ART. XXIII.—*On the constitutional formulæ of Urea, Uric Acid, and their derivatives;* by Professor J. W. MALLET, University of Virginia.

FEW classes of organic compounds have given rise to more difference of opinion amongst chemists than that which includes urea and its conjugates.

The remarkable number of such compounds, their complicated relationships, the varied circumstances of their production and decomposition, and their variety of chemical character, have led to nearly every one of them being viewed in several different lights, and represented by several different formulæ, by those who have given the subject special attention.

The structure of the simple molecule of urea itself is by no means settled. The arguments of Heintz* and Kolbe† in favor of the view that urea is identical with carbamide ($H_2N—CO—NH_2$) have been opposed by the observation of Wanklyn and Gamgee‡ as to the behavior of urea (unlike that of admitted amides) when oxidized by an alkaline solution of potassium per-manganate. The latter chemists proposed the formula $C\left\{\begin{array}{l}(NH)''\\ NH_2\\ OH\end{array}\right.$, but, as Watts remarks in his Dictionary of Chemistry,§ without assigning specific reasons (other than the difference of behavior just noted) for adopting this instead of the carbamide formula which they reject. Wolcott Gibbs‖ independently put forward the same view, but *did* give some of the grounds upon which it was adopted by him. It has also been proposed to represent urea as $O{=}C{=}NH_2—NH_2$, in which formula one of the nitrogen atoms is pentad. Most recent writers of text-books, however, as Fittig¶ and Naquet,** seem to have fallen back upon the view that urea is simply carb-

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* Ann. der Chem. u. Pharm., cxl, 276; cl, 73.

† Zeitschr. für Chem., II, iii, 50.

‡ Jour. Chem. Soc., Jan., 1868, 31.

§ 1st Suppl., 1115.

‖ Amer. Jour. Sci., II, xlvi, 290, Nov., 1868.

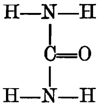
¶ Wöhler's Grundriss der org. Chem., 8te. Aufl., 206.

** Principes de Chimie, troisème éd., t. ii, 532–533.

amide. Bunte* has suggested as the means of deciding between these opinions the determination of the maximum number of isomeric products obtainable from the body in question by substituting an alcoholic radical for hydrogen.

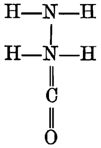
The most obvious point of difference between the three formulæ above mentioned consists in the first being symmetrical while the others are not so. If urea be carbonic diamide (1), viz:

1.



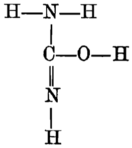
$$\begin{array}{c} H-N-H \\ | \\ C=O \\ | \\ H-N-H \end{array}$$

2.



$$\begin{array}{c} H-N-H \\ | \\ H-N-H \\ \| \\ C \\ \| \\ O \end{array}$$

3.



$$\begin{array}{l} H-N-H \\ \quad\;\; | \\ \quad\;\; C-O-H \\ \quad\;\; \| \\ \quad\;\; N \\ \quad\;\; | \\ \quad\;\; H \end{array}$$

the two nitrogen atoms are placed exactly alike, and so are the four atoms of hydrogen. If the third formula (2) be adopted, the two nitrogen atoms will be unlike, while there will be two pairs of hydrogen atoms with no difference between the members of each pair. But if the formula (3) be the true one, the two nitrogen atoms, while exhibiting the same atomicity, are dissimilarly connected, and hydrogen is found in three different relations to the rest of the molecule, only two atoms of the latter element being quite alike in position. Clearly we should the rather expect from this highly unsymmetrical disposition of the atoms such a number and variety of substituted and conjugated products as urea actually affords.

But not only does this last view enable us easily to account for the large class of derivatives furnished by the substance in question, but it seems to lend itself remarkably well to the explanation of the special character which these derivatives severally exhibit, whereas many of the formulæ hitherto proposed for the "ureides" differ much from those of other bodies of the same type, the acid or basic character, degree of basicity, etc., not being satisfactorily accounted for. In this respect Wanklyn, Gamgee and Gibbs seem scarcely to have done justice to the merits of the formula they suggested, and I propose by a few examples of the better known substances related to urea to illustrate the advantages of assuming for it this molecular constitution. In doing so I have to suggest a structural composition for most of the conjugated bodies spoken of unlike that which Gibbs has adopted in the paper above referred to. It will conduce somewhat to clearness to use fully expanded graphic formulæ, and for the conjugated compounds

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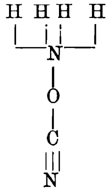
* Ann. der Chem. u. Pharm., cli, 184.

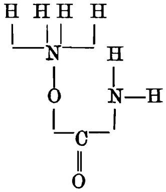
to use dotted lines to represent the bonds connecting residues derived from different molecules.*

Let then urea be represented by the last formula, No. 3, derivable from ammonium cyanate

1. Ammonium cyanate.



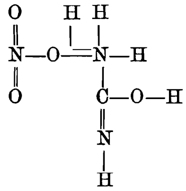
2. Ammonium carbamate.



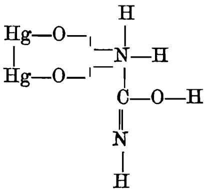
by intermolecular transposition, and from ammonium carbamate by change of the same sort with elimination of water. In both cases one of the two nitrogen atoms shows the usual tendency to revert from pentad to triad character by elevation of temperature.

The *direct compounds* of urea (like those of ammonia) with acids involve a re-assumption of pentad relation by this one atom of nitrogen; not by both, as we might expect if they were alike in position in the molecule; as, for instance, in the case of urea nitrate.

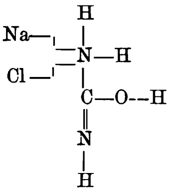
Urea nitrate.



Urea and mercuric oxide.

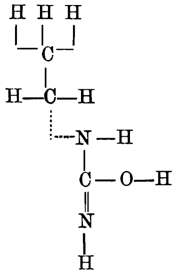


Urea and sodium chloride.

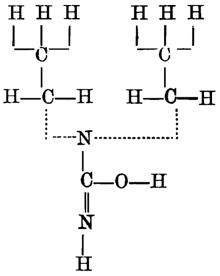


Similar relations are entered into with some metallic oxides, as for instance, mercuric oxide, and certain salts, as with sodium chloride.

1. Ethyl-urea (basic).



2. Normal di-ethyl-urea (basic).



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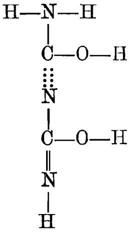
* Some of these graphic formulæ would look rather simpler and better were it not for difficulty on the part of the printer in using *oblique* lines with movable type.

Products of substitution by alcoholic radicals, *in which the urea type and character are preserved*, are exemplified by ethyl-urea, $C_3H_8N_2O$, in which one of the two similarly related hydrogen atoms is replaced, and by normal di-ethyl-urea, $C_5H_{12}N_2O$, in which the replacement extends to both of these atoms. One hydrogen atom of this pair and another (unlike) atom at the same time are probably replaced in the isomeric di-ethyl-urea, and tri-ethyl-urea, if this compound really exist, will represent the replacement of both the similar and one unsymmetric (probably imide) atom of hydrogen.

Formulæ for condensed ureas containing polyatomic radicals, such as ethylene, follow easily enough from the above.

In biuret, $C_2H_5N_3O_2$, we may suppose the residues of two urea molecules united with elimination of ammonia from unlike (amidic and imidic) extremities of the chain of atoms—thus,

Biuret (feebly basic, uniting (by its amidic end probably) with one equivalent of HCl).

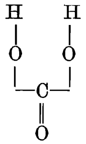


this giving a very obvious explanation of the formation of biuret by heating urea, ammonia being at the same time liberated.

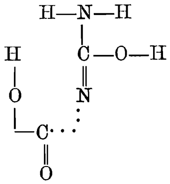
Conjugated compounds of urea residues and acid radicals form a more numerous class. In these the type of the original acid seems usually to predominate, but *the urea residue modifies the character of the substance in different ways according to the mode of attachment.* This last point seems to have been the chief one overlooked in the arrangement of most of the structural formulæ hitherto proposed.

Thus, from carbonic acid, CH_2O_3 (di-basic), we get allophanic acid, $C_2H_4N_2O_3$,

Carbonic acid (dibasic).

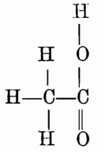


Allophanic acid (monobasic).

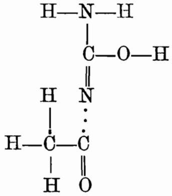


only one of the two basic hydrogen atoms present in the original acid remaining in place. A comparison of allophanic acid thus viewed with the above formula for biuret will show how the latter is produced by the action of ammonia upon ethyl allophanate. From acetic acid, $C_2H_4O_2$, we have acetyl-urea, $C_3H_6N_2O_2$ (exhibiting neither acid nor basic character),

Acetic acid (monobasic).

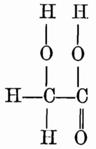


Acetyl-urea.

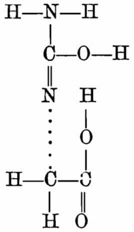


the one basic atom of hydrogen of the original acid having been replaced by the urea residue at its imide extremity. From glycollic acid, $C_2H_4O_3$, we have glycoluric (hydantoic) acid, $C_3H_6N_2O_3$.

Glycollic acid (monobasic).

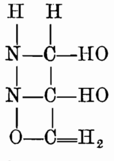


Glycoluric acid (monobasic).



the urea residue replacing the methylic hydroxyl, while the original oxatyl remains unaffected and the acid character is preserved. In the formula for glycoluric acid proposed by Gibbs, viz: (misprinted in his paper in the transposition of the — and = in the bottom line):

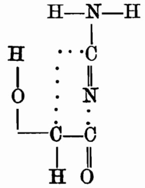
Glycoluric acid.



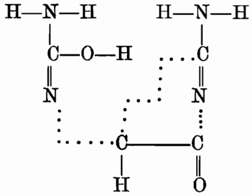
the mono-basic character is not obvious, nor does it readily appear which is the replaceable (basic) atom of hydrogen.

If glycollic acid be differently conjugated with urea, the residue of the latter attaching itself in place of the *basic* hydroxyl, and a molecule of water being eliminated, we get hydantoine, $C_3H_4N_2O_2$ (1).

1. Hydantoine (neutral).

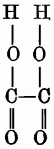


2. Glycolurile (neutral).

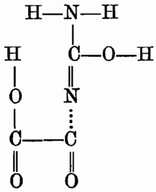


By reference to the formula proposed further on for allantoine it will be seen how simply the production from it of hydantoine occurs with separation of urea. Glycolurile, $C_4H_6N_4O_2$, appears (2) as the corresponding di-ureide of glycollic acid, and its relation to allantoine (from which it is producible by the action of sodium amalgam) will be easily seen by reference to the formula for the latter, although I prefer to view these bodies as derivatives of two different acid nuclei. The breaking up of glycolurile by an acid in the presence of water into hydantoine and urea is easily traced. From oxalic acid, $C_2H_2O_4$, we get oxaluric acid,* $C_3H_4N_2O_4$,

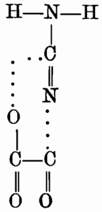
1. Oxalic acid (dibasic).



2. Oxaluric acid (monobasic).



3. Paraban.



easily breaking up in presence of water into oxalic acid and urea.

The absence of well determined acid character in paraban (parabanic acid), $C_3H_2N_2O_3$, justifies the above formula, No. 3, which well explains Ponomareff's† synthesis of this body by the action of phosphorus tri-chloride on a mixture of oxalic acid and urea, as well as the ready conversion into oxaluric acid by assumption of water; while the so-called metallic salts formed by this body (including those described by Menschutkin),‡ remarkable for their instability, may probably represent merely the substitution of amidic hydrogen in the urea residue, as cholestrophane results from the substitution of both these hydrogen atoms by methyl. It will be seen presently that this formula makes paraban bear exactly the same relation to oxalic acid that alloxan does to mesoxalic acid.

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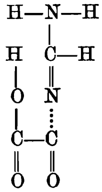
* There is some misprint in the formula for this acid in the memoir of Gibbs (loc. cit., p. 292), since it contains an atom of oxygen too much.

† Bull. Soc. Chim. de Paris, II, xviii, 97.

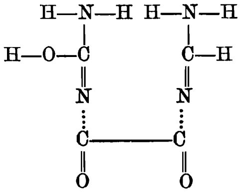
‡ Ann. der Chem., clxxii, 73.

If in the ureic residue of oxaluric acid we substitute hydrogen for hydroxyl, we get the formula for allanturic (lantanuric) acid, $C_3H_4N_2O_3$,

1. Allanturic acid (monobasic).

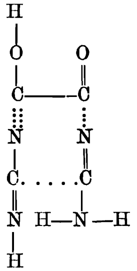


2. Allantoine (neutral).



and the mode in which this acid is produced from allantoine by assimilation of water and separation of urea becomes evident if we give to allantoine, $C_4H_6N_4O_3$, the following formula (2), viewing it as a di-ureide derivative of oxalic acid, with which it appears in fact to be closely connected, producing oxalates by heating with alkaline solutions, by fermentation with yeast, &c. By reference to the formula proposed further on for uric acid it will appear how this latter yields allantoine on boiling an aqueous solution with lead dioxide, the middle carbon atom of the mesoxalic acid residue being removed as carbon dioxide, and hydroxyl and hydrogen respectively taken up from a molecule of water by the two ureic residues, which at the same time assume a different mode of attachment to the oxalic acid nucleus; the further action of an excess of lead dioxide decomposing the allantoine itself, with formation of urea and lead oxalate. The formula of Gibbs for allantoine (as for hydantoine and glycolurile) would lead us to expect an acid character, whereas such compounds as are formed by this body with metals and metallic oxides manifestly are of the same order as those produced with similar substances by urea itself. In the other di-ureide, viz: mycomelic acid, $C_4H_4N_4O_2$,

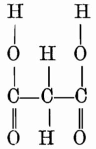
Mycomelic acid (monobasic).



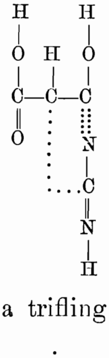
we have an example of what I agree with Professor Gibbs in assuming as very probable, namely, the similarity of function of nitrogen with two free bonds to the outside oxygen in oxatyl,[*] so that I represent one of the two such oxygen atoms in oxalic acid as replaced by a urea residue connecting itself by its amidic extremity, the hydrogen of the corresponding hydroxyl of the acid retaining its basic character; while the second residue of urea, attached by the opposite end of its chain of atoms, replaces hydroxyl instead of oxygen, and thus changes a di-basic into a mono-basic acid. Here we have an instance of what seems to me the error arising in many of the older formulas from considering merely the number of atoms, with their additions or subtractions, without noticing the character of the compounds in question as an indication of molecular structure. Odling[†] says of mycomelic acid that it bears "exactly the same relation to oxalic acid that uric has to mesoxalic acid." So it does, in so far as the summation of the atoms present is concerned, but the two last named acids are both di-basic, while oxalic and mycomelic acids are di-basic and mono-basic respectively. It will be seen presently that the formulæ I propose account fully for this, the two urea residues in uric acid being similarly connected with the residue of the original acid, while in mycomelic acid they are connected by what I have called the amidic and imidic ends respectively.

Passing to the 3-carbon acids, from malonic acid, $C_3H_4O_4$, No. 1, may be derived barbituric acid, $C_4H_4N_2O_3$, No. 2.

1. Malonic acid (dibasic).



2. Barbituric acid (dibasic).



Gibbs' formula (in which there is a trifling misprint) would imply a mono-basic acid.

Naquet[*] speaks of "l'hydantöine, qui représente de l'acide allanturique moins un atome d'oxygène, et qui est, par conséquent, à l'acide allanturique ce que l'acide barbiturique est à l'acide dialurique." But of these two pairs of substances,

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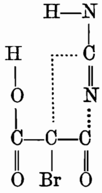
[*] As in the polymerides of true cyanic acid. Prof. Gibbs proposes to call $(CNOH)''$ cyanyl, as analogous to $(COOH)'$, oxatyl.

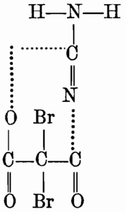
[†] Lectures on Animal Chemistry, London, 1866, p. 132.

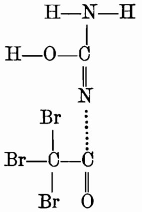
[‡] Principes de Chimie (1875), ii, 578.

hydantoine is neutral, and allanturic acid a mono-basic acid, while barbituric and dialuric acids are di-basic and mono-basic respectively. The formulæ proposed in this paper furnish an explanation of the difference.

Any formula I have seen for bromo-barbituric acid, $C_4H_3BrN_2O_3$, would lead one to expect for it exactly the same degree of basicity as that of barbituric acid. But the following (No. 1) with the urea residue oppositely attached) will show how the former acid is mono-basic, while the latter is di-basic.


1. Bromo-barbituric acid (mono-basic).

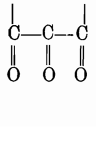

2. Brom-alloxan or di-bromo-barbituric acid (non-acid).

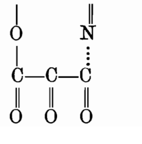

3. Tri-brom-acetyl-urea (neutral).

A further replacement of hydrogen by bromine gives us what has been called di-bromo-barbituric acid, $C_4H_2Br_2N_2O_3$, a body which is, however, really devoid of acid character, not forming salts. With the formula now proposed (No. 2, above), this non-acid character becomes intelligible, and the name brom-alloxan, originally employed by Baeyer, becomes fully justified on comparison with alloxan as represented further on. The conversion of this body into dialuric acid by the action of hydro-sulphuric acid in the presence of water is explained by the formula for dialuric acid given further on.

On pushing the action of bromine still further, brom-alloxan is converted, with separation of carbon dioxide, into tri-brom-acetyl-urea, $C_3H_3Br_3N_2O_2$ (from the 2-carbon acid residue), the formula of which (No. 3, above) is very simply derived from No. 2, and brings us back to that of acetyl-urea as already given.

From mesoxalic acid, $C_3H_2O_5$ (No. 1), we get the acid mon-ureide dialuric acid, $C_4H_4N_2O_4$ (No. 2),

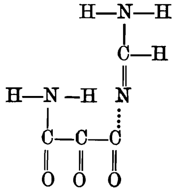

1. Mesoxalic acid (di-basic).


2. Dialuric acid (mono-basic).

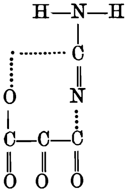
in which the ureic hydroxyl is replaced by hydrogen. The production of this acid by hydrogenation of alloxan will be seen presently to be readily intelligible.

And from dialuric acid is derived the amide, uramile (dialuramide), $C_4H_5N_3O_3$ (No. 1).

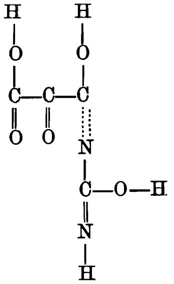
1. Uramile (neutral).



2. Alloxan (neutral).



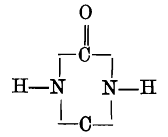
3. Alloxanic acid (di-basic).



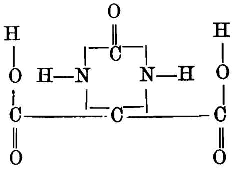
For the production of this body from alloxantine by the action of ammonium chloride, with separation of alloxan and hydrochloric acid, see the formula given beyond for alloxantine.

The formula of alloxan, $C_4H_2N_2O_4$, also a mon-ureide, becomes as represented in No. 2, while alloxanic acid, $C_4H_4N_2O_5$, formed by attachment of the urea residue by its opposite extremity, and with assumption of a molecule of water, may be viewed as in No. 3 above. Claus and Emde* have noticed the difference of character between the last two substances, and suggested in explanation the following formulæ:

1. Alloxan.



2. Alloxanic acid.



one of the few instances in which I find an attempt made to carry out the idea urged in this paper. Gibbs's formulæ would imply that both substances were acid, and of the same degree of basicity. The parallelism between alloxan and paraban is seen to be brought out by the mode of representation now suggested, and an explanation is afforded of the fact that whereas, as Naquet† says (looking only at the number of atoms concerned), alloxanic acid bears the same relation to alloxan that oxaluric acid does to paraban, the former acid is di-basic and the latter mono-basic only.

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* Ber. d. deutsch. chem. Gesellsch., vii, 226. † Principes de Chimie (1875), ii, 578.

(To be continued.)