Crosslinking Reaction Mechanism of Diisopropyl Xanthogen Polysulfide Accelerator in Bromobutyl Elastomer for Medical Device Applications

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ABSTRACT: The use of an accelerator based on diisopropyl xanthogen polysulfide (DIXP) to formulate bromobutyl elastomer (BIIR-DIXP) compositions for sealing medical devices was published in the Journal of Applied Polymer Science (Ohbi, D. S.; Pureval, T. S.; Shah, T.; Siores, E. 2007, 106, 526). In this publication, a reaction scheme for the DIXP accelerator *in situ* with BIIR is proposed. It is based on the evolved volatile chemical species determined during the curing reaction of BIIR-DIXP composition, and is formulated in the light of generally accepted mechanism of crosslinking elastomers using sulfur-based accelerators. The volatile chemical species were determined using coupled thermogravimetric infrared analysis (TGA-IR) and head space gas chromatography mass spectroscopy (GC-MS) analysis. The main volatiles evolved during the curing reaction were carbonyl sulfide, carbon disulfide, and isopropyl bromide. These are considered to be associated with the formation of the active rubber-bound DIXP sulfurating species required for the crosslinking reaction. Analysis of the acetone extract of cured BIIR-DIXP also showed that the DIXP is totally consumed during the cure reaction, and the formulation is largely free of cure reaction byproducts. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 4013–4020, 2008

Key words: bromobutyl elastomer; crosslinking mechanism; drug delivery; infrared spectroscopy; mass spectroscopy

INTRODUCTION

There are stringent safety requirements[1,2] for the use of elastomers in medical drug delivery devices as they can significantly affect the safety and efficacy of drug formulations. The elastomer compositions generally contain various organic processing aids, antioxidants and crosslinking agents added for their processing, and the development of desired physical properties. In the cured elastomer some of these additives are not connected to the crosslinked elastomer network and thus over time, can leach out and are regarded as potential contaminants[3] for drug products. In medical inhaler devices, the leachable species obtained from the elastomer component by solvent extraction can be identified using mass spectroscopy techniques. However, the identification and control of leachable species originating from the peroxide and sulfur accelerators components in elastomers is problematic as they produce a number of cure reaction byproducts.[4] In our previous publication[5] we reported the use of an environmentally safe accelerator diisopropyl xanthogen polysulfide (DIXP), for curing a bromobutyl (BIIR-DIXP) composition for medical device applications. DIXP is nitrogen free and thus it is not capable of producing harmful *N*-nitrosamines during curing.

The aim of this study is to identify the main reaction byproducts evolved during the curing of the BIIR-DIXP composition. Based on this analysis and the established crosslinking mechanisms for the elastomers, a reaction scheme for DIXP in halobutyl BIIR has been proposed. Further analysis of the cured BIIR-DIXP has also been made for residual chemical species remaining in the elastomer for the assessment of possible risks associated with them in medical device applications.

EXPERIMENTAL

Elastomer composition

The experimental work was carried out using a general purpose BIIR-DIXP composition given in Table I. The ingredients of the formulation were as received standard commercial materials.

Test methods

Coupled thermogravimetric infrared analysis

The evolved species from the neat DIXP accelerator and the BIIR-DIXP composition were analyzed using

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TABLE I
BIIR-DIXP Formulation; Component Weight Expressed as Per Hundred Parts of BIIR Rubber (phr)

Material	Concentration (phr)
Bromobutyl	100
Zinc oxide	3
Stearic acid	1
Mineral filler	120
Sulfur	0.5
DIXP	1.0

coupled thermogravimetric infrared analysis (TGA-IR). The experimental conditions are as follows:

Instrument: Perkin Elmer Pyris 1 TGA coupled with a Perkin Elmer 2000 IR spectrometer.

Sample size: circa 5–10 mg.

Running programme:

1. Isothermal at 30°C for 5 min.
2. Heat to cure temperature (150, 160, 170, and 180°C) at 200°C/min.
3. Hold isothermal cure temperature for 15 min.

The evolved species were transferred to an IR gas cell via a transfer line heated to 240°C. Individual spectra were collected using eight scans with a peak resolution of 8 cm^{-1}.

The time delay for the completion of IR spectra after volatile evolution was typically 30 s. The IR spectra were interpreted using the Timebase Spectrum Software© and IR literature references.[6,7]

Gas chromatography mass spectroscopy analysis

About 500 mg samples of BIIR-DIXP were sealed in helium-filled headspace vials and heated for 15 min at curing temperatures of 150, 160, 170, and 180°C. One microliter of the collected volatiles was then injected into the gas chromatography mass spectroscopy (GC-MS) using the following conditions:

Instrument: Agilent 6890N with 5973 MSD.

Column: 30 m × 0.25 mm × 0.25 μm HP5.

Oven programme:

1. 30°C for 5 min.
2. Heat to 20°C/min to 300°C and hold for 1.5 min.

For the analysis of the acetone extract of BIIR-DIXP the hold time was 15 min.

GC-MS analysis of acetone extract of the cured BIIR-DIXP

Approximately 3 g of samples of cured BIIR-DIXP were Soxhlet extracted in 100 mL of acetone for 18 h. The extract obtained after flashing off the solvent was dissolved in 2 mL of chloroform and spiked with two internal standards, 20 μg of fluorine-d10 and 100 μg of *p*-terphenyl-d14 to obtain semiquantitative analysis of the components. The GC-MS conditions have been described earlier under GC-MS analysis.

A single total ion chromatogram (TIC) was obtained for the extracted material and the semiquantitative value of each component calculated using the formula:

$$\frac{\left(\frac{\text{Peak Area}}{\text{Molecular Weight}}\right)_{\text{Component}}}{\left(\frac{\text{Peak Area}}{\text{Molecular Weight}}\right)_{\text{Internal Standard}}} \times \text{Amount of Internal Standard} = \text{Amount in } \mu g$$

Calculations were made using each standard individually, and the two values obtained averaged for

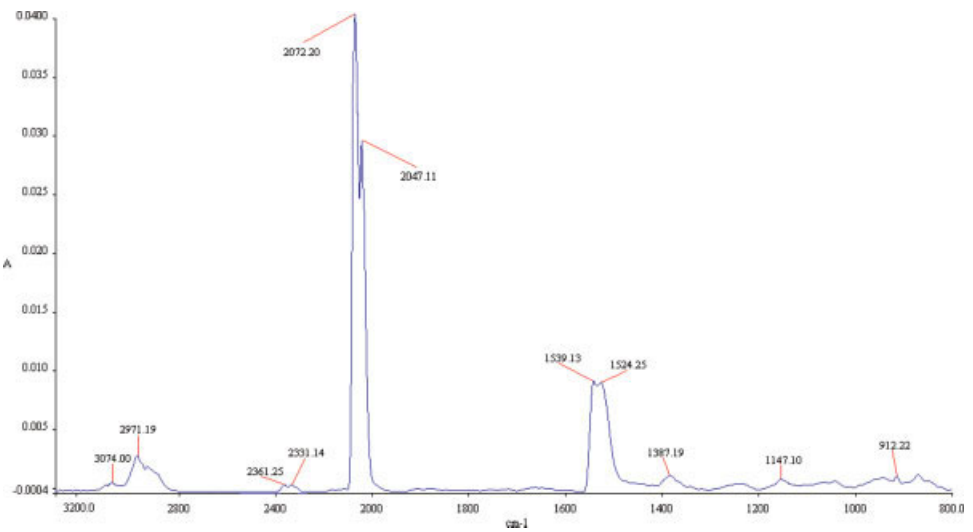

Figure 1 TGA-IR spectrum of neat DIXP accelerator showing characteristic peaks of volatiles generated at 180°C; COS (2072, 2047 cm^{-1}), IPA (1147, 2971, 3074 cm^{-1}), and CS_2 (1539, 1524 cm^{-1}). The CO_2 doublet (2361, 2331 cm^{-1}) is not related to DIXP. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II
Characteristic IR Peaks of the Decomposition Products of DIXP at 180°C

IR peak position (cm^{-1})	Assignment
3074, 2971	Various C—H
2361, 2331	Carbon dioxide
2072, 2047	Carbonyl sulfide
1539, 1524	Carbonyl disulfide
1387	CH_3 groups
1147	C—OH possibly from isopropyl alcohol
912	Possibly $CH{=}CH_2$ from propene

the result. The average value was divided by the weight of the sample to give the result in μg/g.

RESULTS AND DISCUSSION

Analysis of reaction byproducts of DIXP

The IR spectrum of the volatile species generated from the neat DIXP accelerator during the TGA analysis at 180°C is shown (Fig. 1). The volatiles consisted mainly of carbonyl sulfide (COS), isopropyl alcohol (IPA), and carbon disulfide (CS_2). The assignment of the characteristic IR peaks of these species was made using the Perkin Elmer Timebase Spectrum Software© and literature references,[6,7] and is given in Table II.

TGA-IR analysis of reaction byproducts of BIIR-DIXP

The volatile cure reaction byproducts obtained by heating 5–10 mg samples of BIIR-DIXP at isothermal temperatures 150, 160, 170, and 180°C were analyzed using TGA-IR. The IR spectra of the cure reaction byproducts at 170 and 180°C are shown (Figs. 2 and 3). The generation of COS was clearly seen by its strong doublet peak at ca 2070 cm^{-1} at all cure temperatures.There was some evidence of CS_2 at low levels but the assignment of IPA related peaks was not so clear, possibly because of insensitivity of the method to the low levels of evolved species (<0.5 wt % of sample size). The identification of the cure reaction species evolved from larger (500 mg) samples of BIIR-DIXP using headspace GS-MS is discussed later.

Kinetics of BIIR-DIXP reaction byproducts

The maximum rate (k) of the volatile reaction byproducts generated during the curing of BIIR-DIXP at specified isothermal temperatures (150–180°C) was determined from the first derivative weight loss TGA curves and are given in Table III. Examples of the TGA curves obtained at 170 and 180°C are shown in Figure 4. The activation energy E for this reaction was determined using the Arrhenius equation (1).

$$\ln k \propto -\frac{E}{RT} \tag{1}$$

where R = gas constant and T = absolute temperature.

According to eq. (1), the following linear regression calculation (2) was obtained between $\ln k$ and $1/T$.

$$\ln k = \frac{-7821.6}{T} + 16.208 \tag{2}$$

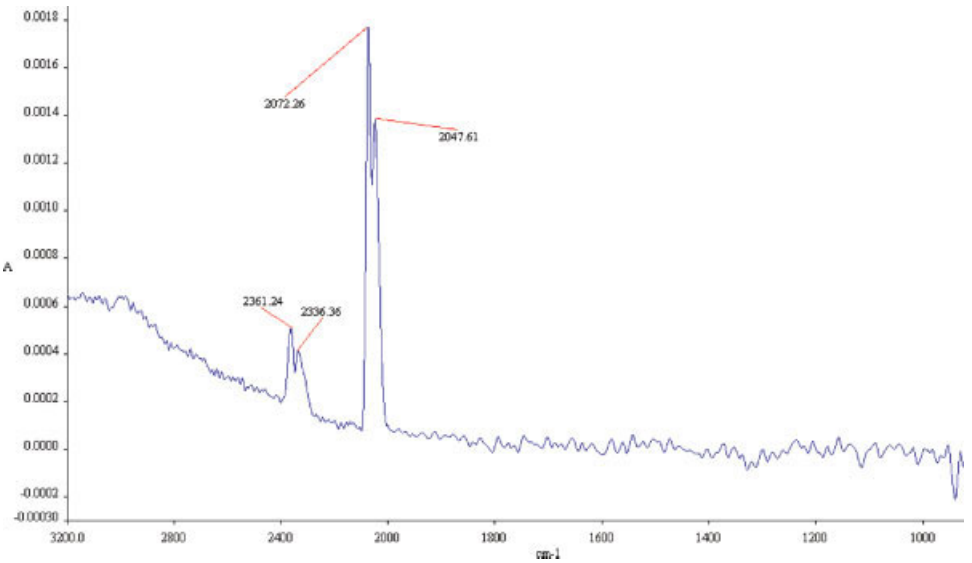

Figure 2 TGA-IR spectrum of BIIR-DIXP composite's cure at 170°C shows doublet peaks of reaction byproduct COS (2072, 2047 cm^{-1}). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

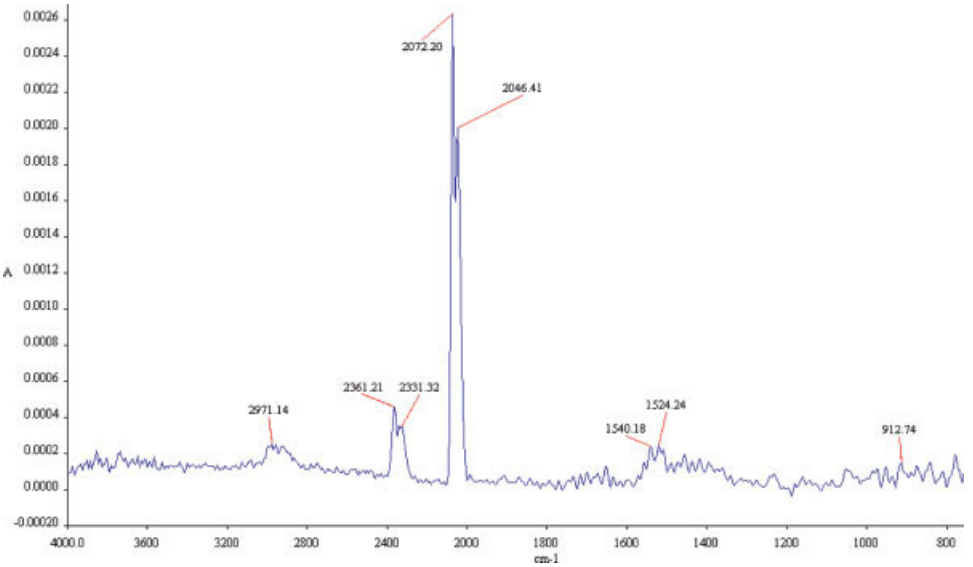

Figure 3 TGA-IR spectrum of BIIR-DIXP composite at cured at 180°C shows emission of COS (2072, 2046 cm^{-1}); CS_2 (1540, 1524 cm^{-1}) is also evident. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The coefficient of determination for this regression $RSQ = 0.9987$ indicates a very good fit of data.

The activation energy calculated for the cure reaction byproducts (65.06 kJ/mol) is considerably less than for the two crosslinking regions of BIIR-DIXP (122.6 and 103.33 kJ/mol) determined in our previous work.[5] It is thus likely that they originate in the induction phase prior to the crosslinking regions of the elastomer. It is understood[4,8] that during this induction phase, elastomer accelerator reactions occur to form the ''active rubber-bound sulfurating species'' required for the formation of crosslinks in elastomers.

GC-MS analysis of BIIR-DIXP cures byproducts

The volatile cure reaction byproducts generated during the curing of larger samples (500 mg) of BIIR-DIXP at defined temperatures were identified using headspace GC-MS and are given in Table IV.

The knowledge of volatilized components obtained from the TGA-IR analysis (Table II) of the neat DIXP accelerator was used to calculate the expected theoretical GC-MS parent ions generated during the curing of BIIR-DIXP:

Carbonyl sulfide – $m/z = 60$ Da
Carbon disulfide – $m/z = 76$ Da
Isopropyl bromide – $m/z = 122$ Da

The formation of isopropyl bromide was expected to occur as a side reaction of IPA with the halogenated species generated during curing and is discussed later.

The GC-MS ion chromatograms for each expected species was extracted and the peak areas measured. Their relative trend in the vapor phase as calculated from the peak areas seems to suggest the abundance of COS^+ ion at all cure temperatures. It was also noted that the mass spectrum for isopropyl bromide showed two peaks of comparable height, corresponding to m/z values of 122 and 124 (Fig. 5). These correspond to the ^{79}Br and ^{81}Br isotopes at naturally occurring ratio of $\sim 50 : 50$, and the calculation carried out using either parent ion gives similar results.

TABLE III
Maximum Rate of BIIR-DIXP Cure Byproduct Evolution

Cure temperature (°C)	Rate of weight loss (%/min)
150	0.101
160	0.157
170	0.241
180	0.341

Proposed crosslinking mechanism of DIXP *in situ* with BIIR

Based on the above experimental findings a reaction mechanism of DIXP in the BIIR-DIXP composition is proposed.

The general course of accelerated sulfur vulcanization involves a series of complex reactions,[4,9] and the chemistry which can be divided into stages:

1. Reactions between accelerator, activators, and sulfur for the formation of sulfurating species.
2. Crosslinking and post-crosslinking chemistry.

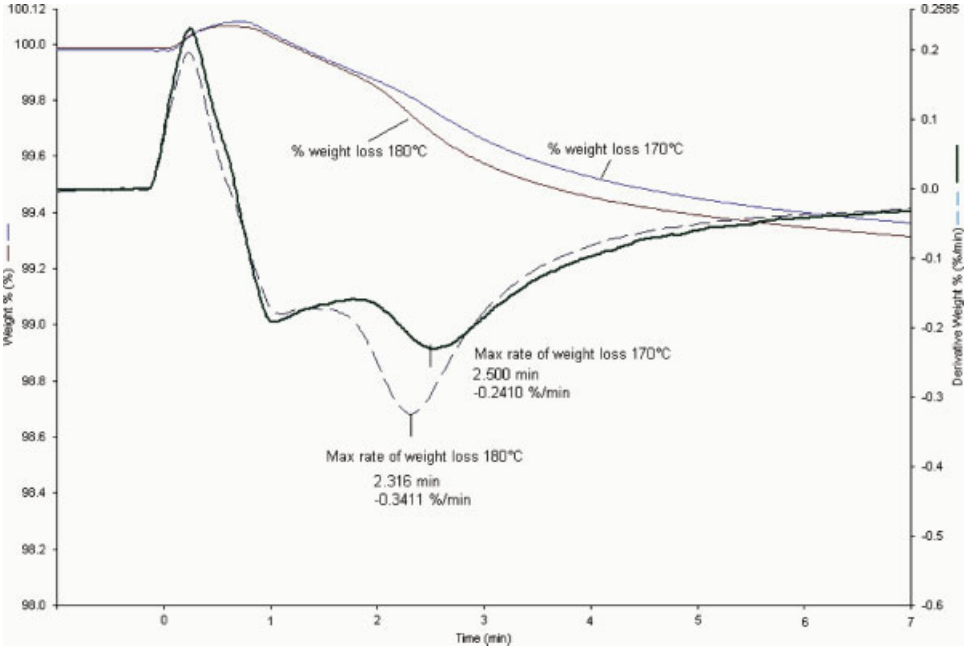

Figure 4 TGA curves of BIIR-DIXP composite at 170 and 180°C curing temperatures. Upper curves show % weight loss and the lower show first derivative curves. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Reactions between accelerator, activators, and sulfur for the formation of sulfurating species

The studies on the crosslinking of halobutyl BIIR[10] using only zinc oxide as a curative show that an allylic carbocation intermediate is formed via the elimination of the halogen. The zinc oxy bromide (ZnOBr) or zinc bromide ($ZnBr_2$) generated by the elimination of halogen catalyses the crosslinking reaction and the formation of crosslinks in the elastomer occurs via the intermediate carbocation. In the BIIR-DIXP composition, the formation of the possible BIIR carbocation (1) is shown (Fig. 6).

It is known that during the induction phase of vulcanization of elastomers containing an accelerator, zinc oxide, sulfur, and stearic acid, the formation of an active accelerator sulfurating complex[4,8] occurs via a number of complex chemical reactions. The addition of molecular sulfur to the accelerator to form this complex can be by either free radical or ionic mechanisms or both simuntaneously.[11–13] The stearate ligands (L) arising from zinc stearate coordinate with the complex, and are believed to enhance its solubilization[14–16] in the rubber . The formation of zinc stearate is by a reaction of zinc oxide and stearic acid reaction with the release of water. The formation of the active DIXP species (2) is shown (Fig. 7).

Generally in elastomers, the above sulfurating species react with another elastomer chain to form active ''rubber-bound'' sulfurating species. Their formation can also be either by free radical or ionic mechanisms[4,8,16,17] and is dependent on the type of the accelerator. However in the case of halobutyl (BIIR-DIXP) composition, the sulfurating species

TABLE IV
Relative Trend of the Abundance of Main GC-MS Ion Fragments

Temperature (°C)	Carbonyl sulfide m/z = 60 (%)	Carbon disulfide m/z = 76 (%)	Isopropyl bromide m/z = 122 (%)
150	76.2	4.2	19.6
160	79.3	4.4	16.3
170	85.7	5.3	9.0
180	86.7	5.7	7.6

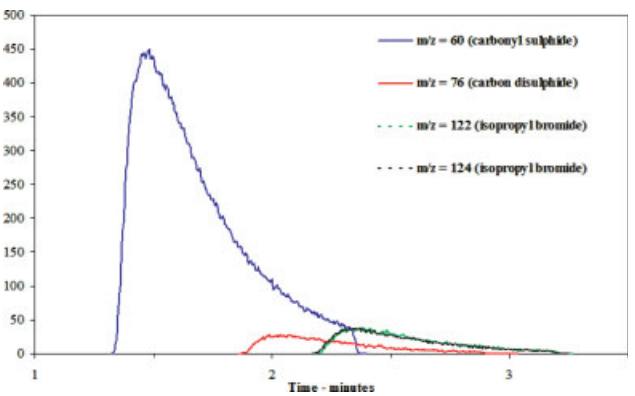

Figure 5 Relative trend of ion fragments from BIIR-DIXP at 180°C. Vertical axis shows response in arbitrary units in thousands. Shown in the lower right are the two comparable height overlapping peaks of isopropyl bromide (m/z = 122 and 124) corresponding to the ^{79}Br and ^{81}Br isotopes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

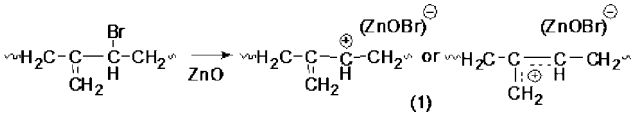

Figure 6 BIIR carbocation (1) formation occurs in the presence of ZnO with elimination of Br^-; zinc oxybromide formed catalyzes the crosslinking reaction.

could react with the carbocation (1) (Fig. 6) formed in the elastomer chain by an ionic mechanism. The carbocation would provide a site for the nucleophilic addition of the isopropyl xanthic ion $(CH_3)_2CHOCSS_x^-$ from the DIXP sulfurating complex to form the active ''rubber-bound'' sulfurating species (3) shown in Figure 8.

Crosslinking and post-crosslinking chemistry

The active rubber-bound precursors thus formed could then react with another elastomer chain in the presence of $ZnO/ZnBr_2$ by a direct or disproportionate reaction to form the initial polysulfidic crosslinks. The polysulfidic crosslink formation in the BIIR-DIXP composition by a direct reaction with an adjacent BIIR chain is shown (4) in the reaction scheme (Fig. 9).

The crosslinking reaction mechanism of halobutyl BIIR-DIXP thus differs from other elastomers like polyisoprene, nitrile, and styrene butadiene in the following aspects:

Zinc oxide has a dual role; it is not only involved in the formation of the active sulfurating species, but it also provides a reaction site in the halobutyls elastomer chain by the creation of carbocations.

The zinc isopropyl xanthic acid and isopropyl xanthic ion byproducts under acidic conditions decompose to form the COS, CS_2 and isopropyl bromide species as determined by GC-MS and is shown in Figure 10.

It is probable that IPA is formed prior to isopropyl bromide and the acidic condition created by $ZnBr_2$, a Lewis acid during the curing of BIIR converts it to isopropyl bromide by a substitution type reaction.[18] It is noted that the formation of IPA and CS_2 in non halogenated polyisoprene elastomer lattices cured using DIXP has been determined by Chakraborty and Couchman.[19]

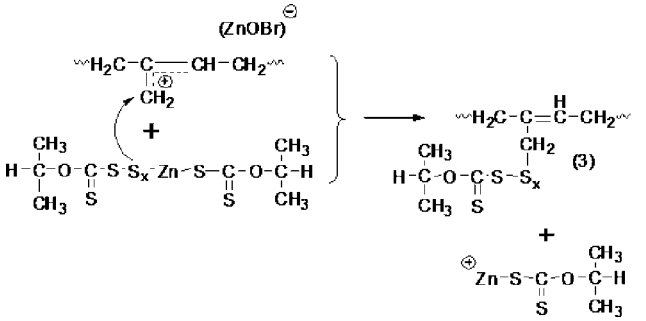

Figure 8 Rubber-bound DIXP sulfurating species (3) formation by the nucleophilic addition of $(CH_3)_2CHOCS_2S_x^-$ ion of the DIXP accelerator sulfurating species and separation of $(CH_3)_2CHOCS_2Zn^+$ ion.

There is also the possibility of the two xanthic ions combining to form zinc xanthate (bis(*O*-isopropyldithiocarbonato) zinc (II)) as shown in Figure 11.

Its fragmentation species are also known to include COS, IPA, CS_2, and ZnS from the thermal chemical vapor deposition studies of this product by Cheon et al.[20] However, the formation of zinc xanthate in the BIIR-DIXP is unlikely because of the high curing temperatures, as Palaty and Joseph[21] have found that it is unstable at 150°C and above.

The polysulfidic crosslinks initially formed in BIIR-DXIP are unstable and during the post-crosslinking stage, part of them would be converted to the shorter di- and monosulfidic crosslinks.[4,16]

Residual cure reaction by products

The GC-MS analysis of volatiles collected from the heating of a cured sample of BIIR-DIXP and from its acetone extract did not show the presence of residual cure byproducts.The acetone extract however did show very low levels (0.5–30 μg/g) of non DIXP residual species (Table V).

These originate from the BIIR-DIXP formulation additives (Table I). The residual stearic acid and its related species; palmitic acid, ethyl palmitate, and isopropyl palmitate have been safely used at up to 25% concentration in the preparation of cosmetic products such as eye lotions, skin makeup, lipsticks, antiperspirant sticks, skin care, and shaving products.[22,23]

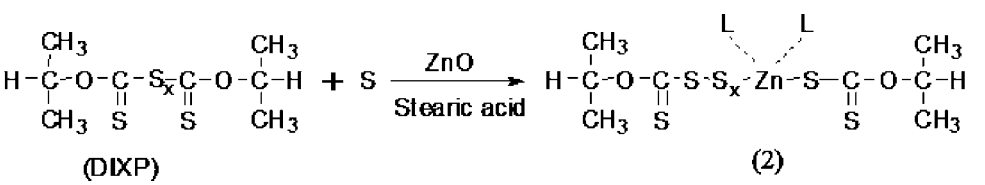

Figure 7 DIXP accelerator species (2) formed by the insertion of zinc and sulfur; stearate ligands (L) coordinate to this complex and aid its solubilization in BIIR.

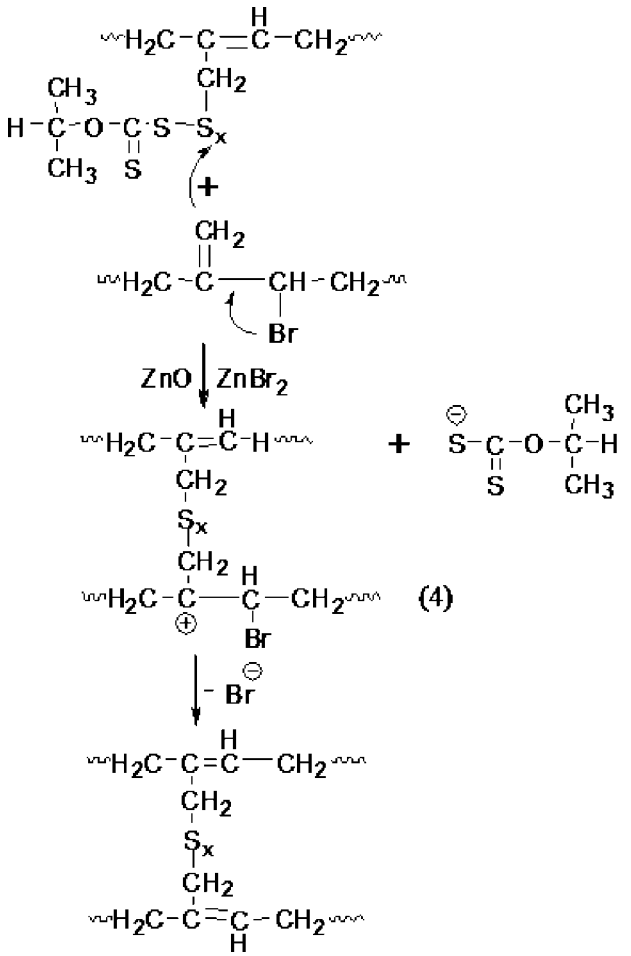

Figure 9 The formation of initial polysulfidic crosslinks (4) occurs by the ionic addition of the rubber-bound DIXP species to an adjacent BIIR chain; $(CH_3)_2CHOCS_2^-$ and Br^{-1} ions are separated in the reaction.

The parental BIIR molecular ion fragments were present at low levels (3–19 μg/g), and the use of BIIR in drug vial seals is well established. The antioxidant 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (BHT) is present at a very low level (1 μg/g), and its use in food stuffs and topical pharmaceuticals is established.[24]

Taking into consideration the low level of residual species obtained by acetone extraction, and the precedence of their use in pharmaceutical products, the BIIR-DIXP composition is potentially suitable for use in pharmaceutical medical devices.

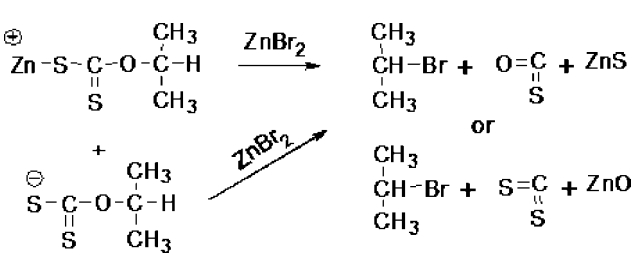

Figure 10 Conversion of xanthic ions $(CH_3)_2CHOCS_2Zn^+$ and $(CH_3)_2CHOCS_2^-$ in the presence of Lewis acid $ZnBr_2$ to volatiles isopropyl bromide, COS and CS_2.

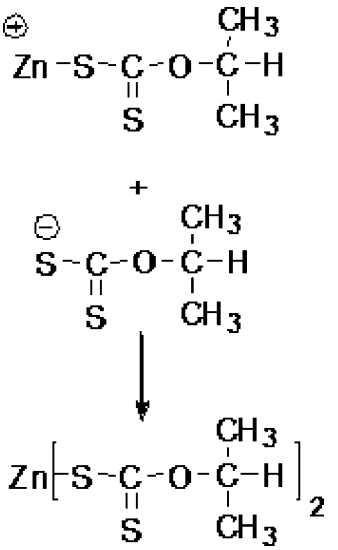

Figure 11 Formation of zinc xanthate (bis(*O*-isopropyldithiocarbonato) zinc (II)) by the addition reaction of xanthic ions $(CH_3)_2CHOCS_2Zn^+$ and $(CH_3)_2CHOCS_2^-$.

CONCLUSIONS

The main gases evolved during the curing of BIIR-DIXP composition were COS, CS_2, and isopropyl bromide and are associated with the formation of the active rubber-bound DIXP sulfurating species required for the crosslinking reaction.

A reaction scheme for the DIXP accelerator *in situ* with BIIR has been proposed based on the evolved gases determined during curing, and taking into account the generally accepted mechanism of crosslinking elastomers using sulfur-based accelerators.

TABLE V
Residuals from the Acetone Extract of BIIR-DIXP

Component	μg/g
Pentadecane	0.5
Hexadecane	0.1
7-Methylheptadecane	5
3,5-di-*t*-butyl-4-hydroxybenzaldehyde (BHT)	1
Palmitic acid	30
Ethyl palmitate	–
Isopropyl palmitate	27
Stearic acid	18
Isopropyl stearate	29
Unknown 1 (possibly S-based)	19[a]
Unknown 2 (possibly S-based)	8[a]
Unknown 3	3[b]

[a] Based on a calculated molecular weight of 292.
[b] Based on a molecular weight of 281; assumed to be the parent molecular ion fragments.

Analysis of the cured BIIR-DIXP shows that the DIXP is totally consumed during the cure reaction. Even the acetone extract of the cured BIIR-DIXP did not show any of the DIXP cure reaction byproducts.

The composition does have very low levels of residual species originating from the non-DIXP formulation constituents. These species have been safely used as additives in pharmaceutical type preparations. The BIIR-DIXP composition thus, can be potentially used in sealing medical devices.

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