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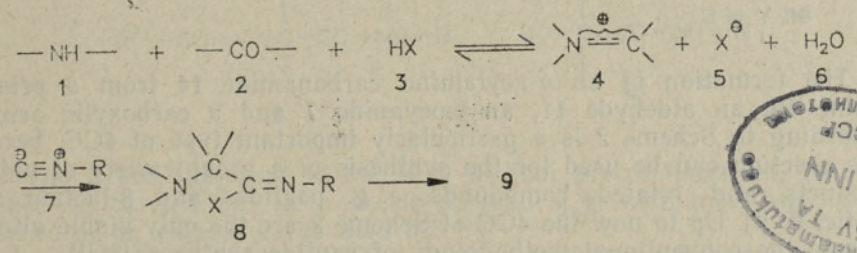
FOUR COMPONENT CONDENSATIONS, A VERSATILE PRINCIPLE IN SYNTHESIS

Summary: A brief review of the four component condensation (4CC, Ugi reaction) of amines and carbonyl compounds with suitable acids (water, thiosulfuric acid, hydrazoic acid, hydrogen cyanate, thiocyanic acid, carboxylic acids and monoalkyl carbonic acids), or their anions, is given; some new results are presented. The 4CC are usable as one-pot synthesis of a wide variety of compounds. They offer particular advantages in the synthesis of peptides, β-lactam antibiotics and related compounds. Furthermore, some developments and results are discussed that evolved from 4CC studies, e. g. in the areas of ferrocene, supernucleophile, oxaziridine, phosphorus and oligonucleotide chemistry, experimental and theoretical stereochemistry, as well as in logic-oriented computer chemistry and its formal foundations.

Four component condensation

An amine **1**, a carbonyl compound **2**, a suitable acid **3**, and an isocyanide **7** undergo a so-called four component condensation [1, 2] (4CC, Ugi reaction[1]) to yield an α-amino acid derivative **9**, as was discovered in 1959 [5]. In 4CC an iminium ion **4**, formed from **1** and **2**, or from a condensation product of these (imine, enamine, or aminal), and the anion **5** of the acid component **3** react with the isocyanide **7** by α-addition. Subsequently the α-adduct **8** undergoes a spontaneous secondary reaction, and a stable α-amino acid derivative **9** results [1, 6, 7].

Scheme 1



The type of secondary reaction, and the chemical nature of the α-amino acid derivative **9**, depend primarily on the acid component. With some acid components the kind of product depends also on whether a primary or secondary amine is used [1, 7, 8].

With water as the acid component, the 4CC produces an α-amino carbonamide **9a**. Thiosulphate and hydrogen selenide lead analogously to the respective thio and seleno amides, **9b** and **9c**. A tetrazole derivative **9d** is obtained when hydrazoic acid is the acid component of a 4CC. Note that in the formation of **9a-9d** the secondary reaction of the α-adduct **8** proceeds without the participation of the N-atom of the amine component **1**.

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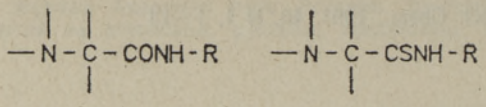
[1] The abbreviation "4CC" is frequently used for "four-component condensation", as is the term "Ugi reaction", which was introduced by Opitz, G., Merz, W. Justus Liebigs Ann. Chem. 1962, **652**, 163, and propagated by McFarland [3] and Sjöberg [4] (see footnote 12 in [2]).

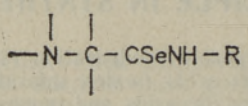


(HX = H_2O)

9a

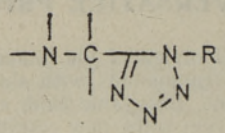
($X^{\ominus}$ = $S_2O_3^{2\ominus}$)

9b



($X^{\ominus}$ = $HSe^{\ominus}$)

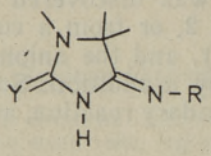
9c



($X^{\ominus}$ = $N_3^{\ominus}$)

9d

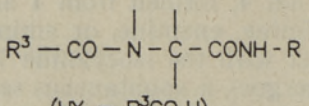
However, with hydrogen cyanate, hydrogen thiocyanate and carboxylic acids as **3**, and with a primary amine as **1**, the N-atom of **1** participates in the secondary reaction. Cyanate and thiocyanate lead to **9e** and **9f**, and carboxylic acids produce α-acylamino carbonamides **9g**, whereas diacylimine derivatives **9h** are generated by a 4CC of a carboxylic acid as **3** in combination with a secondary amine component **1** [1, 7, 8].



($X^{\ominus}$ = $NCY^{\ominus}$)

9e: Y = O

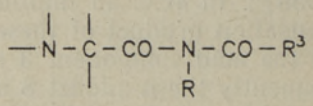
9f: Y = S



(HX = R^3CO_2H)

from prim. amine 1

9g



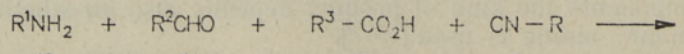
(HX = R^3CO_2H)

from sec. amine 1

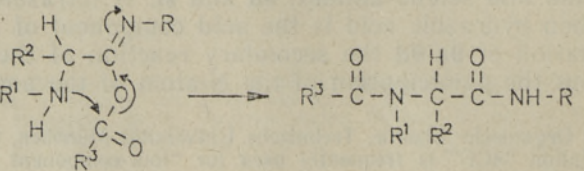
9h

The formation of an α-acylamino carbonamide **14** from a primary amine **10**, an aldehyde **11**, an isocyanide **7** and a carboxylic acid **12** according to Scheme 2 is a particularly important type of 4CC, because this reaction can be used for the synthesis of a great variety of natural products and related compounds, e. g. peptides and β-lactam antibiotics [8–10]. Up to now the 4CC of Scheme 2 are the only viable alternative to the conventional methodology of peptide syntheses [9–11].

Scheme 2



10 11 12 7



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Side reactions and reaction conditions

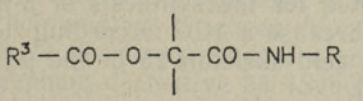
Being one-pot reactions, syntheses by 4CC are simple to execute [1, 2]. In order to obtain satisfactory preparative results, any 4CC must be carried out under its particular optimum conditions, since the outcome of a 4CC is strongly dependent on the chosen reaction conditions. There are no general optimum reaction conditions for 4CC. These differ for each individual 4CC [10].

Incorporation of a 4CC into a synthesis is always an advantage. Syntheses comprizing 4CC have generally fewer steps and better yields than the alternatives. The price for the benefits of 4CC is some systematic effort that must be spent on searching for the optimum conditions for the required 4CC.

Since the desirable product of a 4CC according to Scheme 2, e. g. in peptide syntheses by stereoselective 4CC, may be one of two or more possible stereoisomers, the optimization of 4CC has often two aspects. On the one hand, there is the need to avoid competing irreversible side-reactions in order to obtain a maximum overall yield of the 4CC product, and on the other hand, one must choose reaction conditions that favor the highly stereoselective formation of the desired stereoisomer. There are some general rules for selecting the reaction conditions for 4CC. These follow from the knowledge of the most important side reactions of the 4CC. Some other aspects of optimizing the reaction conditions of 4CC are discussed with the respective individual cases.

The main side reactions of the 4CC according to Scheme 2 have been reviewed previously [2, 10]. Here only two important side-reactions, the Passerini type reactions and the formation of α-acylamino malonamides, as well as measures for their avoidance will be described briefly.

The formation of α-acyloxy carbonamides **15** from **2**, **7** and **12** by the Passerini reaction [2, 7, 12, 13], and the related acid-catalyzed formation of **16** from **2**, **7** and water [2, 7, 12, 13] can be completely avoided by reacting, instead of **1** and **2**, their condensation products, e. g. the imines.



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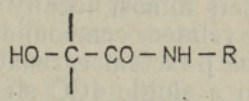

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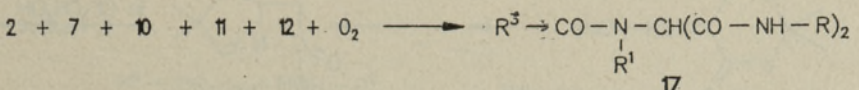
If **1** and **2** are subjected to the 4CC without precondensation, the 4CC should be carried out in a protic solvent, e. g. methanol, and in the absence of an excess of the acid **3** [2, 10].

Another side reaction of 4CC according to Scheme 2 is the formation of α-acylamino malonamides **17** by an extremely complex reaction between six reactants that has only recently been elucidated by a combination of ^{13}C-labelling/NMR experiments [14] and computer-assisted elaboration of

Scheme 3



17

conceivable mechanistic pathways by program RAIN 2 [15].

Since oxygen is required for this side reaction, it can be avoided by executing the 4CC in deoxygenated solvents under a blanket of nitrogen or argon.

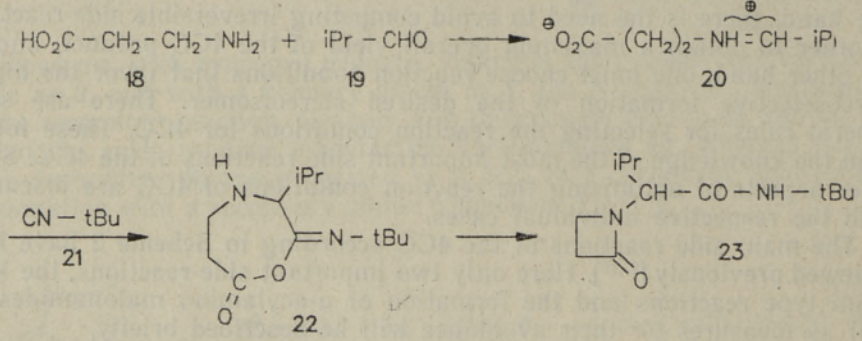
Although the degree of stereoselectivity of some 4CC is the highest at low temperatures (≈ −80C°) [16], it is recommendable to run also the stereoselective 4CC at temperatures ≥ −20C°, because otherwise the reproducibility of the results is endangered by reactants that may precipitate from supersaturated reaction mixtures [2].

Synthesis of β-lactams

During the early exploration of the scope and limitations of the 4CC it was found that they are ideally suited for the synthesis of the β-lactams that are otherwise still difficult to prepare [1, 8, 17].

The conversion of β-amino acids, e. g. **18**, into β-lactams, e. g. 23, is illustrated by Scheme 4 [17].

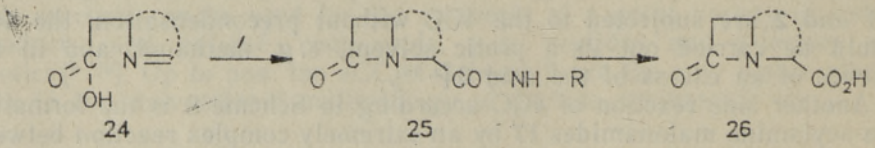
Scheme 4



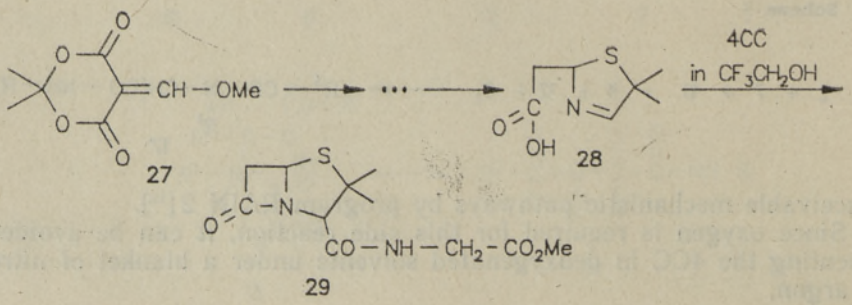
Such β-lactam syntheses proceed via a seven-membered α-adduct **22** which is easily formed from the iminium zwitterion **21**. The β-lactam results from the α-adduct by the ring contraction **22**→**23**, a transannular O,N-acyl transfer with a strong thermodynamic driving force.

The 4CC is almost ideally suited for the synthesis of β-lactam antibiotics and related compounds, because a 4CC according to Scheme 5 generates the β-lactam carboxylic acid skeleton **25** of the β-lactam antibiotics **26** in a single 4CC step [8].

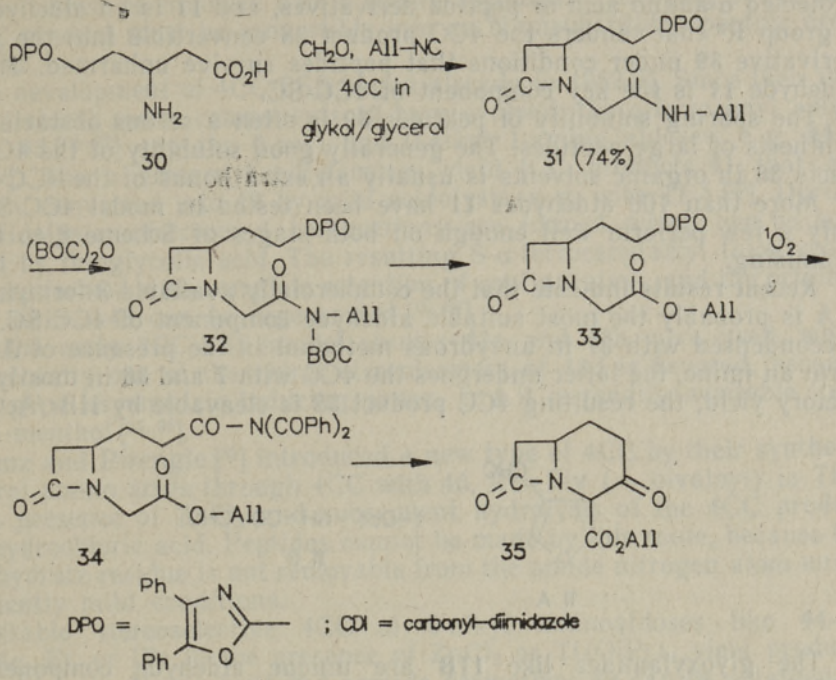
Scheme 5



Scheme 6



Scheme



The synthesis of simple monocyclic β-lactams like **23** and nocardicine derivatives by 4CC proceeds smoothly in methanol [18, 19], whereas the formation of β-lactams with a more complex structure requires some "magic solvents", e. g. trifluoro ethanol [20], or ethylene glycol/glycerol mixtures [21]. In ordinary organic solvents the synthesis of bicyclic β-lactams produces appreciable amounts of polymeric by-products.

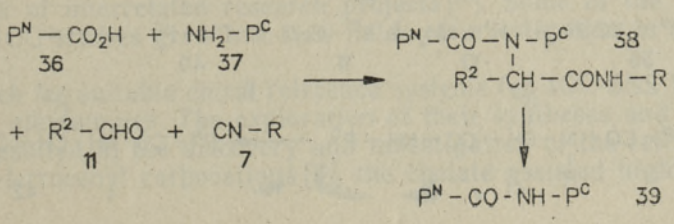
In a recent review the synthesis of numerous types of β-lactam antibiotics and their analogs has been described [8]. Two recent examples may further illustrate the preparation of a penam derivative **29** (Scheme 6) [21] and a cerbacepham derivative **35** (Scheme 7) [22] by 4CC.

Peptide segment coupling

The so-called segment strategy is presently the preferred approach to peptide synthesis [11]. In the segment strategy, first peptide segments of three to twelve amino acid units are prepared, and then these segments are coupled to form larger peptides. The racemization of amino acids is still a major problem in peptide synthesis, and in particular in segment coupling [11, 23].

Segment coupling by 4CC according to Scheme 8 (4CC-SC) seems to be an attractive alternative to the conventional methods via the racemization-prone activated α-amino acid derivatives [10, 23, 24].

Scheme 8

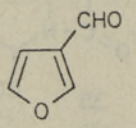


In Schemes 8 and 9 **36**, **37** and **40** are N- and respectively C-terminally protected α-amino acid or peptide derivatives, and **11** is an aldehyde with a group R^2 that renders the 4CC product **38** convertible into the peptide derivative **39** under conditions that peptides survive unharmed. Thus the aldehyde **11** is the key component of 4CC-SC.

The sparing solubility of pektides **39** is often a serous obstacle to the synthesis of large peptides. The generally good solubility of the 4CC products **38** in organic solvents is usually an extra bonus of the 4CC-SC.

More than 100 aldehydes **11** have been tested in model 4CC-SC, but only a few perform well enough on both stages of Scheme 8 to be still promising.

Recent results indicate that the commercially available 3-formyl furane **11A** is probably the most suitable aldehyde component of 4CC-SC. When precondensed with **37** in anhydrous methanol in the presence of Al_2O_3 to form an imine, the latter undergoes the 4CC with **7** and **36** in mostly satisfactory yield; the resulting 4CC product **38** is cleavable by HBr/AcOH [25].



11 A

t–Oct – NH - CO - CHO

11 B

The glyoxylamides like **11B** are unique aldehyde components of 4CC-SC, because the glyoxylamides are the only aldehydes whose 4CC with properly chosen isocyanides **7** do not generate a new center of chirality that may give rise to diastereoisomer mixtures of **38** [25]. The 4CC products **38B** of **11B** and isooctyl-isocyanide

$$P^N - CO - N(CH(CO - NH - iOct)_2) - P^C$$

38 B

are cleavable in the sense **38**→**39** by O_2 in the presence of copper ions.

Stereoselective synthesis of peptide segments

The synthesis of peptide segments by stereoselective 4CC (4CC-SSS) according to Scheme 9 is an attractive alternative to the conventional peptide syntheses. Peptide syntheses by 4CC-SSS have several distinct advantages. Here a new amino acid unit is generated from a simple aldehyde in the desirable configuration, together with two new covalent bonds of the peptide backbone. This is particularly beneficial in the case of peptides containing unnatural or isotopically labelled amino acids, because otherwise these must be synthetized in the chiral form and subsequently be incorporated into the peptide system [2, 10, 26, 27].

Scheme 9

$$\underset{36}{P^N - CO_2H} + \underset{10}{R^1 - NH_2} + \underset{11}{R^2 - CHO} + \underset{40}{CN - P^C} \longrightarrow$$

$$P^N - CO - N(R^1) - CH(R^2) - CO - NH - P^C \longrightarrow P^N - CO - NH - CH(R^2) - CO - NH - P^C$$

41 **42**

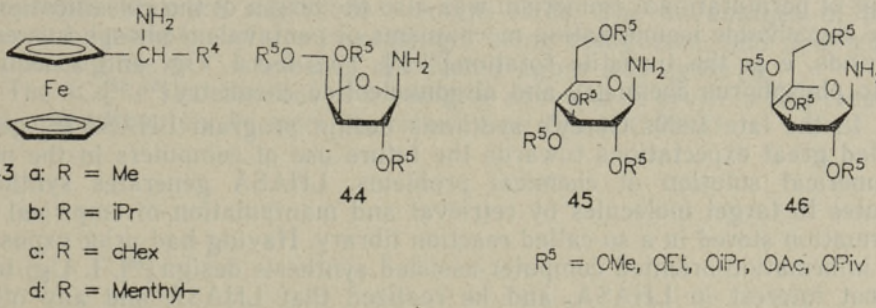
The key component of 4CC-SSS is the chiral amine component **10**, because it must be endowed with a strong asymmetric inducing power and its 4CC product must be convertible into an N-unsubstituted peptide derivative **42**.

The development of 4CC-SSS began already in 1962 [1]. Since then two types of chiral amine components **10** have evolved: the α-ferrocenyl alkylamines **43** [28–32] and the 0-acyl and 0-alkyl 1-amino aldoses, e. g. **44**—**46** [33, 34]. The α-ferrocenyl alkylamines yield 4CC products **41** that are smoothly converted into **42** by mild acidolysis, e. g. with TFA [29]. During this acidolysis α-ferrocenyl carbocations are formed which can be scavenged by thioglycolic acid. The resulting S-α-ferrocenylalkyl thioglycolic acids are formed with complete retention of configuration, and the original chiral amines **43** can be regenerated [16, 30].

In the early 4CC-SSS model studies **43a** and **43b** were used, while more recently one of the chiral stereoisomers of **43d** is favored, because it has good asymmetric inducing power, and it is readily available from 1-(+)-menthol [35, 36].

Kunz and Pfrengle [33] introduced a new type of 4CC by their synthesis of chiral amino acids through 4CC with **46**, R^5=Piv (= pivaloyl) in THF in the presence of $ZnCl_2$ and subsequent hydrolysis of the 4CC product with hydrochloric acid. Peptides cannot be made by this route, because the carbohydrate residue is not removable from the amide nitrogen atom under sufficiently mild conditions.

Suitable stereoselective 4CC of 0-alkyl aminoaldoses like **44-46**, R^5=Me, Et, or iPr in the presence of $ZnCl_2$ or $Ti(OiPr)_4$ yield products from which the N-unsubstituted peptide derivatives **42** can be obtained by acidolysis with HBr/AcOH [34]. The degree of stereoselectivity of such 4CC is often rather high (⩾95 : 5).



43 a: R = Me
b: R = iPr
c: R = cHex
d: R = Menthyl–

44

45

46

R^5 = OMe, OEt, OiPr, OAc, OPiv

Besides the continuing search for readily available well-suited chiral amine components for 4CC-SSS, the optimization of the yield and stereoselectivity of 4CC-SSS by computer-assisted factorial design methods is an important project in this field [37].

Four component condensation as a stimulus to other research endeavours

The development of peptide syntheses by stereoselective 4CC gave rise to a network of interrelated research projects [30]. Some of the auxiliary projects of 4CC studies grew into new fields of investigation in their own right.

The search for suitable chiral reference systems for 4CC-SSS led to the α-ferrocenyl alkylamines. The exploration of their syntheses and chemical properties resulted in the discovery and investigation of the retentive S_Ni involving α-ferrocenyl carbocations [38], the chelate assisted highly stereo-

selective lithiation of N,N-dimethyl α-ferrocenyl alkylamines [39] that is now widely used in the synthesis of chiral phosphine ligands of organometallic catalysts [40], as well as the synthesis of α-ferrocenyl alkyl compounds from ferrocene and aldehydes in strongly acidic media [41].

The development of the β-halogenated alkyl protective groups, removable by Co(I) supernucleophiles is due to the fact that peptide syntheses by 4CC require protective groups whose cleavage conditions are "orthogonal" to those of the customary protective groups [42].

The search for efficient stereoselective syntheses has resulted also in a computer-assisted elucidation of complex kinetic systems of parallel and consecutive reactions like the reaction mechanism of stereoselective 4CC [7, 28], and also in the elaboration of the stereochemical analogy model [43], a general theory of stereoselectivity on the basis of statistical thermodynamics and group theory, a joint project with the theoretical physicist Ernst Ruch. Furthermore, a computer program for finding the optimum combinations of 4CC and conventional methods for peptide syntheses [28] has been used.

Since the customary (R, S)-nomenclature system [44] is not unambiguously applicable to polysubstituted ferrocenes, the concept of permutational isomerism [45] was introduced which may serve as the basis of a stereochemical nomenclature and classification system that is also applicable to many otherwise intractable molecular systems including the flexible ones. The non-geometric view of stereochemistry and the representation of its logical structure by the theory of chemical identity groups [46], with the set-valued mappings [46–48] as a powerful new mathematical tool, evolved from permutational isomerism, together with the concept of chemical chirality and the chiral genus as its quantitative measure [49]. Through the chiral genus it became also possible to give, for the first time, a precise and generally valid definition of asymmetric reactions. The concept of permutational isomerism was also the origin of the classification of the conceivable isomerization mechanisms of pentavalent phosphorus compounds, e. g. the turnstile rotation [50, 51]. This led I. Ugi and associates into phosphorus chemistry and oligonucleotide chemistry [52, 53].

In the late 1960s Corey's synthesis design program LHASA [54] generated great expectations towards the future use of computers in the non-numerical solution of chemical problems. LHASA generates synthetic routes to target molecules by retrieval and manipulation of empirical information stored in a so-called reaction library. Having had prior exposure to information-oriented computer-assisted synthesis design [28], I. Ugi took great interest in LHASA, and he realized that LHASA and any other chemical computer program based on empirical data, will just produce combinations and analogies of the chemistry stored in its data bank, and that none of such computer programs will ever spawn new chemistry.

I. Ugi came to the insight that a suitable mathematical representation of the inherent logic of chemistry, its logical structure, is needed as a foundation for chemical computer programs, in order to endow them with the power of innovation [55]. The understanding that the edifice requires the participation of an excellent mathematician, induced I. Ugi to join forces with a mathematical partner. In 1970 the topologist James Dugundji and I. Ugi began an intense collaboration that lasted until the death of J. Dugundji in 1985 [56].

After introducing some new notions and redefining some of the customary basic concepts of chemistry, J. Dugundji and I. Ugi formulated in 1970—72 the theory of the BE- and R-matrices, an algebraic representation of the logical structure of constitutional chemistry [55] and in 1976—84 the theory of the chemical identity groups, a representation of the logical structure of stereochemistry [46].

Since 1971 I. Ugi and associates have developed computer programs for the deductive solution of chemical problems on the basis of the theory of the BE- and R-matrices. The program PEMCD (Program for determining the Exact Minima of Chemical Distance) [57] finds reaction pathways with the redistribution of a minimum number of valence electrons, i. e. reaction pathways in accordance with the classical principle of minimum structure change [58]. PEMCD determines at the same time atom-by-atom matchings of interconvertible reactants and the potential reactive centers [48].

The program IGOR 2 (Iterative Generation of Organic Reactions and Structures) generates chemical reactions and structures from electron redistribution patterns [59, 60].

IGOR has already produced several new chemical reactions that have been realized in the laboratory [59, 61, 62]. IGOR has also played an important role in the development of a new type of phosphorylating and oxidizing reagents for oligonucleotide syntheses [52, 53]. From 1990 on IGOR is available as a public domain program [60].

The program RAIN (Reaction And Intermediates Networks) [62, 63] generates from an ensemble of reactants a tree of reaction pathways, or from two isomeric ensembles of molecules (EM) a network of conceivable reaction pathways by which the two EM can be interconverted.

RAIN has served well in the elucidation of the formation of malonamide derivatives **17**, a side reaction of the 4CC [2, 8]. RAIN will be available as a public domain program from the fall of 1990 on.

Conclusion

The 4CC is a versatile and widely useful device for the synthesis of compounds that are related to α-amino acids. The advantages of this powerful synthetic tool are increasingly being recognized, and new ways of utilizing the 4CC are being discovered again and again [2].

The 4CC is also the root of a pedigree of research projects and results that may ultimately be more important than the 4CC itself.

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NELJA KOMPONENDI KONDENSATSIOON KUI MITMEKÜLGNE SÜNTEESIPRINTSIIP

On antud lühiülevaade nelja komponendi kondensatsioonist (4CC ehk Ugi reaktsioon), mille puhul amiine ja karbonüülühendeid või nende anioone sobivate hapetega (vesi, tiovääveihape, lämmastikvesinikhape, tsüaanhape, tiotsüaanhape, karboksüülhapped ja monoalküülsüsihapped) kondenseeritakse, ning esitatud mõned uued tulemused. 4CC-d võib kasutada paljude ühendite ühissünteesiks, reaktsioon on eriti kasulik peptiidide, β-laktaami ja teiste samalaadsete ühendite sünteesimisel. Lisaks on kirjeldatud 4CC tööst väljakasvanud suundi, nagu ferrotseeni, supernukleofiili, oksaziridiini, fosfori ja oligonukleotiidi keemia, eksperimentaalne ja teoreetiline stereokeemia ning loogikal põhinev arvutikeemia ja selle formaalsed alused.

Ивар УГИ

ЧЕТЫРЕХКОМПОНЕНТНАЯ КОНДЕНСАЦИЯ КАК УНИВЕРСАЛЬНЫЙ ПРИНЦИП СИНТЕЗА

В сжатом виде дается характеристика реакции четырехкомпонентной конденсации (4CC или реакции Уги), в случае которой аминовые и карбонильные соединения или их анионы конденсируются с подходящими кислотами (тиосерной, азотистоводородной, циановой, тиоциановой, карбоновыми, моноалкилугольными или с водой), и приводятся некоторые новые результаты. Реакцией 4CC может быть осуществлен совместный синтез многих соединений, но наибольший эффект она дает в случае синтеза пептидов, β-лактамов и других родственных им соединений. Описывается также ряд химических направлений, выросших из работ по 4CC, — химия ферроцена, супернуклеофилов, оксазиридина, фосфора, олигонуклеотидов, экспериментальная и теоретическая стереохимия, компьютерная химия, основанная на принципах формальной логики.