.2×10^{-4}
Morphine glucuronide.	10^{-4}	10^{-6}	10^{-10}	99.99		
Aminoacetic acid.....	5×10^{-5}	5×10^{-5}	2.5×10^{-9}	>99.99	2×10^{-12}	4.5×10^{-10}
Taurine..............	>1	10^{-5}	$>10^{-5}$	>99.99		1.8×10^{-9}

neutralized the base. In the case of these guanidine derivatives, the main contributing form to the resonance hybrid is not a form with a separation of charge $H_2N{-}\overset{{}^{+}NH_2}{\overset{\|}{C}}{-}\overset{-}{N}{-}B$ but a form without a separation of charge $H_2N{-}\overset{NH_2}{\overset{|}{C}}{=}N{-}B$ which is more stable. Recently it has been shown from chemical, dipole moment, dissociation constant and spectra data that nitroguanidine, nitroaminoguanidine, nitrosoguanidine, 2-nitriminoimidazolidine, 1-nitro-2-nitriminoimidazolidine, and azo-bis(nitroformamidine) have structures of this type which are properly designated nitroimines (3–8). In these cases the nitroimine form is more stable not only because it does not have a separation of charge, but also because the double bond is now conjugated with the nitro group $H_2N{-}\overset{NH_2}{\overset{|}{C}}{=}N{-}\overset{O}{\overset{\|}{N}}{\rightarrow}O$ and additional stabilization results from this conjugation. With the evidence from these compounds plus the theoretical aspects discussed previously it can be stated with some certainty that compounds of the following type are written incorrectly as $H{-}\overset{H}{N}{-}\overset{NH}{\overset{\|}{C}}{-}\overset{H}{N}{-}B$ and should be written $H{-}\overset{H}{\overset{|}{N}}{-}\overset{NH_2}{\overset{|}{C}}{=}N{-}B$ if B is of appreciable electronegativity. This structure for these compounds is consistent not only with their observed dissociation constants, but with their other properties as well. The position of cyanoguani-

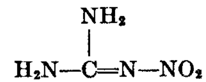
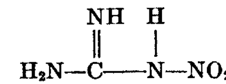
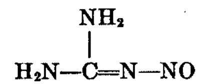
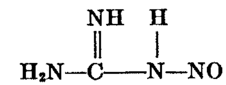
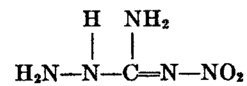
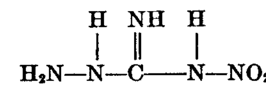
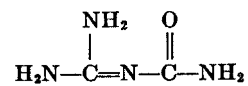
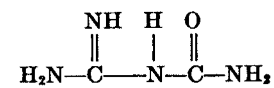
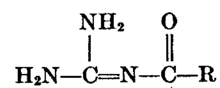
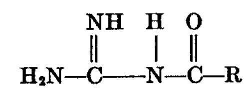
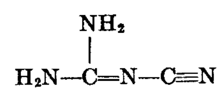
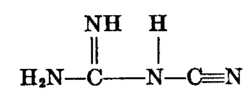
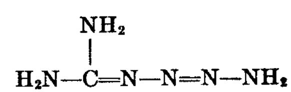
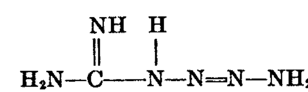
$H_2N{-}\overset{NH}{\overset{\|}{C}}{-}NH_2$	$H_2N{-}\overset{NH}{\overset{\|}{C}}{-}\overset{H}{N}{-}CN$	$H_2N{-}\overset{NCN}{\overset{\|}{C}}{-}\overset{H}{N}{-}CN$	$H_2N{-}\overset{NH_2}{\overset{|}{C}}{=}N{-}CN$
Guanidine very strong base	Cyanoguanidine neutral, but acid structure	Dicyanoguanidine very strong acid	Cyanoguanidine neutral structure

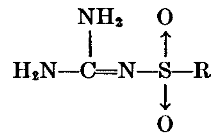
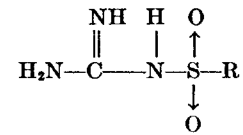
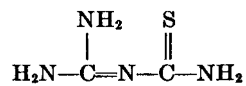
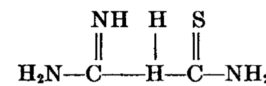
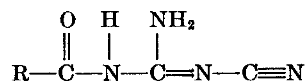
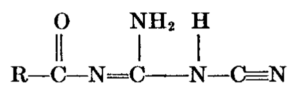
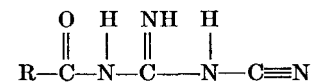
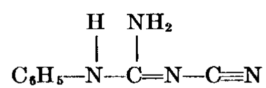
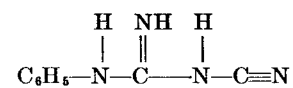
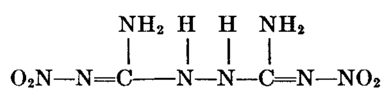
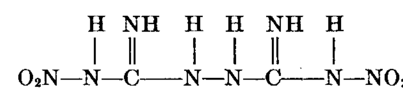
dine in the series is not understandable on the basis of the old structure because it has essentially the same grouping in it that makes dicyanoguanidine a very strong acid namely $-\overset{N^-}{\overset{\|}{C}}{-}\overset{H}{\overset{|}{N}}{-}CN$. If cyanoguanidine had such a structure it would be weaker than dicyanoguanidine by about 2 pK_a units but this means it still would be a relatively strong acid, so its neutrality is incomprehensible on the basis of such a structure. On the other hand, the neutrality of cyanoguanidine is completely understandable if the compound has the cyanoimine structure for then the molecule has no grouping that would give rise to acidity and the inherent basic character of the $H_2N{-}\overset{NH_2}{\overset{|}{C}}{=}$ structure is reduced to neutrality by attachment of the very electronegative $=N{-}CN$ group just as the structure becomes neutral when the $=O$ group of similar electronegativity is attached and urea results.

The above series is inconsistent from another viewpoint. If the cyanide group replaces a hydrogen on a NH_2 to form cyanoguanidine, it would also be expected

TABLE IV

GUANIDINE DERIVATIVES

Name	Most Probable Structure	As Frequently Written
Nitroguanidine		
Nitrosoguanidine		
Nitroaminoguanidine		
Guanylurea		
Acylguanidine		
Cyanoguanidine		
Aminodiazoguanidine		

Sulfonylguanidine		
Guanylthiourea		
Acylcyanoguanidine	 or 	
Phenylcyanoguanidine		
1,6-Dinitrobiguanidine		

to replace a hydrogen on the other NH_2 to form dicyanoguanidine so the structure of this compound would be $NC\text{—}\overset{H}{N}\text{—}\overset{\overset{NH}{\|}}{C}\text{—}\overset{H}{N}\text{—}CN$ and not as written. If it had this structure, however, it would be a dibasic acid, which it is not. Table IV contains examples of a number of compounds written correctly with an electronegative group attached to the imine nitrogen and incorrectly as usually given with a $=N\text{—}H$ group. All the compounds in Table IV have one or more groups of appreciable electronegativity substituted in guanidine and it is obvious that the table can be greatly extended. The multiple bonds are conjugated in the more probable structures but not in the less probable ones. This is a further stabilizing influence in addition to that resulting from the neutralization of the acidic groups by basic groups.

A compound in which there is some doubt if there is present a group of sufficient acidity to neutralize one of the basic $=NH$ groups is biguanide which is usually written $H_2N\text{—}\overset{\overset{NH}{\|}}{C}\text{—}\overset{\overset{H}{|}}{N}\text{—}\overset{\overset{NH}{\|}}{C}\text{—}NH_2$. The hydrogen on the central nitrogen is the most acidic but whether it is sufficiently strong to neutralize one of the base groups is not certain. However, if it did the resulting structure $H_2N\text{—}\overset{\overset{NH_2}{|}}{C}\text{=}N\text{—}\overset{\overset{NH}{\|}}{C}\text{—}NH_2$ would have the double bonds conjugated and would be more stable as a result. This imine structure is therefore more probable.

The structure of compounds such as methylaminoguanidine $H_2N\text{—}\overset{\overset{NH}{\|}}{C}\text{—}\overset{\overset{H}{|}}{N}\text{—}\overset{\overset{H}{|}}{N}\text{—}CH_3$ or $H_2N\text{—}\overset{\overset{NH_2}{|}}{C}\text{=}N\text{—}\overset{\overset{H}{|}}{N}\text{—}CH_3$ cannot be arrived at by these considerations since they have only one double bond and do not have any group of appreciable acidity. It is possible that even here the N-imino form may be more probable. The hydrogen on the central nitrogen in the first structure is certainly the most acidic, although very weakly so. If it goes off it can return either to the same place or to the $C\text{=}NH$ nitrogen. There appears little doubt that this nitrogen would be more basic than the one from which the hydrogen came because a nitrogen attached to a carbon and another nitrogen usually is less basic than one attached to a carbon and hydrogen.

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