The Conversion of Ammonium Cyanate into Urea—a Saga in Reaction Mechanisms

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The year 1978 is the sesquicentenary of Wöhler's discovery that ammonium cyanate may be converted spontaneously into urea.[1] Most chemists know of Wöhler's work as evidence against *vitalism*, but it is less widely known that the mechanism of the ammonium cyanate–urea conversion has been discussed for over 80 years, and the topic is not yet exhausted. The history is remarkable for the eminence of many of the participants and for its confusions, in spite of early establishment of the basic facts. It seems appropriate to apply the term 'saga'. The saga will be better appreciated after a modern discussion of the mechanism. (Detailed references are deferred; a comprehensive account was given by Frost and Pearson.[2] Throughout the article there will be occasional mention of the related formation of substituted ureas from alkylammonium cyanates *etc.*)

1 A Modern Discussion of the Mechanism

Without prejudice to the question of *mechanism* we may write the *stoicheiometric equation* for the reaction as (1):

$$NH_4^+ + CNO^- \rightleftharpoons CO(NH_2)_2 \qquad (1)$$

In the aqueous or aqueous–organic solutions used in most of the kinetic work the reaction is reversible, but the conversion into urea is nearly complete, the equilibrium constant being *ca.* 10^4 l mol^{-1}. Hydrolysis of cyanate to bicarbonate and ammonia is a side-reaction, which can consume as much as 30% of the cyanate. When these complications are allowed for, the rate of the forward reaction (1), v_1, is found to be proportional to $[NH_4CNO]^2$. Since the salt is highly ionized, this kinetic relationship may be expressed by equation (2):

$$v_1 = k[NH_4^+][CNO^-] \qquad (2)$$

The straightforward interpretation of these findings, which has been accepted by numerous authors, is that the reaction proceeds by the *ionic mechanism* (3):

$$NH_4^+ + CNO^- \rightarrow CO(NH_2)_2 \qquad (3)$$

This is, however, not the only possibility. Ammonium cyanate, as the salt of a weak base and a weak acid, participates in the mobile equilibrium (4),

$$NH_4^+ + CNO^- \rightleftharpoons NH_3 + HNCO \qquad (4)$$

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[1] F. Wöhler, *Poggendorff's Ann. Phys. Chem.*, 1828, **12**, 253.

[2] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism', Wiley, New York, 2nd Ed., 1961, p. 307.

for which the equilibrium constant is *ca.* 2.5×10^{-6} at 25 °C. The equilibrium concentrations of ammonia and cyanic acid[3] (unless added in excess) are thus small but the existence of (4) means that the second-order kinetics may also be expressed as in (5):

$$v_1 = k'[\mathrm{NH_3}]\,[\mathrm{HNCO}] \tag{5}$$

and interpreted in terms of the *molecular mechanism* (6):

$$\mathrm{NH_3 + HNCO \rightarrow CO(NH_2)_2} \tag{6}$$

The connection between equations (2) and (5) is given by (7):

$$k = k' K_a^{\mathrm{NH_4^+}} / K_a^{\mathrm{HNCO}} = k'K \tag{7}$$

where $K_a^{\mathrm{NH_4^+}}$ is the ionization constant of the ammonium ion, K_a^{HNCO} is that of cyanic acid, and their ratio, K, is the equilibrium constant of (4), all of these quantities being *concentration*-based, *i.e.* activity coefficients are neglected.

Whereas addition of potassium sulphate reduces the rate slightly, *ammonium* sulphate or potassium *cyanate* produces considerable acceleration. These facts may be interpreted equally well as direct effects on (3) or as indirect effects on (6) *via* the equilibrium (4). Similarly the observation that addition of ammonia has almost no effect, which is obviously in accord with (3), is also in accord with (6), because increasing the concentration of ammonia will, through (4), decrease that of cyanic acid correspondingly.

Both the slight inhibitory effect of potassium sulphate and a tendency for the rate coefficient k to increase with decreasing initial concentration of ammonium cyanate indicate that the reaction is subject to a negative salt effect. The effect of ionic strength has been studied in detail. At high dilution the slope of the plot of log k *versus* $\sqrt{\text{ionic strength}}$ has the value predicted by the Brönsted–Bjerrum–Christiansen equation for the *kinetic* salt effect on a reaction between singly charged ions of opposite sign. At first sight this accords with the ionic mechanism (3) and not with the molecular mechanism (6), since a reaction between two neutral molecules shows only a minute salt effect. However, if (6) is the mechanism, k must be interpreted as in equation (7). The equilibrium constant K in (7), being concentration-based, will show a salt effect, *i.e.* the *equilibrium* salt effect on the reversible process (4) involving singly charged ions of opposite sign giving neutral products. This will be *quantitatively* the same as a kinetic salt effect on (3).

The dependence of k on the nature and composition of aqueous organic media has also been studied. This solvent effect has been attributed to variation in the dielectric constant of the medium, and again the results may be interpreted either as a direct effect on (3) or as an indirect effect on (6) *via* the equi-

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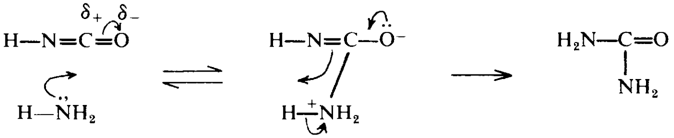
[3] In this article the parent acid of ammonium cyanate will be referred to as cyanic acid. It is, in principle, tautomeric but it exists entirely in the imide form H—N=C=O, the parent of the organic isocyanates R—N=C=O. See T. W. J. Taylor and W. Baker, 'Sidgwick's Organic Chemistry of Nitrogen', Clarendon Press, Oxford, 2nd Ed., 1937, p. 322.

librium (4). There are also other features of the reaction kinetics which are similarly ambiguous.

In so far as the two mechanisms can be distinguished experimentally, information about related reactions is used and arguments other than those of classical reaction kinetics are involved. These will be discussed later. However, we argue now in favour of the molecular mechanism on the grounds that it is *inherently more plausible* than the ionic mechanism. It is easy to envisage the nucleophile ammonia attacking the positively polarized carbon of HNCO to form a zwitterionic intermediate. A simple proton shift is then all that is necessary to form urea, as in (8):



(8)

Such a mechanism must operate in the related reaction of an alkyl isocyanate RNCO, with ammonia to give a substituted urea. The direct reaction of an ammonium ion with a cyanate ion to give urea is difficult to envisage, because the formation of a carbon–nitrogen bond is blocked by the four-co-ordination of the nitrogen. The ions could conceivably form (reversibly) a hydrogen-bonded complex, as in (9),

$$H_3\overset{+}{N}H + N\overset{-}{C}O \rightleftharpoons H_3N\cdots H\cdots NCO \tag{9}$$

but subsequent rearrangement of this to urea seems improbable.

2 The Work of James Walker, 1895–1903

The first kinetic studies were by Walker[4] and Hambly[5] in 1895. They followed the reaction in aqueous solution by argentometric determination of cyanate and demonstrated both the slight reversibility and the occurrence of the side-reaction to the extent of *a few percent*. Both these disturbances were considered to be allowed for in the second-order rate equation (10),

$$k_2 = x/tA(A - x) \tag{10}$$

where x is the concentration of ammonium cyanate that has reacted by time t and A (the 'practical end-point') the limiting value of x as $t \to \infty$. The values of k_2 were constant over the course of the reaction, but increased slightly with decreasing initial concentration of ammonium cyanate. Values of k_2 at eight temperatures from 25 to 80 °C conformed closely to the Arrhenius equation (then a fairly recent development).[6]

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[4] Sir James Walker, F.R.S. (1863—1935). Studied under Crum Brown in Edinburgh and Ostwald in Leipzig. Professor of Chemistry at University College, Dundee (1894—1908) and Edinburgh University (1908—1928). Obituary notice: *J. Chem. Soc.*, 1935, 1347.

[5] J. Walker and F. J. Hambly, *Trans. Chem. Soc.*, 1895, **67**, 746.

[6] S. Arrhenius, *Z. phys. Chem.*, 1889, **4**, 226.

Walker and Hambly suggested three possible bimolecular processes to explain the second-order kinetics. Two of these were the ionic and the molecular mechanism already mentioned (p. 1); the third involved the meeting and rearrangement of two *undissociated* molecules of ammonium cyanate. The authors considered that they could decide between these three possibilities on the basis of their discovery that ammonium sulphate or potassium cyanate produced marked acceleration, whereas potassium sulphate produced slight inhibition and ammonia had little effect. In their view only the ionic mechanism could account for these observations. However (see p. 2), the ionic and molecular mechanisms cannot be distinguished in this way. How did Walker and Hambly's misapprehension on this point arise? It may have been connected with their apparent belief that the molecular mechanism implied the *almost complete* hydrolysis of ammonium cyanate into ammonia and cyanic acid.[7] It is difficult to understand why they did not reject the third possibility mentioned above on the additional grounds that it implied that the degree of dissociation of ammonium cyanate into ions was small. They certainly held ammonium cyanate to be extensively dissociated into ions.

The authors refined their kinetic treatment in terms of the concentrations of free ammonium and cyanate ions as calculated from 'conductivity numbers'. The effect of adding ammonium sulphate conformed to the modified second-order expression and the 'dilution effect' for k_2 in equation (10) was explained by the degree of dissociation of ammonium cyanate varying with concentration. They concluded, 'On no other theory, as it appears to us, can even a qualitative explanation of our results be given'.

Further papers by Walker and his colleagues soon appeared. Walker and Appleyard[8] studied the transformation of alkylammonium cyanates into alkylureas. The reversibility was more pronounced than for the parent reaction and a more complicated kinetic treatment was required. Walker and Kay[9,10] sought further support for the ionic mechanism by studying urea formation in aqueous ethanol (0—90% ethanol) by electrical conductance measurements. The ethanol considerably reduced the degree of dissociation of ammonium cyanate, as indicated by conductance measurements on potassium cyanate as a stable model salt. The 'apparent' rate constants [the equivalent of k_2 in equation (10), reversibility being properly allowed for] varied markedly with dilution. 'True' rate constants were calculated by dividing the 'apparent' values by p^2, where p was the degree of dissociation of ammonium cyanate. The 'true' values did not vary with dilution and this seemed to support the ionic mechanism. The addition of ethanol accelerated urea formation: for 90% ethanol the 'apparent' rate constant at 32 °C was about 30 times that for water and the 'true' rate constants

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[7] Ref. 5, p. 759, line 17.

[8] J. Walker and J. R. Appleyard, *Trans. Chem. Soc.*, 1896, **69**, 193.

[9] J. Walker and S. A. Kay, *Trans. Chem. Soc.*, 1897, **71**, 489.

[10] S. A. Kay (1874—1933) became well-known to several generations of British chemistry students as the co-author of A. C. Cumming and S. A. Kay, 'Quantitative Chemical Analysis', Oliver and Boyd, Edinburgh, 1913; 11th Edn. (revised by R. A. Chalmers) 1956.

differed by a factor of *ca.* 100. Methanol, acetone, glycol, glycerol, and sucrose as additives also accelerated the reaction.

This more or less completed Walker's early contributions, except for the preparation and properties of solid ammonium cyanate,[11] including calorimetric investigation of its thermochemistry. These thermochemical studies led to a brief dispute with C. E. Fawsitt.[12,13] We need not concern ourselves with this, but a word about Fawsitt's studies in reaction kinetics is appropriate. From 1900 to 1902 he worked in Ostwald's laboratory on the decomposition of urea in aqueous solution.[12] Fawsitt showed that the kinetics of the transformation of urea to ammonium cyanate could be studied (at temperatures above 90 °C) if hydrochloric acid was present to destroy the cyanate rapidly and prevent reconversion into urea. The reaction obeyed the first-order rate law. This paper and an extension by Burrows and Fawsitt[14] twelve years later are almost the only papers on the kinetics of urea decomposition. This reaction never seems to have excited the same interest as the urea synthesis, probably because the first-order kinetics of the decomposition shed much less light on mechanism than do the second-order kinetics of the synthesis. The mechanism of urea decomposition must, of course, be the exact reverse of that of the synthesis.

3 Developments to 1914

After James Walker's work, *ca.* 1900, the next well-recognized contribution was by Chattaway[15] early in 1912.[16] The paucity of references in Chattaway's paper may give the misleading impression that little had happened in the interim. However, after referring to Walker and Hambly's[5] support for the ionic mechanism, Chattaway wrote, '*It has several times been pointed out* that this conclusion is not justified, and that the results agree equally well with the assumption that it is the non-ionized portion of the ammonium cyanate which undergoes transformation.' The only reference given in support of this is to a paper by Heinrich Goldschmidt,[17] which does not actually deal with the urea synthesis but with a comparable situation. The point is that, since ions and undissociated molecules are in mobile equilibrium, the product of the concentrations of the ions is proportional to the concentration of the undissociated molecules so that the reaction rate is proportional both to the latter and to the former. Thus the mechanism could involve the *unimolecular* change of undissociated ammonium cyanate.

Other possible participants in the 'several times' can be identified (see below). Chattaway, however, was not only concerned with this particular mechanistic

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[11] J. Walker and J. K. Wood, *Trans. Chem. Soc.*, 1900, **77**, 21.

[12] C. E. Fawsitt, *Z. phys. Chem.*, 1902, **41**, 601.

[13] J. Walker, *Z. phys. Chem.*, 1903, **42**, 207.

[14] G. J. Burrows and C. E. Fawsitt, *Trans. Chem. Soc.*, 1914, **105**, 609.

[15] Frederick Daniel Chattaway, F.R.S. (1860—1944). Studied under Vernon Harcourt at Oxford and von Baeyer and Bamberger in Munich. After a period as Demonstrator in Chemistry at St. Bartholomew's Hospital Medical School, he was Fellow and Tutor of the Queen's College, Oxford (1909—1935). Obituary notice: *Nature*, 1944, **153**, 335.

[16] F. D. Chattaway, *Trans. Chem. Soc.*, 1912, **101**, 170.

[17] H. Goldschmidt, *Z. Elektrochem.*, 1905, **11**, 5.

ambiguity, for he went on to argue seriously for the molecular mechanism involving ammonia and cyanic acid, equation (6). He was not at all original in this (see below) but no references are given except to Walker and Hambly.[5]

According to Chattaway the urea synthesis must be viewed in the context of various aspects of the chemistry of cyanic acid, cyanates, isocyanic esters, and urea. These could be '. . . brought into harmony by regarding them as instances of the well-known tendency of the carbonyl group to add on groups such as R_2NH or ROH, followed by a subsequent atomic rearrangement involving only the transference of a hydrogen atom from an oxygen atom to a nitrogen atom connected with it through the double-linked carbon atom . . . .' Thus NH_3 was envisaged as adding to HNCO to form an intermediate $HN{=}C(OH)NH_2$, which then rearranged to NH_2CONH_2. Note that the intermediate here is not quite as represented in equation (8) (see below also).

Chattaway's paper included a note by his Oxford colleague D. L. Chapman,[18] who showed by formal physical chemistry that all this was consistent with James Walker's results. In particular, he pointed out the fallacy in Walker's interpretation of the absence of any effect of ammonia.[19]

At the time Chattaway's paper appeared, Walker already knew of the suggestion that second-order kinetics could be explained by unimolecular rearrangement of undissociated ammonium cyanate, for he mentioned it in his Presidential Address, 'Theories of Solutions', to Section B, Chemistry, of the British Association at Portsmouth on August 31st, 1911.[20] Chattaway undoubtedly knew this, for he was a life member of the B.A., and although he did not himself refer to the Address, Chapman did. Walker attributed the recognition of the kinetic ambiguity to Wegscheider[21] but maintained that 'other circumstances make it highly probable that the ions are the active participants in the transformation'. In the ensuing exposition, however, Walker left the question open and with both possibilities in mind used the urea synthesis in a discussion of 'normality' and 'abnormality' in the behaviour of ionized and unionized species. The details of this are too lengthy to describe and are difficult to appreciate today, in a very different situation regarding the theory of electrolytes.

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[18] David Leonard Chapman, F.R.S. (1869—1958). Studied under Vernon Harcourt at Oxford. Lecturer at Manchester University (1897—1907), and Fellow of Jesus College, Oxford and Head of the Sir Leoline Jenkins Laboratories in that college (1907—1944). Obituary notice: *Biog. Mem. Fellows Roy. Soc.*, 1958, **4**, 35.

[19] It seems odd that Chattaway should have enrolled Chapman to present a very simple piece of physical chemistry (although admittedly James Walker had overlooked it). After all Chattaway, like Chapman, had been a pupil of Vernon Harcourt, one of the founders of chemical kinetics. The explanation may be that Chattaway, in spite of the influence of Vernon Harcourt, was never really at home with physical chemistry. G. D. Parkes, a pupil of Chattaway, describes him as out of sympathy with the application of physical methods to organic chemistry, and quotes a colleague's remark that Chattaway was the 'true-blue organic chemist'. In a letter to the present author (15.11.77), Professor H. M. N. H. Irving (also a pupil of Chattaway) writes 'F. D. C. did not believe in physical chemistry!', and he substantiates this with various recollections.

[20] J. Walker, *Rep. Brit. Assoc. Advancement Sci.*, 1911, 354.

[21] Rudolf Wegscheider, the distinguished Viennese chemist, was probably in the audience: in the same session he read a paper on 'The Influence of Substituents on Reaction Velocities'. Walker probably had in mind *Z. Elektrochem.*, 1908, **14**, 133, which makes essentially the same point as Goldschmidt's[17] paper.

Towards the end of 1912, Chattaway's paper[16] provoked a short note from A. S. Wheeler.[22] After summarizing Chattaway's views, he suggested a simpler formulation of the molecular mechanism as the direct addition of H and NH_2 (from NH_3) across the C=N bond of cyanic acid: *i.e.* the addition compound and its rearrangement were eliminated. He attributed this suggestion to H. B. Hill[23] in lectures at Harvard in 1896, and stated also that 'Essentially the same explanation is given by Willstätter in his lectures in Zürich'. Hill's view was probably no more than speculation but it is of interest as being contemporary with that of Walker and Hambly and as postulating direct addition to C=N in a way closely resembling that envisaged in equation (8) above.

Hill was not the only late-19th century chemist to speculate about the mechanism of the urea synthesis. In 1899 Michael[24] published two lengthy papers[25] on 'Certain laws and their application in organic chemistry'. They were an ambitious attempt to bring order into a vast amount of information about organic reactions. The mechanism of the urea synthesis was discussed rather elaborately, involving the tautomerism of cyanic acid.[26] Briefly, ammonium cyanate was considered to undergo thermal dissociation to ammonia and cyanic acid: the ammonia then added to the carbonyl group to form $HN{=}C(OH)NH_2$, 'which changes in accordance with Erlenmeyer's rule into NH_2CONH_2'.

The role of the tautomerism of cyanic acid in relation to the mechanism was re-examined a dozen years later by E. A. Werner (see below). In 1899, Michael appears to have been unaware of James Walker's work. Ten years later Michael and Hibbert[27] referred briefly to Walker and Wood's paper,[11] but not to Walker and Hambly[5] or the ionic mechanism. This later paper describes semi-quantitative work on the ease of formation of alkylureas in a wide range of solvents. Michael could see no relationship to dielectric constants or dissociating powers of the solvents. This was held to be another example of the irrelevance of these solvent properties to the ease of 'desmotropic' changes. However, Desch[28] and Lapworth[29] in the *Annual Reports* for 1909[30] used Michael and Hibbert's[27] results

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[22] A. S. Wheeler, *J. Amer. Chem. Soc.*, 1912, **34**, 1269.

[23] Henry Barker Hill (1849—1903). Devoted most of his professional life to Harvard where he was Professor and Director of Chemical Laboratories at the time of his death. His entry in the *Dictionary of American Biography* comments 'His lectures in organic chemistry showed his originality of thought and independence of convention—he frequently reached conclusions on debatable topics ahead of prevailing opinion of other experts in the field'.

[24] Arthur Michael (1853—1942). Probably the most distinguished American organic chemist in the early 20th century. Nowadays mainly remembered for the Michael Reaction but he was a pioneer in the application of thermodynamics to organic chemistry. Obituary notice: *Biog. Mem. Nat. Acad. Sci.*, 1975, **46**, 331.

[25] A. Michael, *J. prakt. Chem.* [2], 1899, **60**, 286—384, 409—486.

[26] Ref. 25, p. 410.

[27] A. Michael and H. Hibbert, *Annalen*, 1909, **364**, 129.

[28] Cecil Henry Desch, F.R.S. (1874—1958). Best known as a metallurgist, but contributed to the organic section of *Annual Reports*, 1907—1910!! Obituary notice: *Biog. Mem. Fellows Roy. Soc.*, 1959, **5**, 49.

[29] Arthur Lapworth, F.R.S. (1872—1941). After study under H. E. Armstrong (ref. 35) and various appointments in London, he migrated to Manchester, occupying the Chair in Organic Chemistry (1913—1922) and in Inorganic and Physical Chemistry (1922—1935). See 'British Chemists', ed. A. Findlay and W. H. Mills, The Chemical Society, London, 1947, p. 353.

[30] C. H. Desch and A. Lapworth, *Ann. Reports*, 1909 (publ. 1910), **6**, 70.

as evidence supporting the molecular mechanism against the ionic mechanism. They gave a rudimentary statement of the arguments which were elaborated two years later by Chattaway and Chapman[16] (who did not acknowledge any debt either to Desch and Lapworth or to Michael).

N. V. Sidgwick[31] (like Chattaway, of Oxford) was also among those who had recognized (in 1910) the kinetic ambiguity with respect to bimolecular reaction of the ions or unimolecular reaction of the undissociated portion.[32] He concluded that 'subsequent investigations have shown that it is on the whole more probable that the reaction is due to the undissociated portion of the salt'. Unfortunately he gave no references to the 'subsequent investigations' and the present author has not identified them.

Another advocate of the molecular mechanism who preceded Chattaway was T. M. Lowry.[33] In 1904 he lectured to the British Association at Cambridge on 'Dynamic Isomerism',[34] and referred to Walker and Hambly's[5] findings on the reversibility of the urea synthesis,[34a] but not to their support of the ionic mechanism. However, his own view was that the mechanism involved the 'dissociation of the cyanate and recondensation of the resulting NH_3 and HNCO', with the ammonia adding across the C=N bond.[34b] It is interesting that Lowry supported the molecular mechanism: he was at that time assistant to H. E. Armstrong[35] at the City and Guilds of London College. Some eight years later, shortly after Chattaway's[16] paper appeared, the molecular mechanism was strongly advocated by Armstrong and some of his colleagues, apparently quite independently of Chattaway.

In 1912 Armstrong was the most outstanding personality in British chemistry, but was at the end of his official career, for in 1911 he had been compulsorily retired from his Chair when his Department was closed after the City and Guilds College became part of the Imperial College of Science and Technology. (He continued active in a private capacity almost until his death a quarter of a century later.) As an organic chemist he was distinguished for his researches in benzene, naphthalene, terpene, and camphor chemistry but his independence of thought showed up most strongly in his vigorous and prolonged opposition to the ionic dissociation theory. During 1906—13 he and his colleagues published many papers on the behaviour of aqueous solutions, in which the results were interpreted without invoking ionic dissociation. It would be naïve, however, to dismiss

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[31] Nevil Vincent Sidgwick, F.R.S. (1873—1952). Like Chattaway and Chapman he was a pupil of Vernon Harcourt. He was Fellow and Tutor of Lincoln College, Oxford (1901—48).

[32] N. V. Sidgwick, 'The Organic Chemistry of Nitrogen', Clarendon Press, Oxford, 1st Edn., 1910, p. 184.

[33] Thomas Martin Lowry, F.R.S. (1874—1936). Studied under H. E. Armstrong (ref. 35) and was later his assistant (1896—1913), as well as holding other appointments in London. Professor of Physical Chemistry at Cambridge (1920—1936). Obituary notice: *op. cit.* in ref. 29, p. 402.

[34] T. M. Lowry, *Rep. Brit. Assoc. Advancement Sci.*, 1904, 193: (*a*) p. 198, (*b*) p. 204.

[35] Henry Edward Armstrong, F.R.S. (1848—1937). Studied under Frankland at the Royal College of Chemistry and under Kolbe at Leipzig. Professor of Chemistry at the London Institution, Finsbury Circus (1871—79) and at the City and Guilds of London College (1879—1911). Biography by J. V. Eyre, Butterworths, London, 1958. Also *op. cit.* in ref. 29, p. 58.

Armstrong's work on solutions as altogether an aberration. In detail, ionic dissociation theory at that time left much to be desired and Armstrong often exposed its weak points.

It seems inevitable that Armstrong would favour the molecular rather than the ionic mechanism for the urea synthesis. His interest in it stemmed from his work on enzymes, for the first comments on the mechanism are in a paper on urease by Armstrong and Horton.[36] After summarizing Walker and Hambly's[5] views the authors continue 'To us it appears easy to interpret the results on ordinary simple principles, without invoking the aid of a mysterious electrolytic-ionic dissociation. It is sufficient to assume that ammonic (*sic*) cyanate undergoes hydrolytic dissociation into cyanic acid and ammonia, and that urea is formed by the gradual interaction of these substances and water . . .'. In the space available we cannot give further details of the discussion, which is often somewhat polemical and difficult to understand.

Armstrong's views on the urea synthesis were further expressed by his assistant E. E. Walker[37] as regards the reaction rate in mixtures of water with alcohols. This was one of five papers on 'Processes Operative in Solutions' read to the Royal Society on December 5th 1912. E. E. Walker criticized James Walker and Kay[9] for not considering the change in the cyanate/water ratio as alcohol is added: the effect of alcohols on the rate should be investigated for fixed cyanate/water ratios. The additives were regarded as producing their accelerating effect by 'concentrating the aqueous solution'. Walker and Kay's factor p is described as 'of doubtful significance' and their conclusion that the 'true' rate coefficient increases by a factor of 100 as between 0 and 90% ethanol is dismissed with the words 'It is impossible to believe that alcohol can have such an influence'. E. E. Walker presented much new experimental work and concluded that alcohols promoted the resolution of an intermediate hydrol $C(OH)_2(NH_2)_2$ into urea and that their action was 'largely mechanical', larger molecules having a greater effect.

James Walker's reply was in work done by his pupil Ross[38] on the rate of reaction in ethanol. The 'true' rate coefficient increased by a further factor of three as between 90% and 99.9% ethanol. Ross criticized E. E. Walker's interpretation on the grounds that it required zero rate in alcohol absolutely free from water, 'which will manifestly not occur'. Burrows and Fawsitt,[14] in work on urea decomposition already mentioned, also criticized the postulated $C(OH)_2(NH_2)_2$: 'We do not think there is any real evidence for the existence of such a substance'.

Finally in this section, we mention briefly the views of E. A. Werner[39] (1913 onwards) on the mechanism of the urea synthesis. Werner criticized Chattaway's discussion of the molecular mechanism for failing to consider properly the

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[36] H. E. Armstrong and E. Horton, *Proc. Roy. Soc.*, 1912, **B85**, 109.

[37] E. E. Walker, *Proc. Roy. Soc.*, 1912, **A87**, 539.

[38] J. D. M. Ross, *Trans. Chem. Soc.*, 1914, **105**, 690.

[39] Emil Alphonse Werner (1864—1951). Associated with Trinity College, Dublin for more than 60 years, holding the main Chair of Chemistry, 1928—46. Obituary notice: *J. Chem. Soc.*, 1952, 2947.

tautomerism of cyanic acid.[40] To Werner ammonium cyanate was a derivative of HOCN, stable at low temperatures, whereas urea was a derivative of HNCO, favoured at higher temperatures. (Werner published many papers on the chemistry and constitution of urea and related compounds from 1902 onwards, and a book in 1923.[41])

It is perhaps to be expected that the compilers of the Chemical Society's *Annual Reports* in 1912, 1913, and 1914 found the situation confusing.[42]

4 Between the Wars

It was not until 1932 that the mechanism of the urea synthesis again featured significantly in the chemical literature. In the intervening period there had been great advances in electronic theories of the atom,[43] of valency,[44] and of organic chemistry;[45] in chemical kinetics;[46] and in the theory of electrolytes, particularly of strong electrolytes.[47]

The most important developments in kinetics had been in gas reactions, but in the early 1930s the collision theory of reaction rates was applied to bimolecular reactions in solution, notably by Moelwyn-Hughes. In a first article,[48] the urea synthesis was treated as a *bimolecular* reaction between *unionized* molecules of ammonium cyanate, but this error was rectified shortly afterwards when Moelwyn-Hughes collected important material on solution kinetics in the form of a book.[49] In this, the urea synthesis was essentially treated as a reaction between NH_4^+ and CNO^-, although Chattaway's views were mentioned. The author asserted that 'The actual mechanism of the reaction is not known, beyond that it is definitely bimolecular . . .'[49a] The urea synthesis is in a Table of reactions used for testing the collision theory,[49b] with a calculated collision number of 4.05×10^{11} l mol^{-1} s^{-1}, which agrees fairly well with the observed Arrhenius non-exponential factor, 4.3×10^{12}. This book was reviewed by Lowry,[50] who devoted part of the review to renewing his support for the molecular mechanism.

In the 1930s there was great interest in kinetic salt effects on ionic reactions. The theoretical equation for these had been variously derived and it is appro-

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[40] E. A. Werner, *Trans. Chem. Soc.*, 1913, **103**, 1010.

[41] E. A. Werner, 'The Chemistry of Urea', Longmans, London, 1923.

[42] H. R. Le Sueur, *Ann. Reports*, 1912 (publ. 1913), **9**, 102; J. C. Irvine, *ibid.*, 1913 (publ. 1914), **10**, 92; J. C. Irvine *ibid.*, 1914 (publ. 1915), **11**, 94.

[43] A. E. Ruark and H. C. Urey, 'Atoms, Molecules, and Quanta', McGraw-Hill, New York, 1930.

[44] N. V. Sidgwick, 'The Electronic Theory of Valency', O.U.P., London, 1927.

[45] J. B. Cohen, 'Organic Chemistry for Advanced Students', Part I 'Reactions', Arnold, London, 5th Edn., 1928.

[46] C. N. Hinshelwood, 'The Kinetics of Chemical Change in Gaseous Systems', Clarendon Press, Oxford, 3rd Edn., 1933.

[47] S. Glasstone, 'The Electrochemistry of Solutions', Methuen, London, 1st Edn., 1930.

[48] E. A. Moelwyn-Hughes, *Chem. Rev.*, 1932, **10**, 241.

[49] E. A. Moelwyn-Hughes, 'The Kinetics of Reactions in Solution', Clarendon Press, Oxford, 1st Edn., 1933: (*a*) p. 36, (*b*) p. 79.

[50] T. M. Lowry, *Trans. Faraday Soc.*, 1934, **30**, 374.

priately called the Brönsted–Bjerrum–Christiansen equation.[51] Its simplest form, for highly dilute solutions, is equation (11),

$$\log k = \log k_0 + 2Z_A Z_B \alpha \sqrt{\mu} \quad (11)$$

where k is the rate coefficient for reaction between ions of valency Z_A and Z_B at an ionic strength μ and k_0 is the limiting value at $\mu = 0$; $\alpha = 0.509$ for water at 25 °C. The equation is closely related to transition-state theory and to the Debye–Hückel theory, which provides the value of α and also more elaborate forms of equation (11) applicable to higher ionic strengths, *viz*, (12):

$$\log k = \log k_0 + 2Z_A Z_B \alpha \sqrt{\mu}/(1 + \beta a \sqrt{\mu}) \quad (12)$$

where $\beta = 0.329 \times 10^8$ for water at 25 °C and a is the closest distance of approach of the ions (in Å).

Warner and Stitt[52] applied the Brönsted theory in 1933 to urea formation in water. The negative salt effect observed was very close to that predicted by theory for $Z_A = +1$ and $Z_B = -1$. This was considered to support the ionic mechanism. The authors showed awareness of the alternative molecular mechanism. This work was extended (1935—39)[53] and in those papers the ionic mechanism was taken for granted: 'Since this reaction is clearly one whose rate depends upon collisions between ammonium and cyanate ions . . .'.[54] This further work concerned first the salt effect in aqueous–organic solvents with a range of values of dielectric constant and, secondly, the influence of dielectric constant D in relation to the Scatchard equation, (13):[51]

$$\log k = \log k_\infty - NZ_A Z_B e^2/DRTr_\ddagger \quad (13)$$

where k_∞ is the rate coefficient for a medium of infinite dielectric constant, e is the electronic charge, N the Avogadro constant, and $r_\ddagger$ the interionic distance in the activated complex. The influence of ionic strength and dielectric constant on the activation energy was also measured and related to the above treatments. Reasonable success was claimed throughout.

Although Sir James Walker had retired from his Chair in 1928, he continued active in research, and encouraged Christina Miller to undertake further studies of the transformation of alkylammonium cyanates into the corresponding ureas in water or ethanol.[55] The ionic mechanism was assumed.[56] Although some use

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[51] Details and refs. in ref. 2, Chapter 7.

[52] J. C. Warner and F. B. Stitt, *J. Amer. Chem. Soc.*, 1933, **55**, 4807.

[53] Mainly by W. J. Svirbely and his colleagues; the last was W. J. Svirbely and J. Lander, *J. Amer. Chem. Soc.*, 1939, **61**, 3538.

[54] J. C. Warner and E. L. Warrick, *J. Amer. Chem. Soc.*, 1935, **57**, 1491.

[55] C. C. Miller, *Proc. Roy. Soc.*, 1934, **A145**, 288; 1935, **A151**, 188; C. C. Miller and J. R. Nicholson, *ibid.*, 1938, **A168**, 206.

[56] In a letter to the present author (28.2.77), Dr. Miller has written: 'As far as I can recall, Sir James Walker never suggested that the conversion mechanism might be connected with cyanic acid and ammonia (alkylamine). His chief concern when I started up was to get more accurate data for testing newer theories involving ionic activities and so forth (Brönsted, Christiansen). Sir James was very broadminded and would no doubt have been delighted had I been able to *prove* that the conversion was based on the reaction of unionized species. I am afraid, however, that I never seriously considered the possibility'.

was made of 'degrees of dissociation' as by Walker and Kay[9] almost 40 years earlier, the Brönsted theory was regarded as superior. Certain limitations of this appeared: conformity to the theory required a considerably temperature-dependent mean distance of closest approach of the ions, and it was suggested that 'thermodynamic' and 'kinetic' activities might not necessarily be exactly the same.

5 The Post-World War II Period to 1965

A new edition of Moelwyn-Hughes's book appeared in 1947.[57] Much of the material about the urea synthesis had been in the first edition. The salt effect was treated in terms of the ionic mechanism.[57a] There is still reference to Chattaway's[16] views but there is also the clear statement that '. . . the velocity of reaction is governed by the number of activating collisions between the ammonium ion and the cyanate ion. . . .'.[57b] In 1949 Amis[58] used the ionic mechanism as an example for the treatment of ionic strength and dielectric effects. However, also in 1949, Weil and Morris[59] revived consideration of the kinetic ambiguity as between ionic and molecular mechanisms. They were led to do this because they had encountered an analogous situation in the reaction of hypochlorous acid with ammonia to give chloramine. They suggested the resolution of the ambiguity on the basis described earlier: *i.e.* it is much easier to visualize a reaction path for the molecular than for the ionic mechanism.

A substantial experimental contribution was made by Wyatt and Kornberg[60] in 1952. They found that the urea synthesis in aqueous solution at 70 °C was accompanied by larger amounts of carbonate than had been supposed. Earlier workers had failed to detect the full amount, because at pH $\sim$ 6.5 (ammonium cyanate solution) the calcium ion test is unreliable, most of the carbonate being present as HCO_3^-. Wyatt and Kornberg measured the disappearance of ammonium and cyanate ion separately and the formation of bicarbonate and urea, biochemical techniques usually being employed. Rate coefficients for urea formation were about 40% lower than earlier results based on cyanate disappearance, and were recorded on the basis of the ionic and of the molecular mechanism. It was suggested that establishing the kinetics (including the salt effect) by cyanate disappearance had not been invalidated by the 'carbonate error' because of a compensation of opposing factors.

In 1953 Frost and Pearson[61] stated very clearly that kinetic studies, including salt and dielectric effects, were insufficient to distinguish between the ionic and the molecular mechanisms. In addition to discussing the various matters dealt with above (p. 2), these authors showed that the Arrhenius parameters

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[57] E. A. Moelwyn-Hughes, 'The Kinetics of Reactions in Solution', Clarendon Press, Oxford, 2nd Edn., 1947: (*a*) p. 98, (*b*) p. 34.

[58] E. S. Amis, 'Kinetics of Chemical Change in Solution', Macmillan, New York, 1949, Chapters 4, 5, and 6.

[59] I. Weil and J. C. Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 1664.

[60] P. A. H. Wyatt and H. L. Kornberg, *Trans. Faraday Soc.*, 1952, **48**, 454.

[61] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism', Wiley, New York, 1st Edn., 1953, p. 257.

calculated on the basis of each mechanism have 'reasonable' values for the type of reaction in question. Frost and Pearson followed Weil and Morris[59] in arguing for the *plausibility* of the molecular mechanism. They further suggested that comparison of the Arrhenius parameters with those for the reaction of alkyl isocyanates with ammonia or amines (ionic mechanism not possible) might settle the issue. Owing to experimental difficulties for the alkyl isocyanate reactions (as mentioned by Frost and Pearson) such a comparison does not yet appear to have been made.

Wyatt and Kornberg's[60] work was confirmed and extended in 1956—58 by Kohnstam and his colleagues in work on the decomposition of ammonium, barium, and sodium cyanates[62] and of alkylammonium cyanates[63] in water. Again the kinetic ambiguity was emphasized, although the authors regarded nucleophilic addition to cyanic acid in the rate-determining step as a most likely feature of the various reactions. They found some relationship between (presumed) reactivity of alkylamines towards cyanic acid and towards other electrophiles, *e.g.* halides or phenyl isocyanate.

In the next few years the molecular mechanism was more strongly supported. In 1959 Jensen[64] studied the formation of alkylureas under conditions in which carbonate formation was slight. He had previously studied the reaction between carbon dioxide and amines in aqueous solution, and had established that this does not occur *via* HCO_3^- and $R^1R^2\overset{+}{N}H_2$. Assuming the molecular mechanism for the urea formation, the two reactions may be written as follows:

$$R^1R^2NH + HNCO \xrightarrow{k'} R^1R^2NCONH_2 \qquad (14)$$

$$R^1R^2NH + CO_2 \xrightarrow{k''} R^1R^2NCO_2H \qquad (15)$$

At 18 °C the following linear free-energy relationship holds:

$$\log k' = \log k'' - 1.08 \qquad (16)$$

and also includes the addition of OH^- and H_2O to the electrophiles. It seems very unlikely that such a simple LFER would hold if the expression of the rate coefficient for the urea synthesis as k' was a mere formalism, with the reaction really proceeding by the ionic mechanism.

Stark[65] in 1965 found further support for the molecular mechanism in the discovery that the relative rates of carbamylation by potassium cyanate (at $pH = 8.0$) or ethyl isocyanate in water are the same for a series of ω-amino-acids. This seems most easily accounted for if the cyanate reaction has the same mechanism as that involving ethyl isocyanate, which must be molecular.

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[62] I. A. Kemp and G. Kohnstam, *J. Chem. Soc.*, 1956, 900.
[63] P. Johncock, G. Kohnstam, and D. Speight, *J. Chem. Soc.*, 1958, 2544.
[64] M. B. Jensen, *Acta Chem. Scand.*, 1959, **13**, 289.
[65] G. R. Stark, *Biochemistry*, 1965, **4**, 1030.

6 The Past Twelve Years

In his book on solvent effects Amis[66] fully accepts the ambiguity of the ordinary kinetic evidence, and delivers a homily: 'This discussion has been given to illustrate the fact that, in general, mechanisms are not unique. Mechanisms are really hypothetical explanations of the rate, and of stereochemical, collisional, isotopic, and other forms of data. However, new ideas or a different experimental approach may lead to a different mechanism from the one commonly accepted. A few mechanisms are so simple and straightforward that they are generally accepted as correct'.

Moelwyn-Hughes, however, in his recent book,[67] remains unconvinced. Under the heading 'The Conversion of Ammonium Cyanate into Urea; an Apparent Paradox' he surveys the various views: 'We do not agree, however, with the conclusion (Frost and Pearson 1961) that the two mechanisms are equally supported by the available kinetic evidence and seem indistinguishable by any kinetic method'. Moelwyn-Hughes argues that certain aspects of the Arrhenius parameters agree better with the ionic than with the molecular mechanism.

In recent years the effect of polyelectrolytes and micelle-forming ionic surfactants on the ammonium cyanate conversion has been examined by Okubo and Ise.[68] Negative catalysis by these electrolytes is distinctly larger than that produced by electrolytes of lower molecular mass. The reaction is treated as ionic, although the ambiguity is conceded. Rates were measured conductometrically and these are claimed to give correct rate coefficients, even when carbonate formation is considerable, owing to a cancellation of opposed factors.

Finally we may mention that in 1974 Williams and Jencks[69] studied the urea synthesis extensively from the standpoint of acid–base catalysis, examining the reaction with cyanic acid of a wide variety of amines. The molecular mechanism was assumed and the studies were considered to shed light on the formation and decomposition of the zwitterionic intermediate (p. 3), especially the details of the transfer of the proton from the amine to the nitrogen atom of cyanic acid. The main conclusion was that for strongly basic amines the formation of the intermediate is rate-determining, whereas for weakly basic amines the decomposition of the intermediate to urea is rate-limiting. In the latter case general acid–base catalysis of the decomposition of the intermediate was observed. Thus the behaviour of the intermediate first postulated in one form or another eighty years ago has now been scrutinized minutely.

The author is grateful to Professor N. B. Chapman for criticizing a draft of this article, and to Mr. P. J. Rowlinson for assistance with library work.

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[66] E. S. Amis, 'Solvent Effects on Reaction Rates and Mechanisms.' Academic Press, New York, 1966, p. 185.

[67] E. A. Moelwyn-Hughes, 'Chemical Statics and Kinetics of Solutions,' Academic Press, London, 1971, p. 187.

[68] T. Okuba and N. Ise, *Bull. Chem. Soc. Japan*, 1973, **46**, 2493; *Proc. Roy. Soc.*, 1972, **A327**, 413.

[69] A. Williams and W. P. Jencks, *J.C.S. Perkin II*, 1974, 1753, 1760.