Chem. Listy *116*, 215–222 (2022) Review

# ROLE OF HYDANTOIN DERIVATIVES IN POLYASPARTATE SYNTHESES

**JIŘÍ PODEŠVA, MIROSLAVA DUŠKOVÁ SMRČKOVÁ, and OLGA TRHLÍKOVÁ**

*Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, Heyrovsky Sq. 2, 162 06 Prague 6, Czech Republic*

Keywords: hydantoin, polyaspartates, coatings, polyurea

https://doi.org/10.54779/chl20220215

## Contents



## 1. Introduction

In recent years, the importance of N-substituted 2-aminosuccinates (N-substituted aspartates) for the coating industry has increased[1]. By the reaction of their secondary amino groups with isocyanates under certain conditions, materials can arise, sometimes referred to (rather inaccurately) as polyaspartates, which can serve as useful intermediates to produce high-quality, hard, glossy, and abrasion-resistant coatings[2]. The so-called bis-aspartates are substances, in which two molecules of an aspartic acid ester are joined together by a suitable spacer (e.g., methylene chain) through the –NH– groups. To get a three-dimensional network, a bis-aspartate is left to react with a compound or a mixture of compounds containing (in average) more than two NCO groups per molecule. For a practical application, the aminic and isocyanate components are mixed together immediately before spreading (for example in a spraying head); hence, an important technological condition is that the rate of curing falls into a certain optimal interval: a too slow reaction can cause flowing down the coat while too fast one may clog the nozzle. Bis-aspartates mostly fulfil this condition, thanks not only to the fact that their amino groups are secondary but also to the existence of hydrogen bonds between the aminic hydrogen and the carbonyl oxygen.

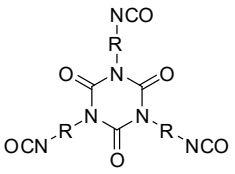
## 2. Polyaspartates

Bis-aspartates can be prepared by, e.g., aza-Michael addition of symmetrical or asymmetrical primary diamines onto maleates (an example is in Scheme 1, where X is a suitable bifunctional substituent).

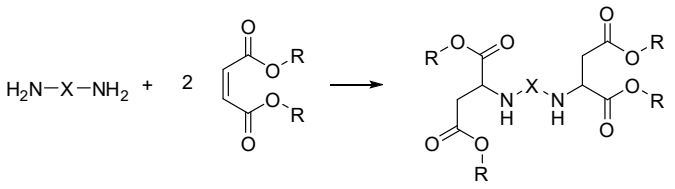
Although not described in the literature, bis-aspartates could theoretically be synthesized using a reductive amination of a suitable dicarbonyl compound by an aspartate bearing a free $NH_2$ group (mole ratio 1:2).

The secondary amino group of bis-aspartate may undergo an addition reaction with an isocyanate group. Isocyanates used in practice are mostly mixtures of compounds showing a certain distribution of functionality, i.e., the number of NCO groups in the molecule. If the average functionality of the isocyanate component is higher than two, 3D polymer networks based on covalent urea bonds are formed.

As an example, three-functional isocyanates are being prepared on an industrial scale (or can origin spontaneously) from α,ω-aliphatic diisocyanates in a form of a six-



Scheme 2



Scheme 1

membered ring (cf. the general Scheme 2, where R is again a suitable bifunctional substituent, e.g., a polymethylene chain):

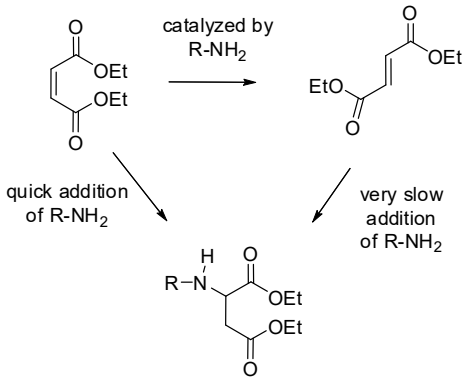
As compared to primary amino groups, the reactions of the secondary amino groups of bis-aspartates (and, in general, of all N-substituted aspartates) with the NCO groups are substantially slower (and thus technologically better controllable).

Urea groups form hydrogen bridges, which contribute to the effective network density[3]. Coatings based on these structures show considerable strength and chemical resistance. They can be quickly cured even at room temperature, thus offering broad possibilities of applications and ways of film formations. Presently, these modern polyurea networks, based on aspartates, already substitute common polyurethane thermosets in a range of applications. Commercial products which use bis-aspartate/isocyanate two-component systems are offered by Covestro Co. (founded by Bayer). Their system Pasquick® protects surfaces even under heavy-duty conditions, such as industrial halls or bridge constructions exposed to the effect of sea water[4].

Further, unlike polyurethanes, the production of which requires a catalyst (*inter alia*, compounds of tin), the formation of polyaspartates need not be catalyzed which brings about a welcome reduction of health hazards.

Another advantage consists in the fact that, thanks to the low viscosity of the starting bis-aspartate resins, the consumption of organic solvents necessary for spraying is lower as compared to polyurethane systems, even to the so-called high-solids ones. This is very important concerning ever-increasing demand to reduce the use of volatile (and often harmful) solvents. In the present EU legislation, the so-called VOC (volatile organic compound) for various chemical systems in practical applications is defined. For example, according to the European directive 1999/13/EC, the present VOC limit for the clear coat (i.e., the upper layer of automotive coatings) is 56 g emissions per $m^2$ of coated surface which corresponds to ca. 25 wt.% of volatile substances in the coating system*.

However, problems arise during the production of polyaspartates, of which two relate to the topic of this review. One of them is connected with the preparation of the intermediate, i.e., the N-substituted aspartate: it is long known that the aza-Michael addition of primary amines onto maleates is always accompanied by the *Z*→*E* isomerization of the C=C bond which means that, simultaneously with aspartates, a certain amount of fumarate is always formed; formally, the amine itself acts here as a catalyst[5–7]. This is represented in the general Scheme 3, where R stands for an alkyl.

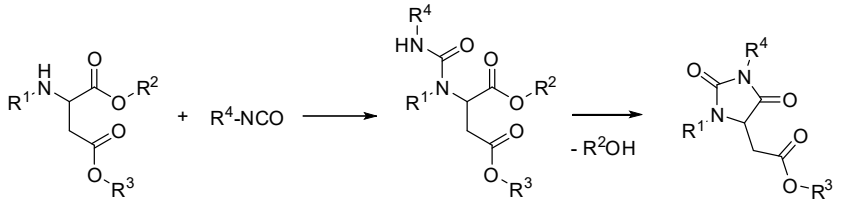



Scheme 3

Since the addition of amines to fumarates is extremely slow and no catalyst has been found for it so far, a few percent of (unreacted) fumarate is always present in the resulting reaction mixture besides the desirable aspartate. The presence of fumarates causes that the product turns yellowish which may have unfavorable consequences for some applications. Moreover, fumarates irritate the skin and may cause problems when inhaled. An efficient way to remove fumarates from the resulting mixture has recently been described[8]: by addition of citric acid to this mixture, desirable adduct is transformed into a more polar ammonium salt, and finally non-polar fumarate is extracted by cyclohexane. This method, however, is suitable for small-scale operations only. Therefore, the admixture of fumarates represents a complication for the technical practice.

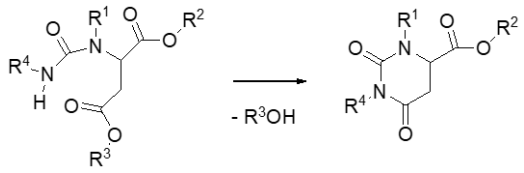
The other problem relies on the fact that the secondary amino groups of the N-substituted aspartates with the NCO group may lead to the formation of heterocycles, such as derivatives of hydantoin. Again, this is an undesirable phenomenon because: (i) the structures containing this cycle cannot take part in continuing branching reactions which disturbs originally balanced stoichiometry and thus deteriorates the processes of curing of polyaspartates; (ii) during the cyclization reaction, alcohol is released which can react with remaining NCO groups, and this leads to the same impact, i.e., the decrease of the attainable degree of branching. In a simplified form, this reaction is depicted in Scheme 4, where $R^1$ through $R^4$ are alkyls. The alcohol $R^2OH$ is released from that ester group which is located more closely to the group $R^1$-N.

*Some solvents, e.g., acetone, are not included in the VOC limit; in the USA, however, also *p*-chlorobenzotrifluoride (oxsol). As early as in 2007, Germany, Austria, and the Czech Republic have implemented in their national legislations a new VOC limit which is somewhat stricter both for original equipment manufacture (OEM, i.e., coating for new cars) and for repair coating systems, namely, 35 g $m^{-2}$, which corresponds to approx. 20 wt.% dilutant concentration in the coating system. For such an estimate, the height of the fresh layer and the average specific weight of the coating system are supposed to be 200 μm and 0.9 g $cm^{-3}$, respectively.



Scheme 4

If the intermediate in Scheme 4 assumes an appropriate conformation, the following step can – at least theoretically – yield a six-membered ring (a derivative of dihydrouracil) while releasing the alcohol $R^3OH$ from that ester group, which is located more distantly from $R^1$-N (Scheme 5, where $R^1$ through $R^4$ are again alkyls). To the best of the authors' knowledge, such a reaction has not been described in the literature yet, but some preliminary experiments performed by us suggested that it cannot be excluded, though even here the reaction is of a minority character.

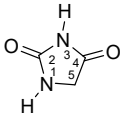


Scheme 5

Both types of ring closure are unfavorable for the technological properties of the final product and it is, therefore, desirable to reduce their extent. Thus, the formation of cycles invokes a need for a more detailed study of reactions leading to hydantoin and similar structures. From the large volume of literature on hydantoin, only those publications have been selected for this review that could lead to a better understanding of mechanisms and conditions of formation, vanishing, and transformation of these cycles, ideally to finding a possibility to suppress such a formation. This is important for the planned research, the results of which should lead to improving the quality of the polyaspartate resins.

## 3. Chemistry of hydantoin

Literature on hydantoin is vast: several reviews can be referred to, devoted to syntheses, substitutions, physicochemical properties, and reactions of this compound[9–11], to its examinations by NMR or X-ray analysis[12], as well as to its biological and pharmacological properties[9,13]. The first of the cited reviews is particularly comprehensive[9].



Scheme 6

In a narrower sense of the term, hydantoin is imidazolidine-2,4-dione (Scheme 6).

Generally, however, a whole group of substances, containing the same heterocycle but substituted in various ways, is referred to as hydantoins. Hydantoin is a natural substance, originating spontaneously by, e.g., oxidation of the cytosine and thymine bases of DNA after the death of an organism.

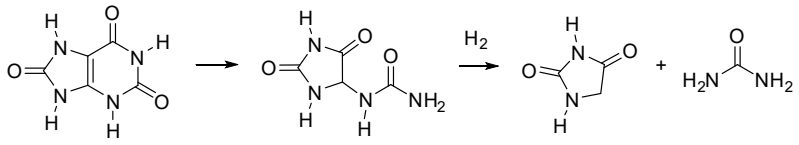
### 3.1. Origin of the hydantoin ring

Hydantoin was discovered not by isolation of natural mixtures but as a product of a reduction of allantoin which is formed by an oxidation cleavage of uric acid. This discovery was made already in 1861 by A. von Baeyer[14], future Nobelist (Scheme 7).

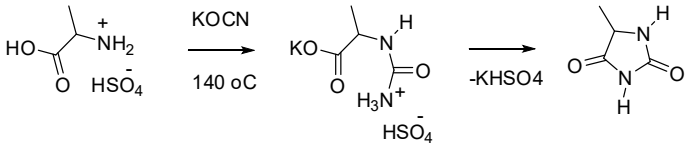
For the focus of the present review, chronologically the second, the so-called Urech synthesis[15] is more important. Here, alanine sulfate reacts with potassium cyanate (Scheme 8).

This procedure was later generalized and applied also for the cases where an ester, substituted amid or nitrile of the amino acid is used[16].

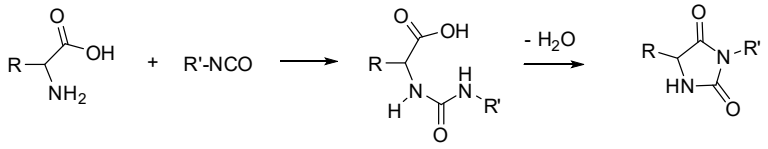
Instead of inorganic cyanate, an organic isocyanate (alkyl- or aryl-) can be used for the addition to amino acids. In this way, a substituted 2-ureidocarboxylic acid (ureido group = R-NH-CO-NH-) is formed in the first step. Then, when water is eliminated, a derivative of hydantoin is created (cf., e.g.[10], Scheme 9).



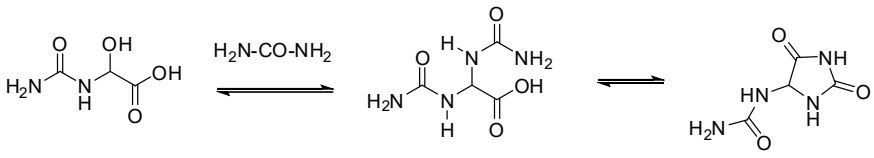
Scheme 7




Scheme 8




Scheme 9




Scheme 10

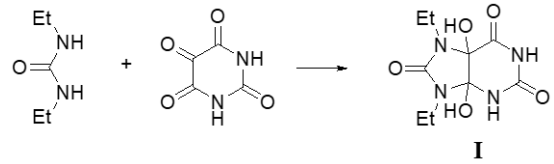
Thus, five- or six-membered rings can easily originate by cyclization of 2- or 3-ureidocarboxylic acids, respectively (ureides for short), e.g., ureidoacetic acid, 3-ureidopropionic acid, possibly of their salts or esters. The former acid can synonymously be called hydantoin acid; this acid and its derivatives thus represent a special case of ureido acids in which the ureido group is attached in position 2 with respect to carboxyl.

By the reaction of glyoxylic acid (or its methyl ester) with urea, 2-hydroxy-2-ureidoacetic acid is formed which, in the following reaction with another molecule of urea, gives a derivative of allantoin acid; after water is released, the cyclization takes place to yield allantoin, i.e., 5-ureidohydantoin (presented already in Scheme 7), cf. Scheme 10.

The reaction of alloxan with *N*,*N*'-diethyl urea leads to compound **I** (Scheme 11). In contrast to uric acid (the starting substance in Scheme 7), here, in positions 7 and 9, ethyls are located instead of hydrogen atoms and hydroxyl groups are on C1 and C6 (ref.[17]).

The initial concept was that the reductive cleavage of the derivative **I** by hydrogen iodide yields 1,3-diethylhydantoin while releasing urea[18] (Scheme 12).

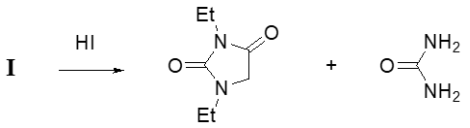
Later, however, the hypothesis of the reaction sequence according to Schemes 11 and 12 was disproved[19] because it was shown that the way to 1,3-diethylhydantoin leads *via* intermediate **II** (Scheme 13), not **I**.



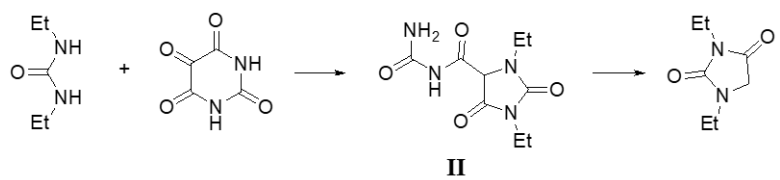
**I**

Scheme 11

A reversible reaction between the cyclic and acyclic form of ureides may proceed in dependence on the presence of acids or bases, leading to equilibrium, an example



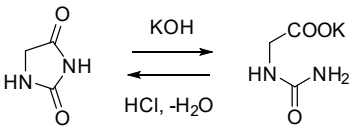

Scheme 12



**II**

Scheme 13

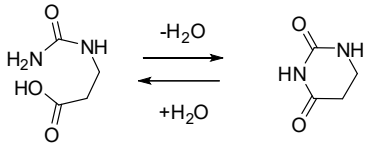
of which is given in Scheme 14 for the case of hydantoin and ureidoacetic acid (hydantoin acid)[11].




Scheme 14

The acyclic forms are sometimes so unstable that they cannot often be isolated and, in some cases, they even cyclize during their crystallization.

3-ureidopropionic acid cyclizes to form dihydrouracil, i.e., a six-membered heterocycle. The kinetics of this reversible reaction has been described[20] (Scheme 15).



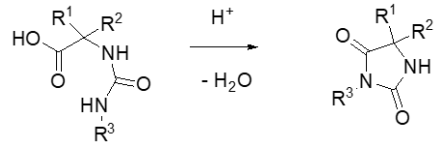

Scheme 15

For the elucidation of the mechanism and conditions of the hydantoin ring formation during the syntheses of polyaspartates, the paper by Rutkovský and coll.[21] can be important, describing the reaction of *N*-methyl derivative of aspartic acid diethyl ester with methyl isocyanate yielding diethyl γ-methyl ureidosuccinate **III** [synonymously 2-(*N*,*N*'-dimethylureido)succinate]. By action of an acid, it cyclizes to (1,3-dimethylhydantoin-5-yl)acetic acid (Scheme 16).

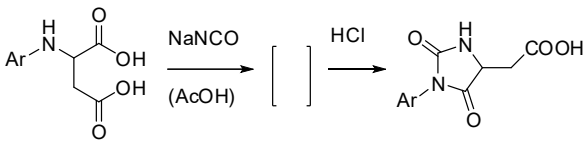
Here, no reverse ring-opening reaction has been observed.

The possibility to catalyze such cyclizations by acids is probably a general phenomenon, as follows from a kinetic study of hydantoin ring formation from the derivatives of hydantoin acids[22] (Scheme 17), in which an effect of the substituents $R^1$ through $R^3$ was studied:

The reaction of *N*-arylaspartic acid with sodium isocyanate in the presence of acetic acid and the following cyclization of the intermediate formed (the structure of which is not mentioned by the authors) by the action of hydrochloric acid leads again to a derivative of hydantoin[23] (Scheme 18).




Scheme 17

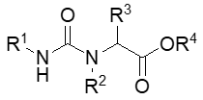



Scheme 18

This represents an analogy of the mentioned Urech synthesis[15].

Hence, it seems that an inorganic isocyanate can react with an amino group in position 2 with respect to carboxyl even in the case that the amino group is substituted and the molecule of the substrate contains one more carboxyl.

The formation of cycles cannot reliably be prevented even in the basic environment. On the contrary, under certain conditions, this environment can catalyze cyclization. The kinetic of the base-catalyzed cyclization of the hydantoin acid esters in water and methanol was studied by a Czech team[24] with several derivatives bearing various substituents $R^1$ through $R^4$ (Scheme 19).

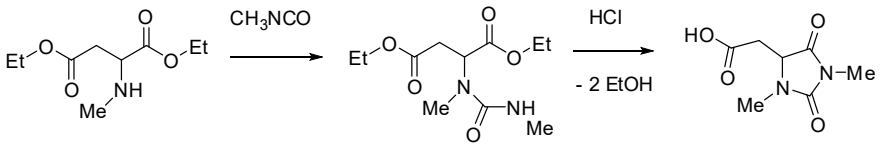


Scheme 19

If $R^4$ is methyl or ethyl, $R^2$ hydrogen, and $R^1$ hydrogen or methyl, then the cyclization is accompanied by the hydrolysis of the ester group, but this is not true for other derivatives. In the overwhelming majority of cases, specific base catalysis takes place here, not the general one.

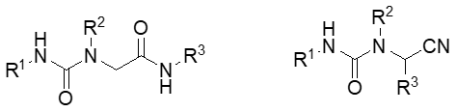
In a subsequent paper[25], a kinetic of the base-catalyzed cyclization of substituted amides and nitriles of hydantoin acids in water or methanol is studied (Scheme 20).

In a basic media, however, amides of hydantoin acids undergo the cyclization by several orders of magnitude slower than esters; consequently, the competitive hydroly-



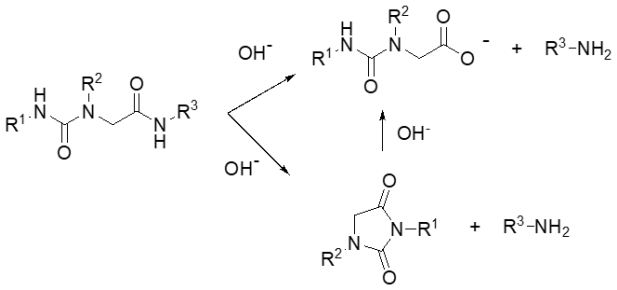

**III**

Scheme 16



Scheme 20

sis of an amide leads to the acid equally to the hydrolytic opening of hydantoin already formed (Scheme 21).

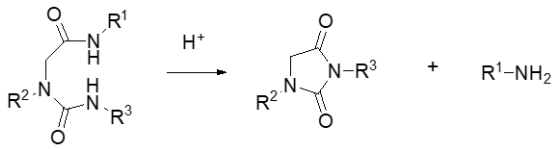


Scheme 21

It is presently impossible to predict whether these findings, i.e., the preferential formation of an acyclic product under basic catalysis in case that an amidic or a nitrile group is present in the molecule instead of the ester group, could be applied also to the adducts of N-substituted aspartates with isocyanates; nevertheless, it might represent a possible solution to the problem.

As expected, under acid catalysis, hydantoin amides cyclize, as described in the third of the series of the papers by this team[26] (Scheme 22).

Obviously, the hydantoin cycle can be prepared by some other routes, e.g., by the synthesis from carbonyl compounds *via* substituted nitriles of amino acids[27], by



Scheme 22

a contraction of a uracil ring (e.g.[28]), or by acetylation of N-hydroxyphenyl urethanes followed by cleaving off the phenolate[29] (Scheme 23), but these procedures will not be presented here in detail.

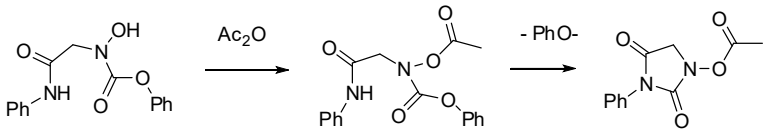
## 3.2. Some important reactions of hydantoin and its derivatives

The opening of the hydantoin ring, proceeding under certain conditions through alkaline hydrolysis to yield ureido acids, has already been mentioned. Two mechanisms have been suggested for it: the attack of the hydroxyl anion may proceed either to a free hydantoin ring or to its N-3 anion[30,31] (Scheme 24).

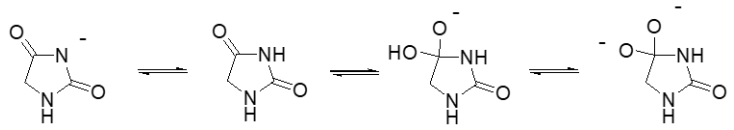
Of the reactions important for the syntheses of polyaspartate resins, the N-alkylation should be mentioned. It can proceed easily to N-3 (the imide nitrogen of the cycle) by the effect of alkyl halogenides in alkaline media, alternatively by the reaction with dimethyl sulfate or diazomethane. An alkylation exclusively to N-1 (amide nitrogen) is more difficult and, prior to performing it, it is usually necessary to suitably protect N-3 (ref.[32]).

The alkylation can be done also under the conditions of the Mannich reaction[33] (Scheme 25).

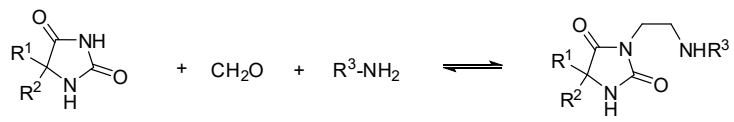
The N-acylation of hydantoin by, e.g., acetic anhydride, begins on the amide nitrogen and then continues on the imide one[11].



Scheme 23



Scheme 24

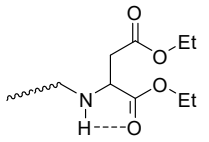


Scheme 25

Another possibility of a chemical modification of hydantoin relies on a reductive action of $LiAlH_4$, leading to a broad spectrum of products in the dependence on the type and number of substituents.

### 3.3. Effect of hydrogen bonds

As has already been mentioned in the introduction, the hydrogen bond between the amine hydrogen and that of two carbonyl oxygen atoms[34] which is located closer to it plays an important role during the reactions of the NH-groups of aspartates with isocyanates; this H-bridge can be depicted as a part of a five-membered ring (Scheme 26).




Scheme 26

Such bridges further contribute to a welcome reduction of the curing rate. The effect of the solvent, too, plays a significant role here, namely, its ability to disrupt or enhance these bridges.

## 4. Prerequisites for planned research

It follows from this review that, to find requirements needed to avoid the formation of cycles during the reaction of a suitable N-substituted aspartate with an isocyanate, a large series of experiments will have to be done in a broad range of reaction conditions. Above all, it will be necessary to find out the effect of the form of the carboxyl groups (ester, amide, nitrile), to examine the influence of pH, temperature, the initial mutual ratio of the reactants, the degree of dilution, the kind of solvent used (as well as the hydrogen bonding affected by it), etc. According to the preliminary experiments, it seems that the course of these reactions and especially the content of minority by-products in the reaction mixture is very sensitive to these conditions. In the beginning, a simple model will have to be used, e.g., the reaction of diethyl 2-(cyclohexylamino) succinate (synonymously: diethyl ester of *N*-cyclohexyl-aspartic acid, cf.[7], where the cyclohexyl group mimics the spacious growing molecule present in a real system bis-aspartate/triisocyanate) with butyl isocyanate, or another simple isocyanate. It would also be of interest, as a secondary aim for the basic research, to find out if and under which conditions a six-membered cycle, i.e., a derivative of dihydrouracil can be formed.

*The authors acknowledge the institutional support of the Institute of Macromolecular Chemistry of the Czech Academy of Sciences, RVO: 61389013.*

REFERENCES

1. https://www.scribd.com/document/235520186/12-18-13 Polyaspartic-Webinar-Protective-and-Marine, downloaded January 16, 2021.
2. https://en.wikipedia.org/wiki/Polyaspartic, downloaded August 24, 2021.
3. Howarth G.: Surf. Coatings Int. Part B Coatings Trans. *86*, 111 (2003).
4. https://solutions.covestro.com/en/highlights/articles/theme/product-technology/pasquick, downloaded August 24, 2021.
5. Clemo G. R., Graham S. B.: J. Chem. Soc. *1930*, 213.
6. Nozaki K.: J. Am. Chem. Soc. *63*, 2681 (1941).
7. Bláha M., Trhlíková O., Podešva J., Abbrent S., Steinhart M., Dybal J., Dušková Smrčková M.: Tetrahedron *74*, 58 (2018).
8. Podešva J., Hrubý M., Trhlíková O., Dušková Smrčková M., Chmelíková D.: Chem. Listy *112*, 117 (2018).
9. Meusel M., Gütschow M.: Org. Prep. Proced. Int. *36*, 391 (2004).
10. López C. A., Trigo G. G.: Adv. Heterocycl. Chem. *38*, 177 (1985).
11. Ware E.: Chem. Rev. *46*, 403 (1950).
12. Kleinpeter E.: Struct. Chem. *8*, 161 (1997).
13. Cho S., Kim S.-H., Shin D.: Eur. J. Med. Chem. *164*, 517 (2019).
14. https://en.wikipedia.org/wiki/Hydantoin, downloaded August 24, 2021.
15. Urech, F.: Ann. Chem. Pharm. *165*, 99 (1873).
16. Read W. T.: J. Am. Chem. Soc. *44*, 1746 (1922).
17. Biltz H.: Ber. Dtsch. Chem. Ges. *43*, 1511 (1910).
18. Biltz H., Max F.: Justus Liebigs Ann. Chem. *423*, 295 (1921).
19. Poje M., Paulus E. F., Rocic B.: J. Org. Chem. *45*, 65 (1980).
20. Pojarlieff I. G.: Tetrahedron *23*, 4307 (1967).
21. Rutkovskij G. V., Ivin B. A., Sočilin E. G., Cereteli I. Ju.: Zh. Obshch. Khim. *40*, 389 (1970).
22. Stella V., Higuchi T.: J. Org. Chem. *38*, 1527 (1973).
23. Baltrushis R. S., Beresnevichyus Z.-I. G., Vizgaitis I. M., Gatilov Yu. V.: Khim. Geterotsikl. Soedin. *1981*, 1669.
24. Kaválek J., Macháček V., Svobodová G., Štěrba V.: Collect. Czechoslov. Chem. Commun. *51*, 375 (1986).
25. Macháček V., Svobodová G., Štěrba V.: Collect. Czechoslov. Chem. Commun. *52*, 140 (1987).
26. Kaválek J., Macháček V., Svobodová G., Štěrba V.: Collect. Czechoslov. Chem. Commun. *52*, 1999 (1987).
27. Bucherer H. T., Steiner W.: J. Prakt. Chem. *140*, 291 (1934).
28. Senda S., Hirota K., Banno K.: Tetrahedron Lett. *15*, 3087 (1974).
29. Hell S. C., Conklin G., McCaully R. J.: J. Heterocycl. Chem. *13*, 51 (1976).
30. Ivin B. A., Rutkovskii G. V., Andreev S. A., Sochilin E. G.: Zh. Org. Khim. *9*, 2194 (1973).

31. Blagoeva I. B., Pojarlieff I. G., Dimitrov V. S.: J. Chem. Soc. Perkin Trans. *2*, 887 (1978).
32. Orazi O. O., Corral R. A., Schuttenberg H.: J. Chem. Soc. Perkin Trans. *1*, 219 (1974).
33. Orazi O. O., Corral R. A.: Tetrahedron *15*, 93 (1961).
34. Williams C. T., Wicks D. A., Jarrett W. L.: J. Coatings Technol. Res. *6*, 37 (2009).

## Abstract

Polyaspartates are industrially important resins formed by reactions of N-substituted 2-aminosuccinates (or, synonymously, N-substituted aspartates) with isocyanates. To obtain sufficiently crosslinked networks, applicable as coatings, bis-aspartates with two secondary NH groups and isocyanates with more than two NCO groups in their molecules must be used. There are two major problems connected with these preparations: (i) bis-aspartates which are mostly synthesized by the aza-Michael addition of $NH_2$ groups of a suitable diamine to C=C bonds of a maleate ester almost always contain a certain amount of a fumarate ester (usually a few percent) as a result of the *Z*→*E* isomerization, unavoidably accompanying the addition; this deteriorates the quality of the resulting product; (ii) during the reaction of bis-aspartate with isocyanate, hydantoin rings are often formed to some extent in addition to the desirable three dimensional structures; the presence of these rings decreases the attainable network density. In this review, those properties, syntheses, and reactions of hydantoin are summarized which could be useful for finding conditions to avoid the formation of hydantoin rings.

● Podešva J., Dušková Smrčková M., Trhlíková O.: Chem. Listy *116*, 215–222 (2022).
● https://doi.org/10.54779/chl20220215