

Reactions of Hydroxymethyl Derivatives of Uric Acid with Oxiranes. II. An Analysis of Reaction Course and Product Structure

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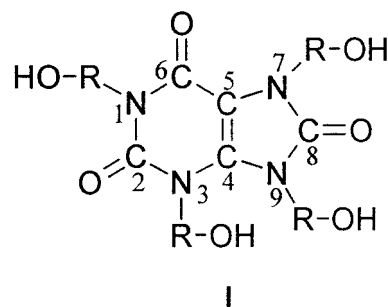
ABSTRACT: Polyetherols containing thermostable purine rings are obtained in reactions of hydroxymethyl derivatives of uric acid with an excess of ethylene oxide or propylene oxide. By using elementary analytical tools and $^1\text{H-NMR}$ spectroscopy, it was possible to follow the course of reaction at various molar ratios of reagents. A migration of formaldehyde molecules from *N*-hydroxymethyl groups or from oligooxymethylene bridges to the end of oxyalkyl chains was observed. At the same time, the *O*-hydroxymethyl groups are successively blocked by oxiranes. The most probable structure of polyetherols is proposed. © 2002 John Wiley & Sons, Inc. *J Appl Polym Sci* 83: 1955–1962, 2002

Key words: uric acid; formaldehyde; oxiranes; gradual addition; intermediate products; purine-ring-containing polyetherols

INTRODUCTION

Hydroxymethyl derivatives of uric acid (HMUA) constitute an interesting group of new compounds which when reacted with a large excess of oxiranes, such as ethylene oxide (EO) or propylene oxide (PO), yield tetrafunctional polyetherols containing thermostable purine rings. The presence of the rings improves thermal properties of polymeric materials (e.g., polyurethane foams) obtained from them.¹

In a reversible reaction of 1 mol uric acid (UA) with 7 mol formaldehyde (aqueous solution), a noncrystalline semisolid product is obtained which when mixed with 5% water easily dissolves in oxiranes and reacts with them at elevated temperatures (65–70°C) in the presence of triethylamine (TEA) catalyst to the polyetherols mentioned above. Their structure can be written as:



The conditions at which the purine-ring-containing polyetherols were obtained were described in ref. ¹ It was found that at a small excess of oxiranes, the resulting oligoetherols contained unstable semi-acetal group at the ends of polyether chains. They decomposed at elevated temperature, releasing free formaldehyde. No formaldehyde release was observed when the excess of oxiranes exceeded ~ 12 mol per mole HMUA. Physical and spectral properties of the polyetherols as well as directions of their potential applications were also presented in ref. ¹

In this work, we try to explain the course of reaction of successive oxirane molecules (EO or

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PO) with N- and O-hydroxymethyl derivatives of UA and the expected structural formula of the products.

EXPERIMENTAL

Reagents

Uric acid, pure (Loba Feinchemie, Germany); ethylene oxide, pure, and (\pm)propylene oxide, pure (Fluka, Switzerland); and formaldehyde (36–37% aqueous solution), pure (POCh, Gliwice, Poland) were used as reagents.

Syntheses

HMUA

The derivative was obtained according to the procedure described in ref. ¹ at the molar ratio of UA : CH₂O = 1 : 7.

Reaction of HMUA with Oxiranes

In a 500-cm³ three-necked round-bottomed flask equipped with a mechanical stirrer, 378 g (1 mol) HMUA was placed. Then, 18.9 g water (5 wt %) and 52.2 cm³ (36.2 g) TEA were added. The content was stirred at room temperature until it became homogeneous. A sample was withdrawn (~ 9 g), diluted with about the same amount of dimethylsulfoxide (DMSO), and placed in a 250-cm³ autoclave. A calculated amount of oxirane was added to the sample in one portion. The molar ratio of HMUA : oxirane was adjusted to vary from 1 : 1 through to 1 : 16. The autoclave was heated to 40°C and kept at this temperature until completion of the reaction.

Analytical Methods

The end of reaction was established by determining the epoxy number of reaction mixture by titrating a sample with dioxane solution of hydrochloric acid.² The acid number was determined by titration with 0.1M NaOH and the amount of unbounded formaldehyde was determined iodometrically in the form of N- and O-hydroxymethyl groups.³ ¹H-NMR spectra were recorded on a spectrometer BS586A, 80 MHz, Tesla, Czechoslovakia (in *d*₆-DMSO) after solvent was removed under reduced pressure (20 hPa/15 mmHg, temperature < 80°C).

RESULTS AND DISCUSSION

Bonded Formaldehyde

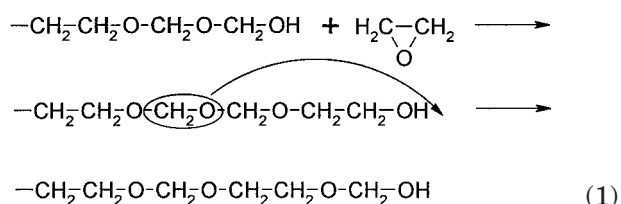
The course of reaction was studied by using the uric acid derivative obtained at the molar ratio UA : CH₂O = 1 : 7. This derivative containing

both N- and O-hydroxymethyl groups was chosen because with excess of oxiranes it yields polyetherols suitable for synthesis of thermostable polyurethanes.¹ The reaction was carried out with 5 wt % water with respect to the amount of the derivative and in the presence of TEA catalyst. After oxiranes had been added, the system became inhomogeneous. Hence, DMSO was added to bring it back to a one-phase system.

The reacting mixture was analyzed by determining the acid number and the changes in the amount of N- and O-hydroxymethyl groups. These groups react with iodine just as free formaldehyde does. The results are presented in Figure 1. As can be seen:

- After 1 or 2 mol of either oxiranes, or after 3 mol EO were added to 1 mol UA derivative, the amount free formaldehyde does not change; further addition of oxirane molecules reduces the amount of free formaldehyde determined iodometrically. Propylene oxide blocks slightly less formaldehyde than ethylene oxide does.
- The whole formaldehyde becomes blocked (cannot be determined by iodometric titration) after 12 or 16 mol EO or PO per mol UA hydroxymethyl derivative was added, respectively.

These results seem to justify the following conclusions concerning the course of the reaction in question. The initial 3 mol EO (or 2 mol PO) do not block N-hydroxymethyl groups or block them only temporarily. Only the third mole of PO or fourth mole of EO starts to block in a permanent way some amount or 1 mol formaldehyde, respectively. Hence, the determinable formaldehyde remaining after the addition of 4 mol oxiranes per mole UA derivative has to be present in the form of oxymethylene bridges: —(CH₂—O)_x— with 0 ≤ x ≤ 2. If x = 2, the next added oxirane molecule should make one formaldehyde molecule to re-group down to the end of chain and form the thermodynamically more stable structure according to the scheme:



The isolated oxymethylene groups within the chain are not determined by the iodometric analysis. They

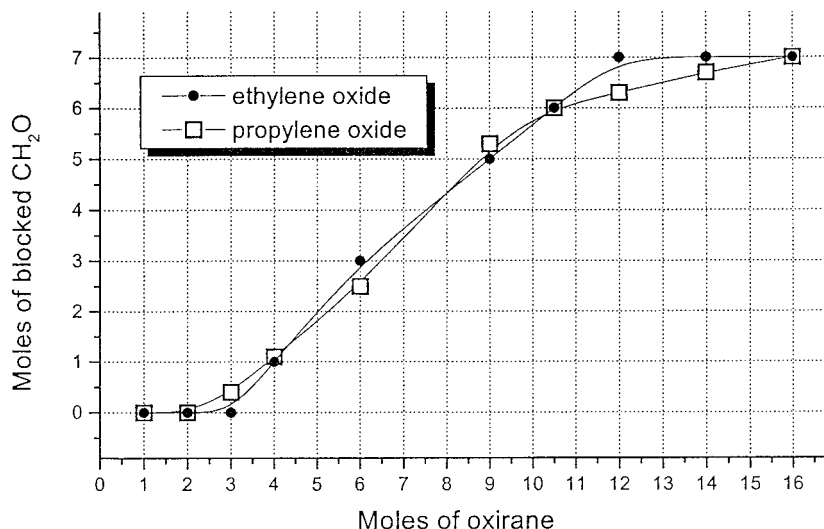
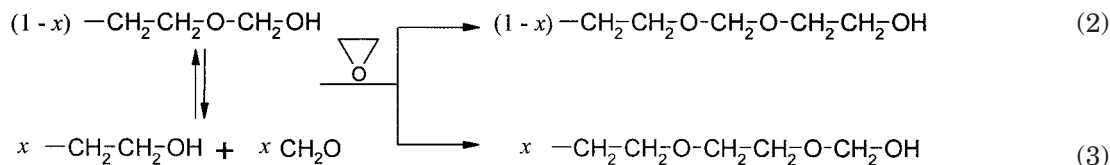


Figure 1 The number of moles of blocked formaldehyde in the reaction of HMUA with oxiranes.

constitute the blocked formaldehyde. Hence, the migration of formaldehyde molecules and formation of O-hydroxymethyl groups at the end of chains explains the results presented in Figure 1. Furthermore, the presence of water facilitates dissociation

of formaldehyde from O-hydroxymethyl groups. Hence, the next moles of added oxirane, starting from, say, the fifth mole are capable of blocking only a fraction of a mole of O-hydroxymethyl groups according to the equilibrium:



One cannot exclude the same mechanism of formaldehyde release (i.e., its dissociation, from *N*-hydroxymethyl group, at the beginning of oxirane addition). More likely, it seems to be, however, the release of formaldehyde from the blocked *N*-hydroxymethyl group and its migration to the end of the chain. This latter process was observed and carefully examined in the reactions of hydroxymethyl derivatives of isocyanuric acid and melamine with oxiranes.^{4,5} The permanent blocking of formaldehyde in these systems was observed after two oxirane molecules were added to one *N*-hydroxymethyl group.

In this work, it was found that 3 mol PO added to 1 mol hydroxymethyl derivative UA are sufficient to block some amount of formaldehyde. The same does not apply to EO (Fig. 1). This seems to be caused by the presence of the purine ring, on one hand, and the oxirane methyl group, on the other. The steric hindrance slows down the pos-

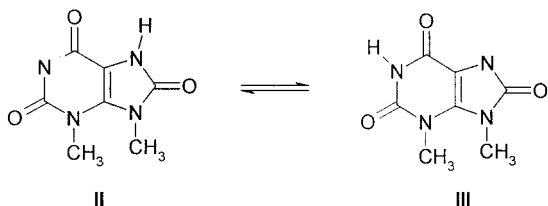
sible migration of formaldehyde molecules. It should be pointed out, however, that PO added in the amount exceeding ca. 3 mol per mole UA hydroxymethyl derivative is capable to block slightly less formaldehyde than the comparable amount of EO. The major role is now played by the reactivities of oxiranes and the rate of reaching equilibrium of dissociation of formaldehyde from O-hydroxymethyl groups. EO seems to manage to react well before the equilibrium is reached and, hence, more formaldehyde is blocked.

The first 3 mol EO do not block formaldehyde at all. As follows from our previous studies,^{4,5} the stability of *N*-hydroxymethyl groups and —N—CH₂—O— grouping blocked by one oxirane molecule depends to a large extent on the acidity of the —NH group formaldehyde has reacted with. The more acidic the group, the easier the release of formaldehyde was observed. As follows from the study by Pfeleiderer,⁶ the acidity of hy-

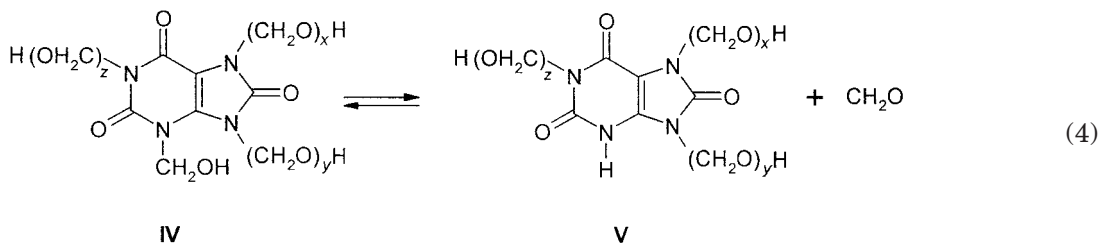
Table I The Results of Acid Number Determination

Initial Molar Ratio of UA : CH ₂ O	Acid Number [mg KOH/g]	
	Calculated	Determined
1 : 6	161.2	150.0
1 : 7	148.8	147.6
1 : 8	137.5	132.7
1 : 10	119.9	117.3

drogen atoms in UA increases in the order: N(3)—H > N(9)—H > N(1)—H \geq N(7)—H. The blocking of formaldehyde by the fourth EO mole only seems to confirm indirectly the lowest acidity of N(7)—H group with sufficiently high acidity of the remaining —NH groups for formaldehyde to migrate relatively easily to the end of their oxyethylene chains. Pfeleiderer⁶ pointed out that in fact it is difficult to discriminate which proton of the two nitrogens, N(1) or N(7), is more acidic. The UV spectra of 3,9-dimethyluric acid anion revealed the two possible tautomeric forms:



This equilibrium suggests that the third oxirane molecule may block the N(1)- as well as the N(7)-

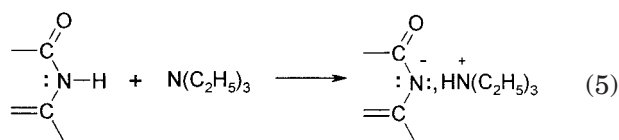


where $x + y + z = 6$. Assuming the acid numbers of successive products of reaction between HMUA and increasing numbers of moles of oxiranes is related to blocking of —N(3)—H group with oxirane, one may estimate from stoichiometry the fraction of these groups that was indeed blocked. The presence of TEA was taken into account in calculations because it blocks the —N(3)—H group as in the following scheme:

hydroxymethyl group before formaldehyde migrates to the end of the chain. From this work, it appears that blocking one of the two groups (obviously, besides the N(3)- and N(9)-hydroxymethyl groups that reacted earlier) makes the other group [e.g., N(1)-hydroxymethyl groups if N(7)- has reacted and vice versa] sufficiently strongly linked to the ring for preventing formaldehyde from migrating. That is the acidity of N(1)—H or N(7)—H proton that is sufficiently small.

The Acid Number

The hydroxymethyl derivatives of uric acid obtained by reacting this acid with formaldehyde at various molar ratios of reagents are water soluble and have acidic character. As follows from the data in Table I, these derivatives as well as uric acid itself behave as monobasic acids, which means that the formaldehyde molecule is eliminated upon neutralization from one hydroxymethyl group only, as previously suggested.¹ If, however, one assumes, following Pfeleiderer,⁶ that hydrogen at N(3) is the most acidic, then the concentration of —N(3)—H groups determines the acidic number of HMUA. It contradicts the first approximation made by us in our previous article,¹ where we assumed the hydrogen in the —N(1)—H imide group to be the most acidic. Therefore, the structures of HMUA and polyetherols derived from it seem different than that proposed by us (cf. structures IV, V, and VI in ref. ¹). According to our present knowledge, the structure of HMUA is better approximated by the scheme (for HMUA with UA : CH₂O ratio equal to 1 : 7):



The results of estimation are shown in Figure 2. Similar proton transfer was observed in hydroxymethyl groups-triethylamine systems.⁷ The resulting alcoholate anions formed by triethyl-

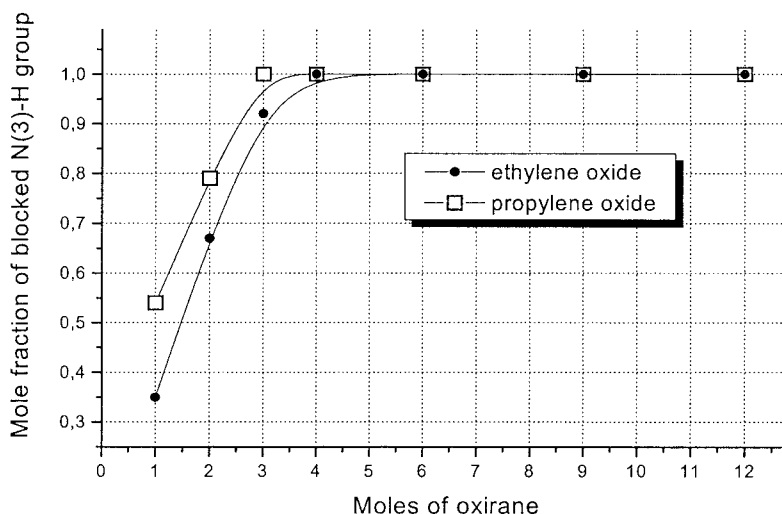


Figure 2 The number of moles of blocked N(3)H groups in the reaction of HMUA with oxiranes.

amine-induced deprotonation are the nucleophilic agents that open oxirane rings. It can be seen that when up to 3 mol oxirane are added to HMUA, the group —N(3)—H is successively blocked by the oxirane. At larger excess, the product is no more acidic.

Furthermore, PO tends to block a larger fraction of —N(3)—H groups than does EO at the same molar excess with respect to HMUA. The difference seems to be the result of higher reactivity and smaller selectivity of EO than with PO. EO more readily reacts with other reactive groups of HMUA than PO and hence less of it is left to react with —N(3)—H .

$^1\text{H-NMR}$ Analysis

The conclusions following the results of chemical analysis are confirmed by $^1\text{H-NMR}$ spectra of the products of reaction of HMUA with oxiranes. The products were purified by distilling off the solvent (DMSO) under reduced pressure at temperatures up to 80°C . Under these conditions, one cannot exclude partial elimination of formaldehyde by decomposition of N- or O-hydroxymethyl groups. Hence, the spectral analysis is rather a qualitative one.

In the spectra (Fig. 3) of successive products of addition of more and more EO to HMUA, the following changes are observed with respect to HMUA substrate (Fig. 1 and Table I in ref. ¹):

A signal at 3.5 ppm appears in the HMUA : EO = 1 : 1 product; it confirms the presence

ofoxyethylene groups.⁵ Its intensity increases with the excess of EO.

The intensities of signals from N-hydroxymethyl group methylene protons decrease successively as the excess of EO increases from 1 to 3 mol per mole of HMUA. Similar signal reduction was observed in the spectra of reaction products of oxiranes with hydroxymethyl derivatives of isocyanuric acid and melamine.^{4,5} Obviously, the reduction indicates that EO addition indeed takes place.

The migration of formaldehyde to the end of oxyethylene chains is indirectly evidenced by the intensity increase of the signals due to methylene protons of O-hydroxymethyl groups as compared to that due to $\text{—N—CH}_2\text{O—}$ ones. This applies to the products with EO excess not exceeding 3 mol per mole HMUA.

The low intensity triplet at ~ 1.0 ppm is due to TEA that cannot be fully removed from the products. It forms strong proton transfer complexes with hydroxy groups, similarly as in polyetherols obtained from isocyanuric acid or melamine.^{4,5}

The signal at ~ 11.0 ppm in the spectrum of HMUA : EO = 1 : 1 product is due to free —N—H proton. It probably comes from —N(3)—H group, which is supposed to be the most acidic one. It probably decomposes most readily when heated, releasing a formalde-

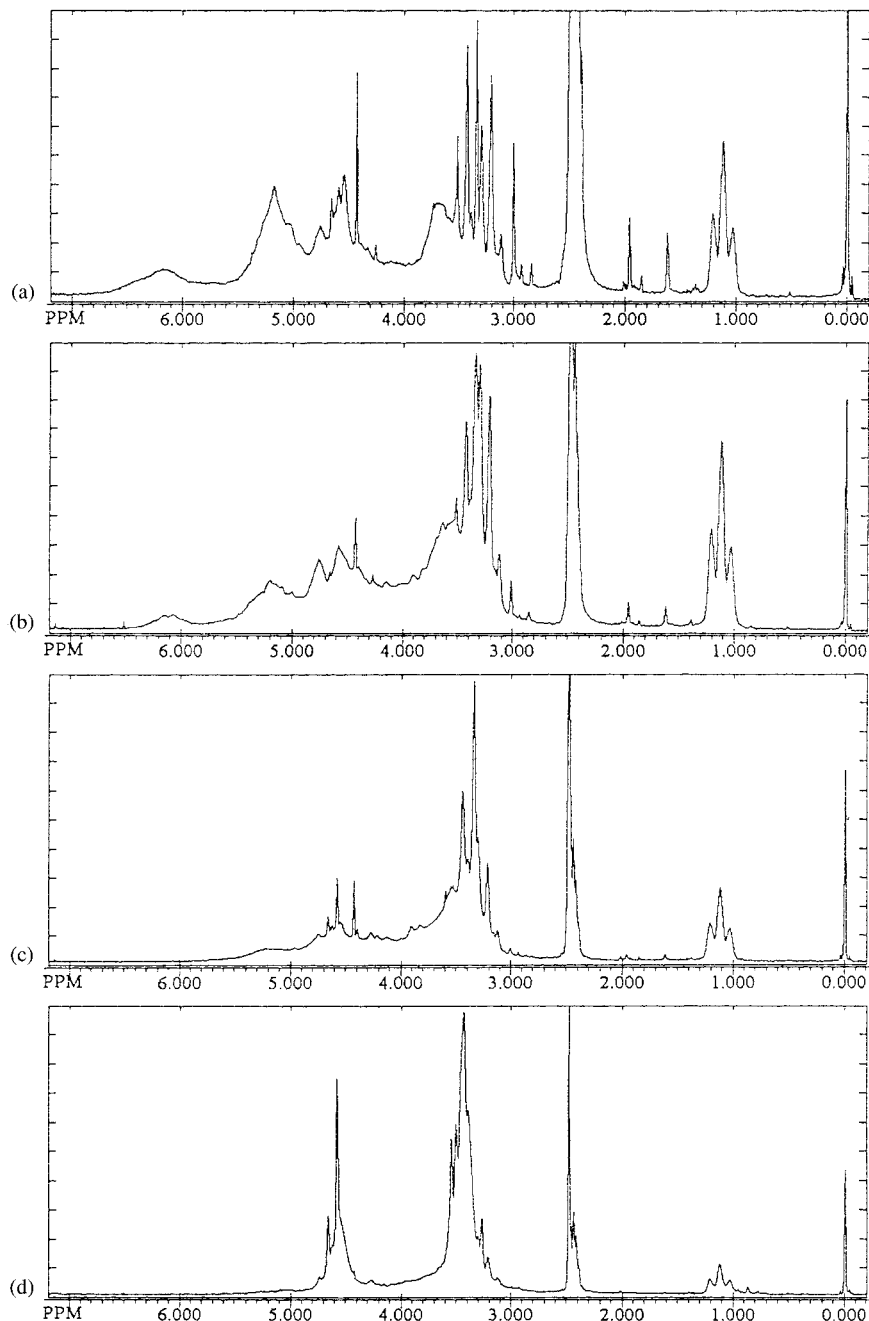


Figure 3 $^1\text{H-NMR}$ spectra of products of reaction of HMUA with (a) 2 mol EO; (b) 4 mol EO; (c) 6 mol EO; and (d) 12 mol EO.

hyde molecule. It seems worth noting that the fraction of free $-\text{N}-\text{H}$ groups estimated from $^1\text{H-NMR}$ spectrum is 0.63 mol per mole of product, whereas the acid number of the aqueous solution of the same product is 0.65.

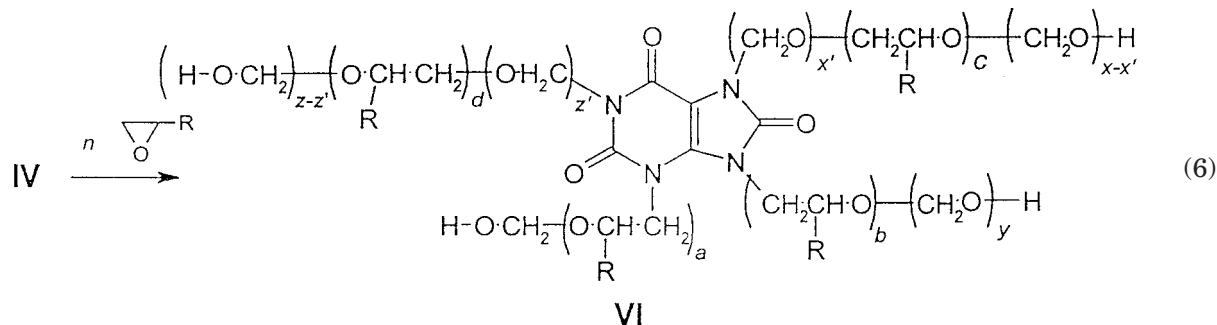
By analyzing $^1\text{H-NMR}$ spectra of products of PO addition, analogous conclusions can be drawn.

The presence of signals due to anomalous fragments,⁸ [i.e., the fragments where atom C(2) of PO rather than C(1) is linked to nitrogen] can be seen in the spectra. The fraction of these fragments estimated by comparing intensities of signals at 1.0 ppm (normal fragments) with those at 1.45 ppm (anomalous fragments) is below ~ 7 mol %.

It should also be noticed that at some $^1\text{H-NMR}$ spectra a weak signal at 8.5 ppm due to free formaldehyde was observed. Its intensity slightly increased after heavy water was added. Hence, the reactions of formaldehyde dissociation described by eqs. (2) and (3) cannot be excluded.

CONCLUSION

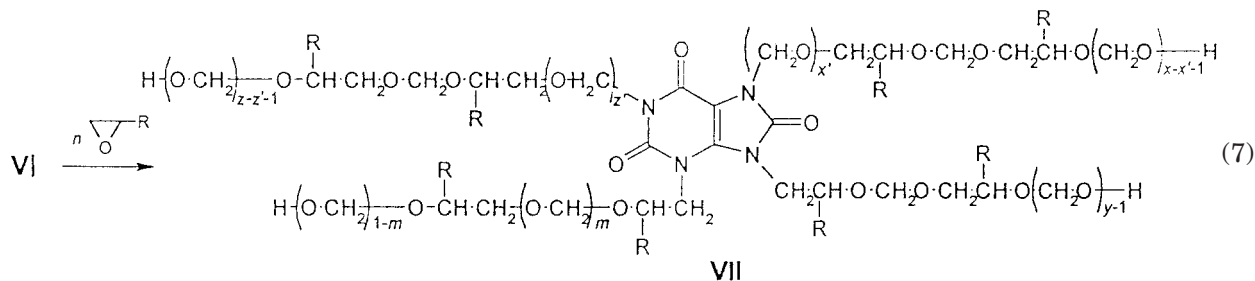
The analysis made in this work seems to justify the following course of the reaction of HMUA with oxiranes as well as the approximate structure of products. When 1–4 mol oxirane is added per mole HMUA, the structure of product might be:



where $\text{R} = -\text{H}, -\text{CH}_3$; $1 \leq n \leq 4$; $a + b + c + d = n$; $x + y + z = 6$; and $x' = 0$ if $z' = 1$ or $x' = 1$ if $z' = 0$.

The further moles of formaldehyde excess, in

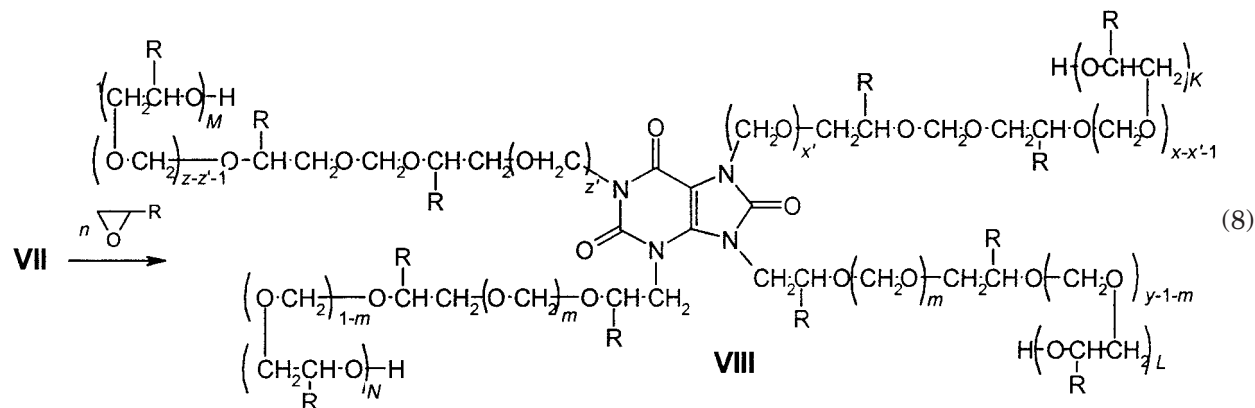
the range of 4 to 6, per mole of HMUA, block one or almost one formaldehyde moiety provided it has the form of $(\text{CH}_2\text{O})_2$ grouping:



where m is the fraction of mole of formaldehyde blocked by 1 mol oxirane; $0 < m \leq 1$; $4 \leq n \leq 6$; $x + y + z = 6$; $x' = 0$ if $0 < z' \leq 1$ or $z' = 0$ if $0 < x' \leq 1$.

The still increasing moles of oxirane block a

fraction of mole of formaldehyde ($0 < m \leq 1$) in O-hydroxymethyl groups. It is shown in the equations of compounds **VI** and **VII** for the chains at N(3) and N(9). The final structure of the product can be described as follows:



where $K + L + M + N = n - 9$.

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