A Study of the Reaction of Chlorosulfonyl Isocyanate with

Polyisoprenes

by

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Submitted in Partial Fulfillment of the

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ABSTRACT

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The human body, though unequalled in design and function, is prone to the effects of aging, diseases and accidents. In these cases, the intervention of science is necessary to preserve the quality of life, or even life itself. When one is considering artificial implants, the most important factor that determines biocompatibility is blood compatibility. In general, the more blood compatible an implant is, the more biocompatible that implant is.

In this paper the reaction of chlorosulfonyl isocyanate ($Cl-SO_2-N=C=O$) with various compounds, especially polyisoprenes, will be examined. The addition products (substituted beta lactams) can then be hydrolyzed to give compounds that have many structural features in common with heparin, e.g., sulfamate and carboxylate groups, as shown by Graf (1,2). Heparin, nature's own anticoagulant, is the perfect compound to model. Using this technique, it should be possible to obtain a more biocompatible surface (3).

Sederel, et al (4), have shown that this methodology can be used to develop an artificial anticoagulant with activities near that of natural products. The resulting compound has many of the same functionalities as heparin, primarily the sulfamate and carboxylate groups, and shows excellent blood compatibility. They were also able to show that as the sulfamate content increases, so does the anticoagulant activity of the resulting compounds.

The work above suggests the methodology of the current paper, carrying out the reaction of chlorosulfonyl isocyanate with polyisoprenes and varying the degree of substitution in order to obtain a polymeric system with the maximum biocompatibility and the desired polymeric chain flexibility. This system could be used to synthesize implants with the best possible characteristics. The present work also involved the improvement of the initial yields and general debugging of the experimental technique to give optimum yields of the desired product (3).

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CHAPTER I

INTRODUCTION

The use of artificial materials to replace defective parts of the body is not new. Many of the so-called current developments in biomaterials engineering have their origins in the beginning of this century. For example, modern heart lung machines are descendants of equipment developed in 1885 by Frey and Gruber (5). In many circumstances implants can be traced back even earlier. In fact, attempts at replacing defective body parts can be traced back to the earliest records of man himself. An example of this would include sutures in use around 4000 BC (6). Of course, the success of the implants increases continuously - primarily due to our greater understanding of the interactions involved and more advanced synthesis techniques (7). Overall, our attempts are much more successful than those of our ancestors. The development of artificial implants has skyrocketed since the early 1950s. Although present attempts at duplicating body organ functions are more successful than the simple attempts of our ancestors, it should be noted that today's artificial implants are far from perfect. A lack of biocompatibility is a major problem.

BIOCOMPATIBILITY

Biocompatibility refers to the manner in which a prosthetic or biomedical device interacts with body fluids and tissues (8). Perhaps the best known example of this is the Jarvik 7 artificial heart. It is constructed of a poly(ether urethane urea) material, and has enjoyed a great deal of media coverage. Despite extensive press coverage, even this technological achievement is far from perfect. Often it is necessary to administer anticoagulants such as heparin, dicumarol, or 4-hydroxycoumarin to the implant recipient to prevent the blood from clotting or forming emboli (7). The

clot is caused by the implant that is being used to maintain the patient's life. This is often in addition to the other forms of rejection that may also occur. In general, today's implants are better than nothing for those cases in which the implant is being used to maintain life. The implants devised are vastly inferior to the healthy parts of the body mimicked. What is needed is a better material with which to construct the implants. Of course, the implant use will determine the characteristics of the best material for the job (7). As an example, a device that would make a good heart valve, requiring great flexibility, would not make a good artificial jaw, which would require great rigidity. As an example of the necessity of the proper flexibility, we will consider blood vessels. The elasticity of blood vessels allows them to cope with the stresses they experience in the body. There is also a great deal of evidence that this elasticity may play a role in determining blood compatibility. Owing to the blood pressure and the ways that the blood flows through the body (i.e., the pulsing nature of blood flow), the walls of the blood vessels experience various stresses, including compressional and tensile stress in the circumference and longitude. These stresses will vary depending on the geometry of the blood vessels, such as bends and branches that disrupt the smooth flow of blood. The shear stress will vary from zero near the center of the vessel to a maximum value at the walls. The stress on the vessels resulting from blood flow is highest in the human aorta and major arteries, intermediate in the vena cava, and smallest in the capillaries. Also, as a result of the external pressure on the blood vessels (resulting from the tissues surrounding those vessels), at a certain critical closing pressure, small vessels such as capillaries may collapse and there will be no blood flow. Of course, the implants will require either subcutaneous or percutaneous implantation, but these operational problems have, in general, been solved and need not concern us here. However, the body has natural defense mechanisms that will become active and try to destroy the polymers. Also, although the body is quite able to defend itself, it is not invulnerable. In what follows, three important problems associated with implanted materials will be briefly discussed: the effects on the implant by the body, histological considerations, thrombosis and blood interactions.

EFFECTS ON THE IMPLANT BY THE BODY

The body provides a surprisingly hostile environment for all types of implants. Not a great deal is known concerning the actual mechanism that the body uses to degrade implants. There are a great number of possibilities that should be considered. For example, the body contains a great deal of water. Hydrolytic breakdown of polyester- or polyurethane-based implants may be initiated by means of a direct chemical attack by hydrogen ions, hydroxyl ions, or by water molecules. The combined effects of oxygen, chloride ions, water, salts, and pH effects lead to an environment that is corrosive to stainless steel, polyethylene, and many other implant materials. The role of enzymes is not completely known, but provides another possible route of degradation of implants. Cleavage of the carbon-carbon bonds in the polymer backbone or on pendant groups can occur, often much more easily than expected. This can be disastrous to the implant since these pendant groups may be essential in determining biocompatibility, or, the implant may be totally destroyed if the cleavage is severe enough. ^{14}C- labeled polyethylene has been found to release radioactive compounds in the urine of rats less than 30 days after the rats received the implants. Polystyrene has been shown to release ^{14}C 21 weeks after implantation, and poly(methylmethacrylate)- implanted rats release ^{14}C 54 weeks after implantation (9). The degradation of such polymers could be initiated by free radicals in the tissue, or by oxygen. The oxidation-reduction enzymes are inaccessible to the polymer since these enzymes are in the mitochondria. The human body is a hostile environment, even to aliphatic compounds. Almost all places in the body expose the implant to an aqueous environment. Depending upon where the implant will be placed, it could be subjected to relatively high acid conditions as well. Given these conditions, hydrolysis will occur when it is possible to hydrolyze any part of the implant. Lyman (8) notes that this occurs in materials that are hydrophilic more rapidly than it does in hydrophobic materials. Polyesters and polyamides are especially likely to undergo this type of degradation, although this may occur with other types of

polymers too. The body will cleave the polymer into low-molecular weight units that could travel throughout the body. Of course, these materials could be toxic.

Oxidation of functional groups will occur when possible. This will convert alcoholic groups to carbonyl compounds, aldehydes to carboxylic groups, or lead to the formation of carbon-carbon double bonds. Alkyl cyanoacrylates readily undergo this type of degradation and are highly toxic because they release formaldehyde and cyanoacetates.

Loss of H_2O or NH_3 groups from the polymer is possible with certain functional groups, possibly leading to the formation of a new double bond in the polymer chain, which may cause a change in the elasticity of the polymer.

Of course, double bonds which are previously present in the implant are subject to reactions forming alcohols, etc. Any double bonds present (and certain other functional groups) can lead to crosslinking of the polymeric chains which will reduce the elasticity of the implant. This may be very important in the function of the implant. For example, it could lead to death if the implant under consideration were a heart valve.

Formation of new carbon-carbon bonds may also occur. These may be within the polymer, or between polymer chains. Crosslinking may occur as a result, or the attachment and nature of the pendant groups may be radically changed.

There may be a loss of plasticizer, catalyst, or other material from the implant. This is why poly(vinyl chloride) is so rarely used, since the addition of a plasticizer and the use of a catalyst is commonplace during it's manufacture. The leached-out material may be carcinogenic, toxic, or thrombogenic (this will be discussed later).

Other forms of degradation will also occur, depending upon the nature of the implant and where in the body the implant is placed. Ultimately, the body will cause changes in durability of the implant arising from a variety of causes. Or, the body may eventually damage the implant to the point that it is no longer functional.

In fact, one of the major adverse effects that an implant has on the body is thrombosis. Blood compatibility will depend on a variety of factors, such as the flow conditions (is the blood flowing or static?), blood flow patterns, whether the blood is

venous or arterial, etc. However, the nature of this particular type of interaction (thrombosis) requires that it be considered independently.

Table 1 lists several considerations that an implant should not cause (modified from 8, 9, and 10)

TABLE 1. EFFECTS OF IMPLANTS ON THE BODY

1. Thrombosis/ abnormal intima formation.
2. Alteration of the configuration or stability of any cellular or soluble materials in blood that may lead to cellular aging or hypersensitivity.
3. Destruction of blood cells.
4. Alteration of plasma proteins.
5. Destruction of enzymes.
6. Depletion of electrolytes.
7. Adverse immunological responses.
8. Damage to adjacent tissues.
9. Cancer.
10. Toxic effects.
11. Allergenic effects.
12. Interference with normal clotting.
13. Foreign body reaction.

Effects of the body on the implant arise in many forms equally as diverse. All too often, the implant has an adverse effect on the body, and the body attempts to alleviate this by rejection of the implant. This class of interaction is perhaps best considered as two different topics: reactions with blood and reactions with tissues. First, the reactions with the tissue will be examined.

1. Adverse effects due to the physical nature of the implanted device. Smooth shapes are in general less readily rejected than shapes with rough edges (given the same composition). The rough edges are irritating and the body responds by trying to immobilize the implant with fibrous tissue encapsulation. This usually causes adverse effects by interfering with the fluid transport in the body- a bladder implant may interfere with urination if fiber growth is severe. If the implant is being anchored, this may be used to advantage by providing holes through which the fibrous tissue can grow.

2. The body may lyse materials off the implant. This may lead to local or systemic effects, as though the lysed material had been injected into the body. Certainly the lysing of a cyanide moiety could be disadvantageous, if not fatal. This will be covered in greater detail shortly, but included here are plasticizers that may be present in the implant material.

3. Other effects. Primary among these are the histological aspects of implantation. This will be discussed later. A good polymer implant material should have the following characteristics (8, 9):

1. Can be reproducably obtained as a pure material;
2. Can be fabricated in the desired form without being degraded or adversely changed;
3. Will have the needed physical and mechanical properties to perform its end use;
4. Can be sterilized without change in properties or form;
5. Will not have its physical, chemical, and mechanical properties altered by the biological environment.

Commercial polymers are relatively impure materials. There are several sources of impurities, with origins such as variables in the preparation of polymers, processing of polymers, (molecular weight, molecular weight distribution, branching of polymer chains, changes in stereoregularity, abnormal linkages, monomer distribution in copolymers, etc.) and from additives to the polymer, both intentional (antioxidants, plasticizers, etc.) and unintentional (degradation fragments, impurities in monomer, solvent or monomer residues, contamination from processing equipment, catalyst residues, etc.). All of these variables can alter the compatibility of implants in a variety of ways. Therefore, the background of the plastic used for implants must be well known (9). When working with polymers, it should be kept in mind that commercial products usually are complex mixtures containing a vast variety of ingredients: plasticizers, catalysts, fillers, stabilizers and unpolymerized monomer.

Histology

Almost immediately after implantation, the body will deposit a coating of plasma proteins on the implant (9, 10, 11). This is completed in about 3 seconds (9) and, due to it's rapidity, is often referred to as a protein snow. The nature of this coating will depend upon the implant's surface characteristics and the nature of the protein coating will change with time. The nature of this coating will ultimately determine the biocompatibility of the implant (7, 10). Adsorbed proteins may then be enzymatically degraded and replaced by other proteins, they may undergo various conformational and configurational changes, or they may be destroyed (11). These changes may lead to platelet aggregation. When thrombus particles are dislodged, emboli can be formed. Implants can also form emboli indirectly by formation of minute platelet and fibrin emboli in the blood stream itself due to the release of thromboplastin. There are several routes of acceptance/rejection that may then be followed:

1. Immediate rejection. Irritation may be either chemical and/or biological and rejection is immediate. In the case of percutaneous implants, this may actually involve pushing out the implant via fibrous tissue. Obviously, this is the worst case of rejection.

2. Delayed Rejection. This may take several months or even years. It is accompanied by round cell inflammation, giant cell formation and unorganized vascular patterns. This is an "uneasy" acceptance of the implant.

3. Encrustment without reaction. The implant is covered completely with fibrous tissue leading to an isolation of the implant. Eventually, the implant may be considered as no longer being in the body if the encrustment is severe enough.

4. Encystment with an incomplete fibrous capsule. Cellular reaction is continuing and ultimate rejection is pending.

5. Slow absorption of the implant. Giant cells dominate the histological pattern. The implant is slowly being dissolved by the body.

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6. Incorporation (complete acceptance) of the implant. Of course, this is the ideal implant, functioning almost identically as the body part that is being replaced without the usual required chemical therapy (such as anticoagulants). Unfortunately, complete acceptance of an implant is seldom ever obtained. Instead, the implants are such that they are required simply to maintain life, they do not restore the quality of life.

The above are general types of interaction that usually occur which will determine whether or not the implant will be accepted: effect of the body on the polymer and effects of the polymer on the body. However, the biggest problem with implants that contact the blood is clotting.

Thrombosis

Blood coagulation, though very complicated, may be considered to occur by a rather simple cascade mechanism (12, 13). In the generally accepted scheme, a clotting factor is activated either by an internal (intrinsic thrombosis) or an external (extrinsic thrombosis) event. This activated factor then causes the activation of the next clotting factor in a sequence until, in the final step, fibrinogen present in the blood is converted to fibrin (9, 12, 13). The clotting process, according to this scheme, may be divided into 4 separate stages. Thromboplastin IX is generated in the first stage, thrombin IIa in the second, and fibrin in the third. The final step is that of fibrin formation and fibrinolysis. The fibrin exists as a three- dimensional network that actually entraps blood components. In this way, the blood clots to form an

actual physical plug. This scheme is shown in Figure 1.

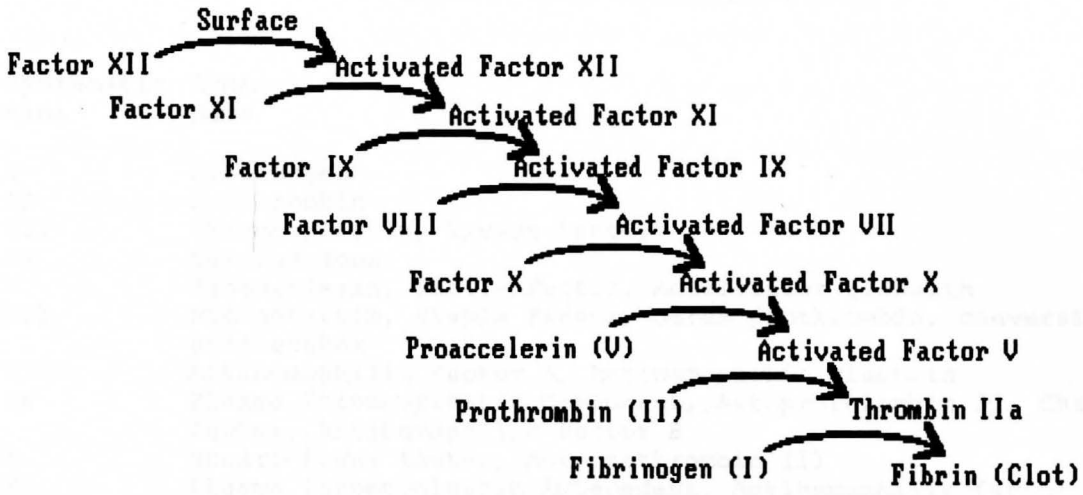


Figure 1. Blood Coagulation Mechanism

There are 12 clotting factors present that are generally agreed upon (12, 14). Unfortunately, there are also several nomenclature systems in use, including a large number of trivial names. The most systematic nomenclature system simply assigns roman numerals from I to XIII to each of the factors (there is no factor VI). These names are listed in Table 2.

TABLE 2. BLOOD COAGULATION FACTORS

Systematic Name	Common Name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin, Tissue Factor
IV	Calcium ions
V	Proaccelerin, Labile Factor, Accelerator globulin
VII	Proconvertin, Stable Factor, Serum prothrombin, conversion accelerator
VIII	Antihemophilic factor A, Antihemophilic globulin
IX	Plasma Thromboplastin Component, Autoprothrombin II, Christmas factor, Antihemophilic Factor B
X	Stuart-Power factor, Autoprothrombin III
XI	Plasma Thromboplastin Antecedent, Antihemophilic factor C
XII	Hageman Factor
XIII	Fibrin Stabilizing factor, Fibrinase, Fibrinase Laki-Lorand factor

Blood Interactions

The number and variety of important implant devices is great. All implants and devices contain materials which are recognized by the body as foreign. This results, in addition to the interactions discussed earlier, in a process of thrombosis, sometimes followed by formation of thromboemboli. This process is generally agreed to involve a sequence of protein adsorption steps followed by blood cell interactions (11, 15, 16). The routes of blood clotting may readily be separated into three general categories: 1. The extrinsic pathway. 2. The direct intrinsic pathway. 3. The indirect intrinsic pathway (1).

The extrinsic pathway occurs as a result of shock or trauma caused by external injury. This injury results in tissue damage, and the damaged cells release tissue factor (Factor III, or thromboplastin) and Antihemophilic factor A (factor VIII). Release of these two factors results in activation of factor X (the Stuart-Power factor), triggering a cascade of enzymatic cleavages of other proteins and enzymatic reactions (in a sequence similar to part of the intrinsic mechanism), thereby leading to

thrombosis and fibrin formation (12, 13). The clotting is, of course, necessary in cases of external injury. Indeed, there are times when materials which assist in rapid clotting are needed in surgical procedures: particularly in brain surgery and the surgery of other organs such as the liver. An additional example is the case of extreme bodily damage where, again, one needs to initiate clotting rapidly. Any fine gauze, wool, or foam may be used to promote the formation of clots. In internal surgical applications, it is necessary that they be absorbed by the body after clot formation and healing is complete (2).

The intrinsic pathway occurs as a result of several possible events, including the rupture of red blood cells, involving a series of enzymatic activation steps presumed to begin with the surface activation of Factor XII (the Hageman factor), and continues to the formation of fibrin on this surface. At this point there is a clot present in the body (9, 11-13).

Implantation of synthetic surfaces into the vascular system may bring about formation of emboli in both direct and indirect fashion: 1. The direct mechanism of implant-induced embolism induces the initial formation of a thromboembolic deposit on the surface of the implant followed by loosening and dislodgment of embolic particles into the blood stream. 2. The indirect mechanism, which is thought to involve the formation of minute platelet and fibrin emboli within the blood stream itself, is due possibly to the release of thromboplastin corpuscles. This process is analogous to that seen in certain instances of wide-spread intravascular coagulation. There will be a resulting microinfarction of the tissues and depletion of clotting factors (10, 14, 15). Another route is the adhesion and aggregation of platelets at the foreign interface, leading to the formation of a platelet thrombus on that surface (11, 17). This adhesion has three phases: the first one, during which no adhesion seems to occur; the second one, during which platelets adhere; and a third one, during which adhered platelets are leached out or lead to an occlusive thrombosis. The occurrence of these phases and their respective duration depends upon many factors, such as the solvents used during the chemical treatment of the surface, effectiveness of washing of the modified surface, and the chemical modification of the new surfaces obtained. The best conditions lead to

materials with the longest phase without any adhering platelets. The last two major mechanisms discussed above are shown diagrammatically in Figure 2 (this diagram is modified after references 15 and 17). Both of these routes (I and II) lead to thrombus formation and possible emboli formation.

Flowing Blood

Foreign Surface----------Protein Adsorption

Protein Adsorption ---------- (I) or (II)

(I). Platelet Aggregation "White Thrombus"

(II) a. Fibrin formation
b. Platelet aggregation
c. Trapped Red Blood cells "Red Thrombus"

Figure 2. Internal Blood Coagulation Mechanism

High flow rate (arterial) blood promotes formation of emboli that are composed mainly of platelets (I above). Slow (venous) flow conditions lead to thrombi composed of red cells and platelets entrapped in a fibrin mesh (II above). Sometimes, a smooth layer of fibrin may also be deposited. Of course, it should be remembered that these thrombi may dislodge to become emboli, and the resulting emboli may lead to infarctions. The cause and prevention of thrombosis and emboli formation at implant surfaces continues to elude a significant number of researchers worldwide. Most researchers in this field agree that there are three key factors which can interact in varying ways and varying degrees, leading to the process of thrombosis and embolization at implant surfaces. They are: (1) the biomaterial, (2) the blood flow (or hemodynamics, (17)) and (3) the biological environment. Some of the most important biomaterial surface parameters are listed in Table 3.

TABLE 3. SOME IMPORTANT BIOMATERIAL INTERFACE PARAMETERS WHICH MAY INFLUENCE BLOOD MATERIAL RESPONSE (modified from 9, 14)

1. Surface composition
   a. polar versus nonpolar groups.
   b. acidic versus basic groups.
   c. hydrogen bonding groups.
   d. immobilized biomolecules,drugs.
   e. double layer effects.
   f. surface energetics.
   g. presence of impurities, particles.
2. Water sorption.
3. Surface crystalline/amorphous structure.
4. Surface roughness, smoothness, and porosity.
5. Mechanical compliance of the surface (in the bulk sense).
6. Regular or irregular distribution of domains of the above.
7. Bulk leachables (including biomolecules), degradation products.

Whicher and Brash (16) note that various specific chemical characteristics (e.g., negative charge, hydrophobic/hydrophilic balance) on the surface of materials used for blood contact influences thrombogenicity. One theory is that the surface of the implant should repel blood cells and platelets as well as being capable of adsorbing and exchanging Ca^{2+}, Na^{+}, K^{+}, Cl^{-} and bicarbonate ions (15, 17). Even more generally, since the endothelium (the lining of natural blood vessels) has a net negative charge (-3 to -13 mv), perhaps negatively-charged surfaces would be more compatible than neutral or positively-charged surfaces (18, 19). Several researchers, assuming that an anionic surface would be more blood and biocompatible, prepared and tested a variety of ionic hydrogels. The lining of the arterial wall contains the highly ionized polysaccharides chondroitin sulfate and heparin sulfate (12, 13, 18). Consequently, the negatively-charged arterial wall repels the similarly charged coagulation factors of the blood (17, 19, 20) such as fibrinogen, platelets, and the Hageman factor, which is thought to initiate clotting (13). Interestingly enough, both moderately anionic and cationic hydrogels as well as neutral species have been shown to be more compatible than highly ionic species of either charge.

There is a negative zeta potential at the surface of the blood vessels resulting from blood flowing over the surface of these blood vessels (14, 21, 22). It would seem, therefore, that any surface that comes in contact with the blood should have a similar

zeta potential. However, there has been a great deal of difficulty in developing an implant with a permanent zeta potential on the surface. Also, the zeta potential has been noted to change upon implantation (14, 22). Shifts have been noted in nylon 66 with water acting as an electron donor (14, 22). Later research was able to demonstrate that there is no relationship between the sign and magnitude of the zeta potential of the surface (measured in Ringer's solution) and the clotting time. The zeta potential of a plastic surface is neutralized when the implant is placed in the body (21). This was attributed to the adsorption of blood proteins onto the surface. Another suggestion was made (15) that conductive surfaces should permit the development of a negative charge in situ.

Other studies have targeted on the surface of an implant and its compatibility, but there has been limited success. Some researchers have suggested that the wettability of a surface improves compatibility, while others suggest that there is no relationship between clot-promoting action and the wettability of the surface. Also, Kronick (23) comments that hydrogels are generally more compatible than other polymers with blood both in vitro and in vivo. A major problem with hydrogels is their lack of mechanical strength and toughness. The mechanical strength can be improved by reinforcement with synthetic fabric-mesh or carbon fibers; but this will not necessarily mean that the elasticity of the implant will not change with time. Hydrogels have had a variety of problems that have prevented their widespread use as implants. The coatings are generally not compatible with the materials that they are being grafted (or coated) onto, because the two phases, hydrophobic and hydrophilic, do not attract each other. Therefore, the interface between the two materials will be unstable and the hydrogel may be easily removed.

One thought (23) concerning the success of implants is that the free energy for forming the interface between the implant and the blood should be as small as possible, ideally it should be zero. If it is not small, the components of the blood will deposit on the implant. The free energy for forming the interface will be smallest when the surface of the implant most nearly resembles the environment in which it will be placed.

Another study of interest was conducted by Lyman, et al (24). These researchers studied the relationship between the elasticities of the implants and their acceptance by the bodies of dogs. The implants prepared were copolymers of polyether-polyurethane-urea. The results of this study are summarized in Table 4. (Percent survival refers to the percent of dogs surviving).

TABLE 4

PHYSICAL PROPERTIES AND TEST ANIMAL SURVIVAL OF 4 mm ID COPOLYURETHANE VASCULAR PROSTHESIS

Prosthesis Series	I	II	III	IV	Dog Artery
Elasticity	11.2	10.8	7.5	5.5	7.4 +/- 1.1
Porosity ($mL/cm^2/min.$)	37	33	34	34	
Number Implanted	15	9	11	4	
Surviving at 1 Month	4	3	9	3	
% Survival	27	33	82	75	

The effect of the elasticity of the implant plays a vital role in determining the success of the implants. Lyman further notes (24) that the implants currently in use have changes in diameter (resulting from the pulsing of blood through the implant) of less than 1% compared to 10 to 15% in natural blood vessels.

Heparin

Anticoagulants are used clinically to prevent and treat thrombi, emboli, myocardial infarction, and are given to patients with prosthetic implants (25). It is necessary to administer anticoagulants such as heparin, dicumarol, or 4-hydroxycoumarin to the implant recipient to prevent his/her blood from clotting or forming emboli. When given to patients, heparin is the most effective, safest and best way to prevent the formation of and to treat thrombi and emboli. But frequent injections and high costs

are major disadvantages in heparin therapy. Heparin is a mucopolysaccharide generally agreed to be composed of partially sulfated alpha-D-glucuronic acid and 2-amino-2-deoxy-alpha-D-glucose joined by 1,4 linkages (12, 25). The generally-accepted structure is shown in Figure 3, and has a molecular weight ranging from 6,000 to 40,000 (25).

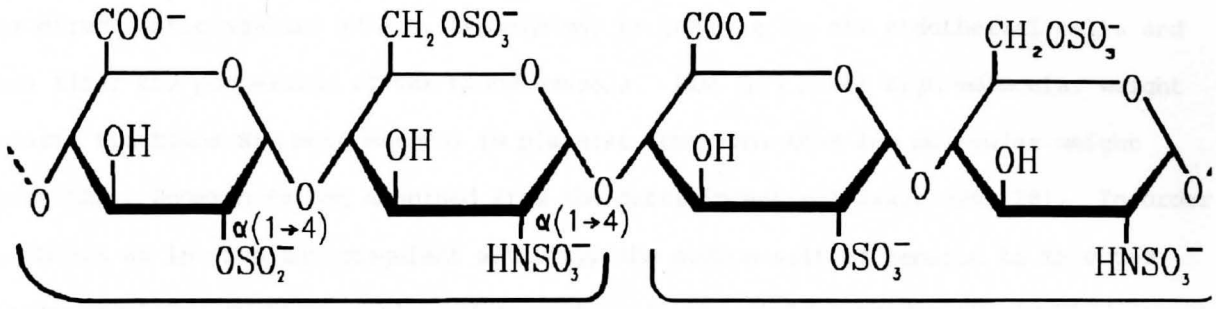


Figure 3. Structure of Heparin

Heparin inhibits clotting of blood both in vivo and in vitro, activating antithrombin III in plasma, and has been shown to inactivate factors IXa, Va, Xa, XIa, thrombin, and factor XIIa (the "a" indicating activated factors). Heparin also enhances the lysis of fibrin by inhibiting antifibrinolysin, thereby reducing thrombi and emboli. Heparin has been shown to induce platelet aggregation independently and to enhance platelet aggregation. It inhibits platelet adhesion, and prevents platelet disintegration and release of phospholipids. Other attributes have been claimed in the past, but have since been disproven (25).

The anticoagulant activity of heparin has been related to several factors. These include: 1. degree of sulfonation, 2. degree of carboxylation, and 3. molecular weight (25). The effect of the degree of sulfonation is readily proven by hydrolysis to remove the sulfate groups. This has been shown to decrease the anticoagulant activity. Similar techniques demonstrate the dependence on the carboxylic content (25). By

fractionation of heparin by molecular weight, it has been shown that the anticoagulant activity directly depends on molecular weight (25). In it's clinical use, heparin promotes bleeding from open wounds and mucous membranes (especially in large dosages), has been thought to decrease blood sugar, and may cause fever. Cerebral hemorrhage can be caused in susceptible patients, especially older women. Hypersensitivity and inhibition of aldosterone and testosterone have also been reported (26). In addition to its direct anticoagulant effect, heparin may be taken up by the endothelial cells and thus alter the properties of the blood vessels. Kim (27) notes high molecular weight heparin fractions are more harmful to platelet functions than low molecular weight fractions. Heparin is not absorbed from the gastrointestinal tract (26, 28). In order to obtain an in vivo anticoagulant activity, the sodium salt of heparin is injected intravenously or subcutaneously. Most workers in the field consider the ideal dosage to be 35 USP units per kilogram of body weight. The anticoagulant half-life of heparin, intravenously, varies from 1 to 2 hours (28). The usual intravenous dose of heparin is an initial 5,000 units followed by doses of 5,000 to 10,000 units every 4 hours, giving a total of 20,000 units of heparin per day. Heparin is metabolized in the liver by partial cleavage of the sulfate groups. It is then excreted by the kidneys as a partially-sulfated product, but as much as 50% may be excreted unchanged when high doses are given. The partially desulfated product excreted has been shown to be about one half as active as heparin in anticoagulant activity.

Heparin sulfate is a polysaccharide found as a by-product in the preparation of heparin from lung and liver tissue. It has a lower sulfate content and its glucosamine residues are partially acetylated and N sulfated. Heparin sulfate isolated from the aorta has also been shown to have essentially no antithrombin activity (25).

How can this information concerning heparin be put to use in the designing of an implant? The anticoagulant activity of heparin has been shown to depend on the sulfamate, sulfate and carboxylic groups. Yet, due to the adverse effects of heparin, the continual injection of heparin is undesirable. Therefore, it would appear that what is needed is a way to put these functional groups on an implant or implanted surface.

The CSI Reaction

During the late 1950s Graf (1, 2) synthesized and expounded upon the uses of a new compound which was formed by the reaction of sulfur trioxide and cyanogen chloride and is known either as N-carbonyl sulfamoyl chloride (NCSA) or chlorosulfonyl isocyanate (CSI). The structure is:

$$Cl-SO_2-N=C=O$$

Its chemistry is similar to that of other isocyanates, but in many ways the chemistry is more complex. Aldrich (the largest producer of CSI) calls it the most reactive of all isocyanates. Graf attributed this reactivity to the particularly high degree of electro-positive polarization due to the direct attachment of the isocyanate group to the strongly electron attracting sulfamoyl chloride. This compound is a colorless liquid with a melting point of -44°C and a boiling point of 107°C. It is also stable to at least 300°C, but may slightly decompose back to the starting materials. It fumes on exposure to air and produces a choking sensation. It reacts quite violently with water to form sulfamic acid, hydrogen chloride and carbon dioxide. Its extreme reactivity makes it highly corrosive, requiring great care in its use. This also limits the choice of solvents that may be used with it. The only solvents that can be used are extremely unreactive and include chlorinated hydrocarbons and aliphatic hydrocarbons. Graf (1) mentions that very often technical CSI contains traces of sulfonyl diisocyanate and pyrosulfuryl chloride, but these do not generally interfere with its reactions. On the other hand, chlorosulfonyl isocyanate may also be contaminated with sulfur trioxide. Even trace amounts of sulfur trioxide are disastrous, particularly in the reaction with olefins. CSI-containing sulfur trioxide will rapidly darken the walls of polyethylene vessels. Graf considers the reaction with the olefins to be the most interesting reactions of N-carbonylsulfamoyl chloride. The reaction products are an unsaturated N-chlorosulfonylamide and a beta-lactam-N-sulfonyl chloride. The structure of the

product of the reaction of 2-methyl-2-butene and CSI is shown (Figure 4).

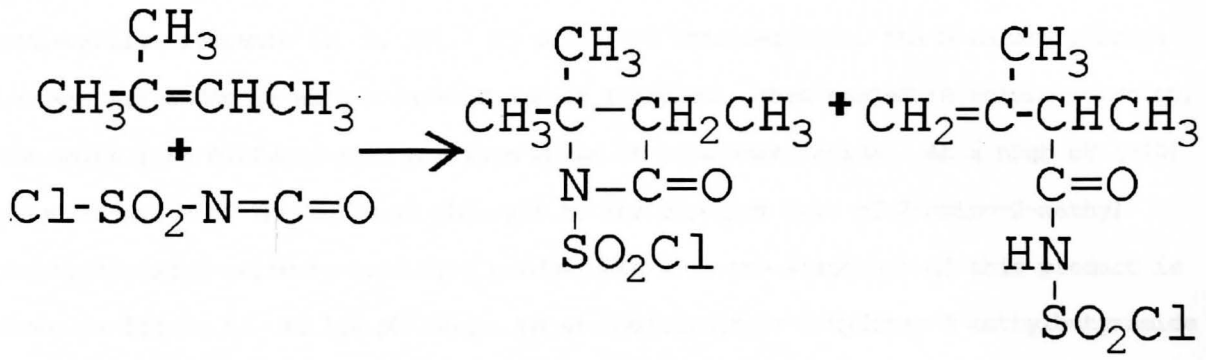


Figure 4. 2-Methyl-2-Butene / CSI Reaction.

The ratio of the conversions by the two routes are determined by the constitution of the olefin. For 2-methyl-2-butene this ratio is 70% of the lactam structure and 30% of the amide structure (1). Generally this ratio cannot be altered by changing either the solvent or the reaction temperature. The lactam structure, however, predominates. In accordance with the Markovnikov rule, the nitrogen in CSI, which carries a partial negative charge, adds on to the carbon atom carrying the smallest number of hydrogens in the olefin (1, 32, 33). Graf also mentions (2) that beta-lactams substituted in the 3-position (adjacent to the carbonyl group) cannot be prepared because the lactam formed has the nitrogen of the CSI attached to the more highly substituted carbon atom of the olefinic bond in Markovnikov fashion. (The nitrogen atom is given the number 1, the carbonyl is number 2, and the two remaining carbon atoms are numbered sequentially).

The N-chlorosulfonyl lactams are generally relatively stable, though their stabilities can vary widely. On prolonged storage or heating, for example, they generally undergo primary rearrangement into unsaturated N-chlorosulfonyl amides. The unsaturated N-chlorosulfonyl amides tend to decompose further. In general, the mono-substituted N-chlorosulfonyl lactams having lower alkyl residues in position 4 have the lowest thermal stabilities. The thermal stability increases with increasing substitution on C-4 (adjacent to the nitrogen atom) and C-3 (adjacent to the carbonyl carbon; 1, 2, 30).

N-chlorosulfonyl lactams (also known as substituted 2-azetidinone-1-sulfonyl chlorides) are cleaved between the nitrogen and the carbonyl group by strongly nucleophilic reagents (1, 2, 30). To carry out this reaction, the N-chlorosulfonyl lactams are added to excess caustic alkali solution. When heated in acidic solution, the salts lose sulfuric acid and form salts of beta-amino acids. At a high pH (>10) saponification of the sulfonyl chloride to the disodium salt of 2-amino-2-methyl butanoic acid-N-sulfonic acid will predominate (1); the structure of this product is shown in Figure 5. At low pH (e.g., pH 0) hydrolysis to 3-hydroxy-3-methylbutyramide will prevail (1, 2, 30, 31).

Therefore, one may in this manner prepare a heparin-like compound (a heparinoid) containing the required N-sulfamate and carboxylic groups that are found on heparin (3, 4, 31).

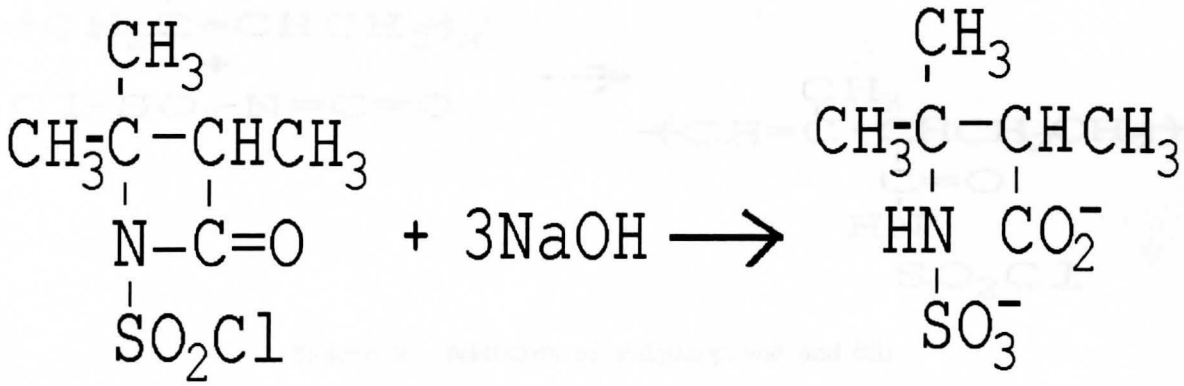


Figure 5. Hydrolysis of 2-Methyl-2-Butene Addition Product

Heparinoids

Amylose and amylopectin when sulfated, gave low in vivo anticoagulant activity, suggesting the importance of N-sulfonation instead of O-sulfonation (26). Sederel, et al., (4) demonstrated that the anticoagulant activity of a synthetic heparinoid is related to its molecular weight (increasing with increasing molecular weight) and to N-sulfate content (also a direct relationship). They accomplished this by the reaction of CSI and polyisoprene to give the lactam structure shown in Figure 6, followed by hydrolysis in refluxing NaOH to give the disodium salt as shown in Figure 7.

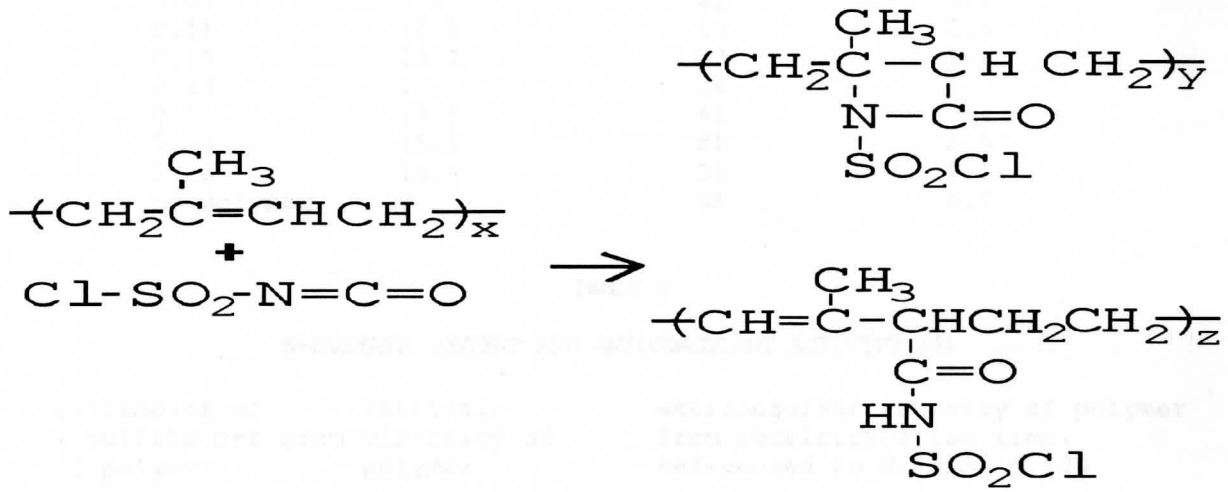


Figure 6. Addition of Polyisoprene and CSI.

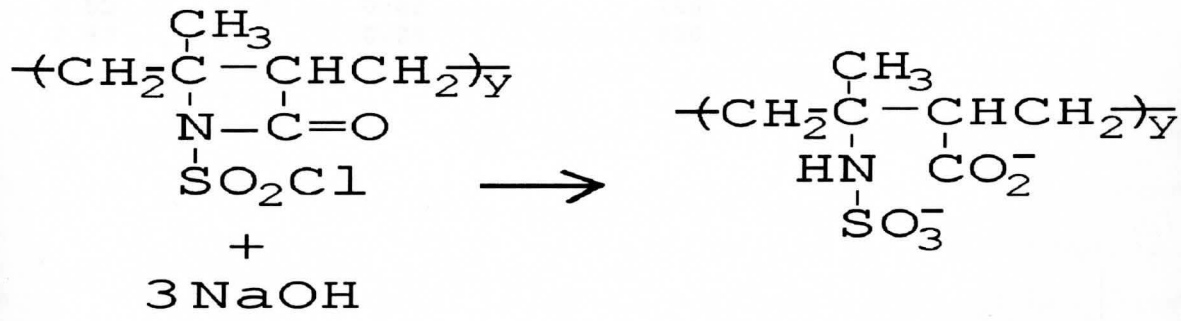


Figure 7. Hydrolysis of Polyisoprene / CSI Addition Product

The compounds obtained by Sederel, et al., were mixed with human plasma and then with calcium chloride, at a pH of 7.4 to obtain the recalcification times of the samples, a gauge of anticoagulant activity. In part, they obtained the following data (Tables 5, 6, 7) relating the recalcification time and the intrinsic viscosity of the polymer in aqueous solution (This data is shown graphically in Figure 8):

TABLE 5

VISCOSITY AND RECALCIFICATION TIME (4)

viscosity of solution	recalcification time (seconds)	Number of observations	Standard Deviation
0.06	7.2	16	0.4
0.08	7.8	21	0.6
0.11	10.5	16	0.4
0.15	13.1	20	1.6
0.15	13	24	1
0.3	15.9	41	2.4
0.55	15.9	31	2.5
1.15	18.4	25	2.1
no polymer	7	36	0.7

TABLE 6

N-SULFATE CONTENT AND ANTICOAGULANT ACTIVITY (4)

millimoles of N-sulfate per gram of polymer	intrinsic viscosity of polymer	anticoagulant activity of polymer from recalcification time, referenced to Heparin = 100
1.94	0.17	60
2.6	0.7	147
2.63	0.76	162
2.82	0.82	196
2.97	0.89	206

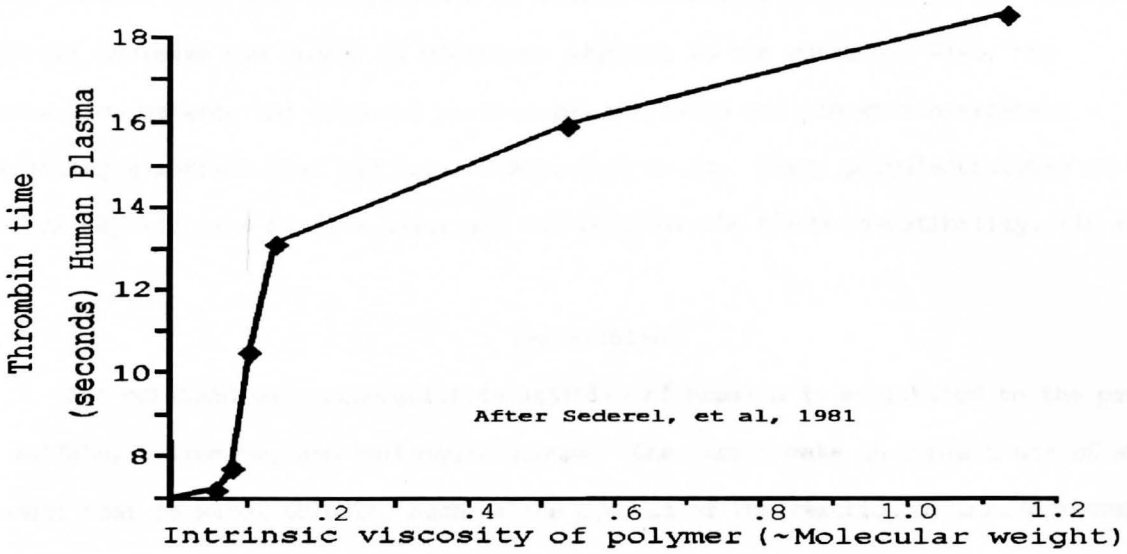


FIGURE 8. INTRINSIC VISCOSITY AND CLOTTING TIME

TABLE 7. RATIO OF NITROGEN TO SULFUR GROUPS AND CLOTTING TIME (4)

N/S ratio	Viscosity	Clotting Time	Number of trials	Deviation
1.4	0.65	19	8	1
1.5	0.45	15.9	8	0.5
1.9	0.35	11.4	8	0.6

As Sederel (4) comments, it is unfortunate that it is impossible to show a more direct relationship between the nitrogen / sulfur ratio, solution viscosity, and the clotting time. Other researchers in the field of artificial anticoagulant research note that sulfonate groups promote the anticoagulant activity of the carboxylic groups; i.e., the carboxylic groups begin to show anticoagulant activity only after a certain degree of sulfonation is present. Synthetic heparinoid polyethylene has also been found to possess anticoagulant activity and has been used for surface modification by grafting onto silicone rubber (35).

Jozefwicz and co-workers (36) prepared polyelectrolytes from natural cis-1,4-polyisoprene (source: Hevea brasiliensis, "Para Rubber") using this technique (reaction with CSI followed by hydrolysis of the lactam). They then grafted the product

onto clean glass rods, using gamma radiation, to produce blood compatible surfaces (36). Their results show that the presence of heparinoid polyelectrolytes on the surface markedly decrease the number of platelets adhering to the surface. Also, the interaction between the prepared surface and the blood was almost non-existent - resembling a surface that had heparin deposited on it. Thus, polyelectrolytes on the surface may act as a passive layer and can increase the blood compatibility. (36-40).

The Problem

The outstanding anticoagulation activity of heparin is attributed to the presence of sulfate, sulfamide, and carboxylic groups. One cannot make an implant out of a product that is water soluble, such as the product of the reaction discussed above. The reason for this is obvious, the implant will slowly dissolve, leaving the patient in a precarious position. Also, it is generally recognized that the implant must have a degree of mechanical flexibility that is suited for its particular end use. The 100%-substituted materials that have been previously synthesized are completely inappropriate for implant synthesis (although, as was shown, they are good for artificial anticoagulants).

Therefore, one must consider that perhaps the ideal implant material is not a 100%-substituted heparinoid material, but is instead a heparinoid material of a lesser degree of substitution. The approach here is shown in Figures 9 and 10. By varying the value of Y, one can find the values that give the desired blood compatibility. Also, by finding an optimum value of X, the optimum flexibility may be found. By finding the proper ratio of these two parameters, the desired solubility may also be found that gives the best implant material. Although many researchers have tried to graft this material onto various other polymers (especially Polyether-Urethane-Urea and silicone rubber), none has considered using a polyisoprene material without the grafting.

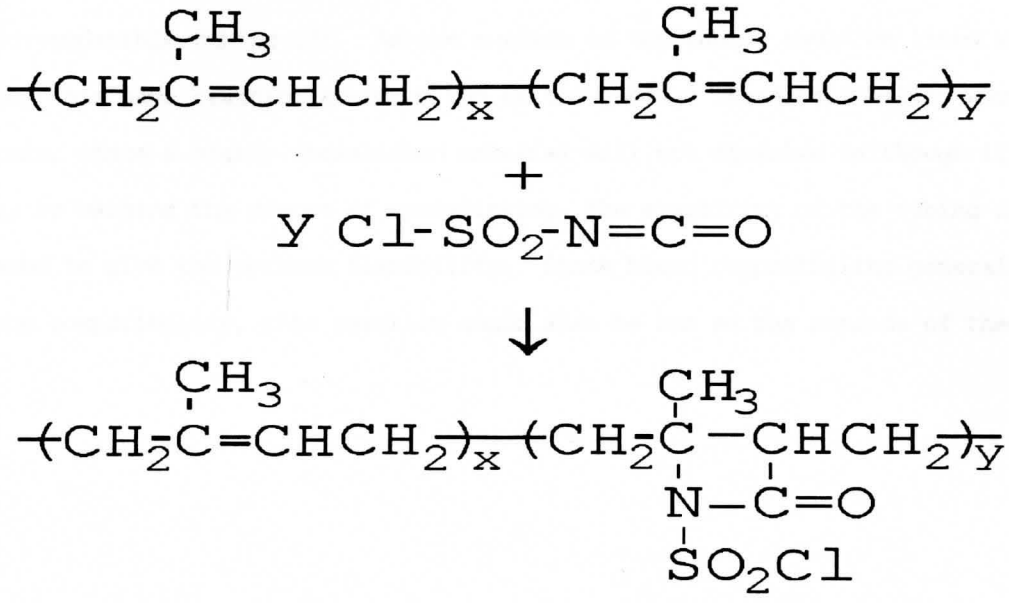


Figure 9. Partial Substitution of Polyisoprene. Step 1. Addition.

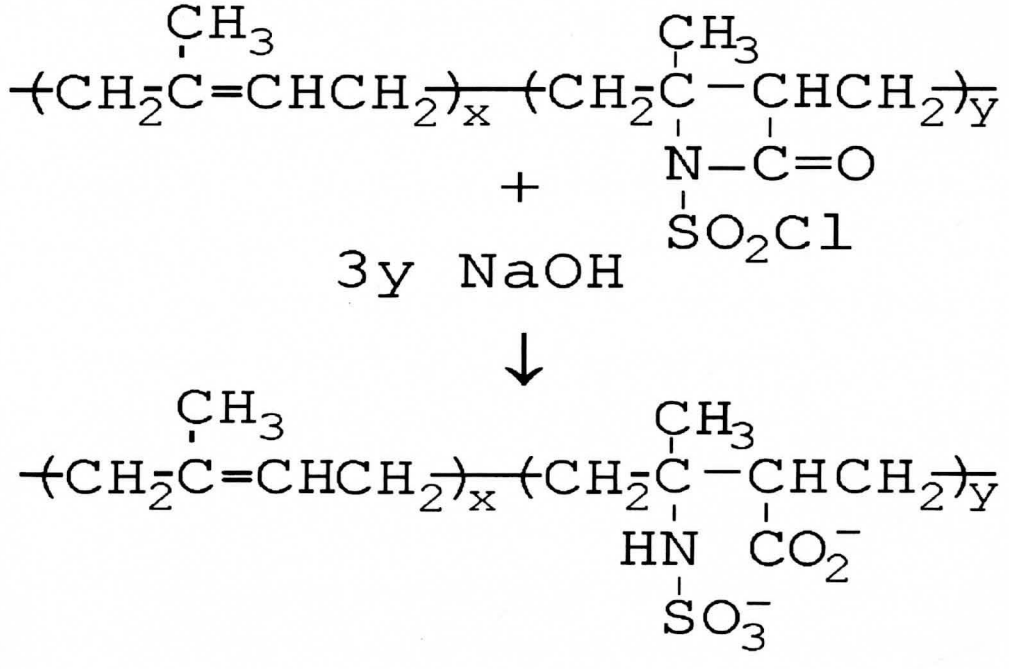


Figure 10. Partial Substitution of Polyisoprene. Step 2. Hydrolysis.

The above also suggests a methodology for the synthesis of a potentially blood-compatible tubing (3). As the surface of the tubing could be lined with double bonds, this same reaction could be run on the tubing. Here, solubility would not be a concern, since a highly crosslinked material will not dissolve (although it may swell). Also, by varying the degree of crosslinking, the elasticity of the tubing could be altered to give the optimum flexibility. Since blood compatibility generally imparts tissue compatibility, this reaction could also be run on the outside of the tubing (3).

CHAPTER II

EXPERIMENTAL

The experimental apparatus consisted of a 1000-mL, 24/40, 3-neck flask, which was fitted with a 125-mL, 24/40 addition funnel, the center neck was fitted with a teflon blade mechanical stirrer, and the third neck was fitted with a gas fitting to allow flushing with nitrogen. This third neck was also connected to an addition funnel. Methylene chloride (600 mL) was then added to the flask. The unsaturated compound was added to the flask, the stirrer was started, and the entire system was alternately placed under vacuum then filled with nitrogen. This process was repeated several times to insure an inert atmosphere. Next, the flask was immersed in an ice water cooling bath for about 2 to 3 hours (to insure thermal equilibrium). The flask was then covered as completely as possible with aluminum foil to prevent any photoexcitation that might occur. In all of the experiments, Aldrich chlorosulfonyl isocyanate (catalog number 14,266-2; lot number 4007HK; formula weight 141.53; boiling point 107 °C; melting point -44 °C; density 1.626 g/mL; 98+% pure) was used as the source of CSI. Due to the extremely high reactivity of the CSI and the fact that the major source of contamination is sulfur trioxide, the CSI was not further purified (except as noted below). The amount of CSI used, except as noted, was 10.00 mL. This amount was found to be easy to handle and corresponds to 0.1149 moles of CSI. Due to the highly reactive nature of the CSI, it was easier to change the amount of the unsaturated compounds that were reacted with the CSI than to change the amount of CSI used. A small amount of potassium chloride (dried at 120 °C) was added to the addition funnel containing the CSI about one-half hour prior to each addition. This reacts with sulfur trioxide in the following manner:

$$SO_3 + 2KCl = Cl_2 + K_2SO_3 \qquad (41)$$

This effectively removes all of the sulfur trioxide by forming a salt (potassium sulfite) that is insoluble in the solvent. Except in a few cases, the solvent used was methylene chloride (Fischer Scientific, Lot #723103, dichloromethane; density 1.3266 g/mL; molecular weight 84.93; melting point -95.1 °C; boiling point 40 °C {constants from label}). The infrared spectrum consists primarily of the peaks shown in Table 8, the infrared spectrum is shown in Figure 11.

TABLE 8

INFRARED SPECTRUM OF METHYLENE CHLORIDE

wavenumber	% Transmittance	Assignment
4453.2	58.5	Unassigned
3054.7	43.7	C-H (44)
2988.9	61.7	C-H (44)
1422.2	60.1	CH_2 wagging(44)
1265.0	0.9	C-H (44)
896.8	56.4	C-H (44)
746.1	0.0	C-Cl (44)
639.5	61.0	C-Cl (44)
500 and lower	0.0	C-Cl

Because this was the solvent used in all of the experiments, except as noted, the infrared spectrum of the CSI was determined in methylene chloride and had the peaks shown in Table 9, the infrared spectrum is shown in Figure 12.

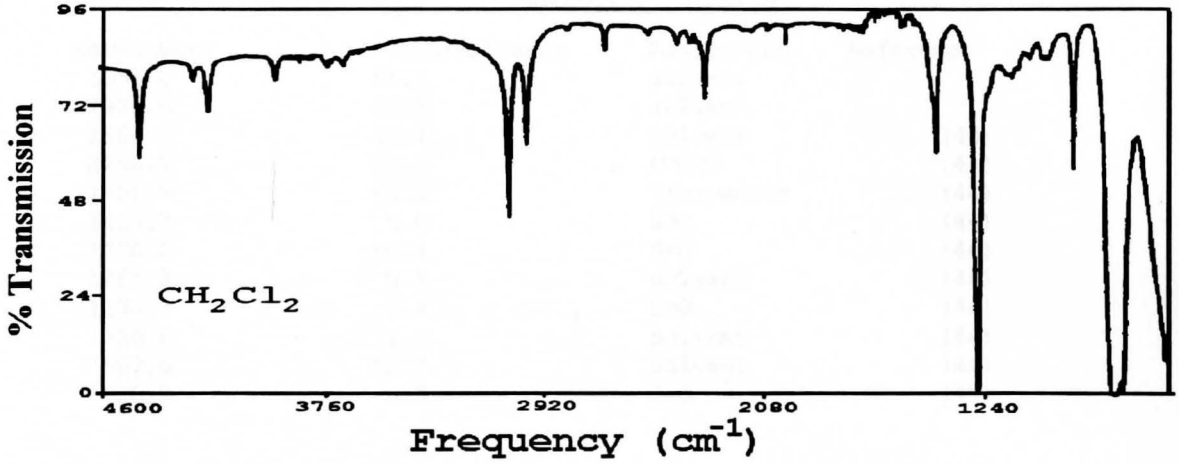


Figure 11. Infrared Spectrum of Methylene Chloride

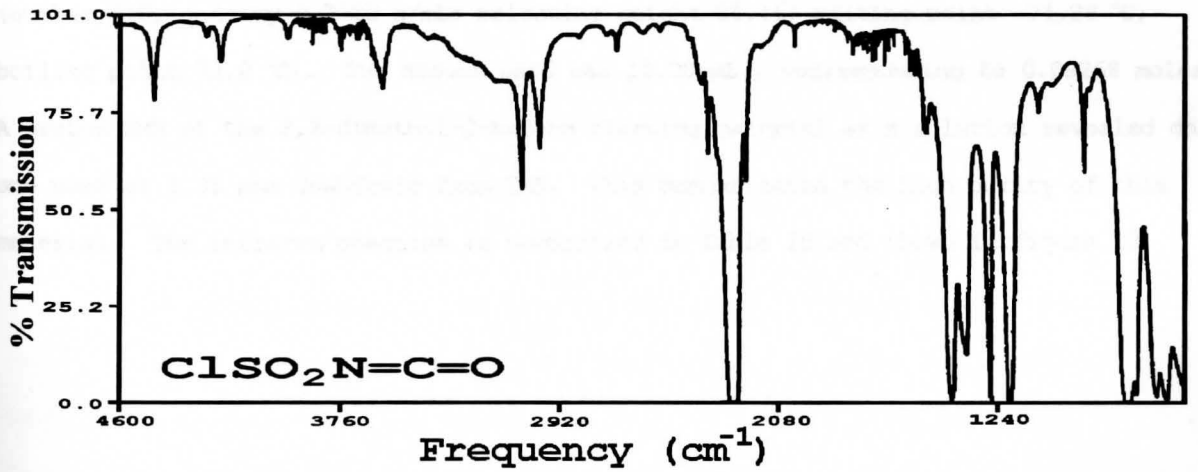


Figure 12. Infrared spectrum of CSI in Methylene Chloride

TABLE 9

INFRARED SPECTRUM OF CHLOROSULFONYL ISOCYANATE IN METHYLENE CHLORIDE

wavenumber	% Transmittance	Assignment	Reference
3056.6	55.5	solvent	
2988.6	65.5	solvent	
2304.7	63.7	solvent	(44)
2266.2	0.0	N=C=O	(44)
1456.9	65.5	Isocyanate	(44)
1413.5	0.0	S=O	(44)
1306.0	66.4	S=O	(44)
1265.5	0.1	solvent	(44)
1190.7	0.4	S=O	(44)
706.6	1.5	solvent	(44)
667.9	42.7	solvent	(44)
626.9	0.8	S=O	(44)

Synthesis of 2,3-Dimethyl-2-Butene CSI Addition Product

The first compound synthesized was the addition product of CSI and 2,3-dimethyl-2-butene. The 2,3-dimethyl-2-butene was obtained from Chemical Samples Co. (number 910, density 0.7080 g/mL; molecular weight 84.16; melting point -74.28 °C; boiling point 73.2 °C). The amount used was 10.00 mL., corresponding to 0.09268 moles. A proton NMR of the 2,3-dimethyl-2-butene starting material as a solution revealed only one peak at 1.35 ppm downfield from TMS. This demonstrates the high purity of this material. The infrared spectrum is summarized in Table 10 and shown in Figure 13.

TABLE 10

INFRARED SPECTRUM OF 2,3-DIMETHYL-2-BUTENE

wavenumber	% Transmittance	Assignment	Reference
2992.0	60.8	CH_3	(44)
2917.7	41.1	CH_3	(44)
2862.7	46.0	CH_3	(44)
2727.2	79.0	unassigned	
1456.9	53.8	CH_3	(44)
1448.2	55.2	CH_3	(44)
1373.0	59.6	CH_3	(44)
1168.5	53.1	C-C	(44)
1157.0	60.3	C-C	(44)
973.2	83.4	C-C	(44)

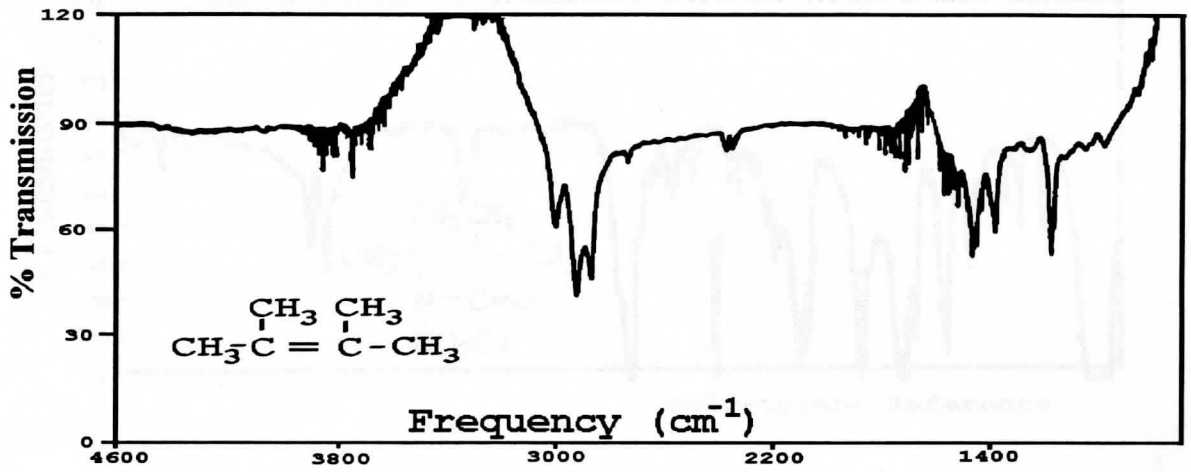


Figure 13. Infrared Spectrum of 2,3-Dimethyl-2-Butene

This synthesis was run with the addition of KCl. A white powder, 19.660 grams (94.0% yield), was obtained. The melting point of this compound was determined to be 66-67°C, in agreement with the literature value (42). This addition product was found to be soluble in chloroform, acetone, butyrolactone and carbon disulfide. An estimate of the addition product's solubility parameter may therefore be made at 9 to 12 hildebrands. The infrared spectrum of the product of this reaction was studied as a solution in CH_2Cl_2 and in CCl_4 in a solution cell (thickness = 0.025-mm) on a Perkin-Elmer 700A infrared spectrometer. The peakes found are summarized in Table 11 and the infrared spectrum is shown in Figure 14.

Table 11. Infrared Spectrum Of 2,3-Dimethyl-2-Butene CSI Addition Product

Wavenumber	Assignment	Reference
3075	CH Stretch	(44)
1845	C=O	(4,31,44)
1460 (strong)	SO_2Cl	(4,31,44)
1430	CN	(4,31,44)
1200 (strong)	S=O	(4,31,44)
800-600 (strong)	solvent	(44)

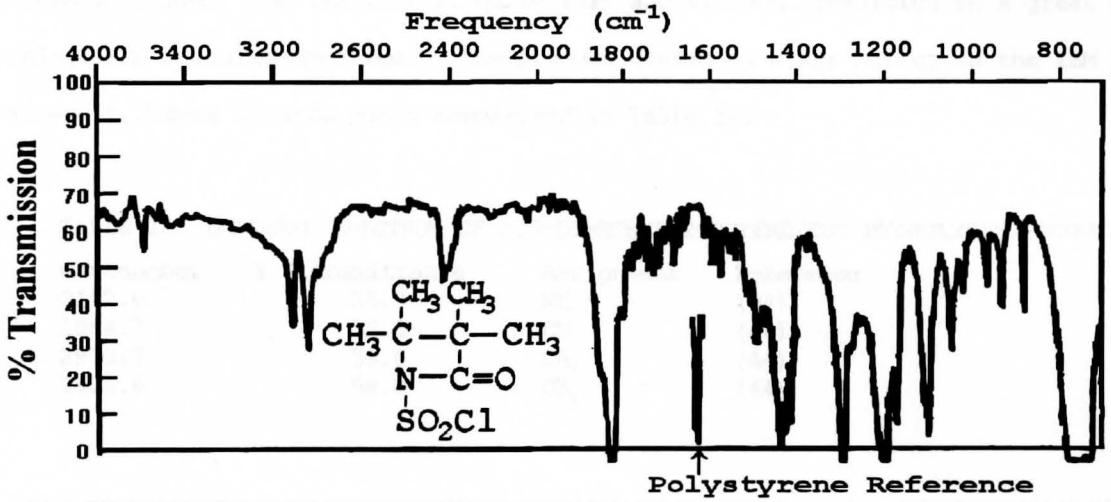


Figure 14. Infrared Spectrum Of 2,3-Dimethyl-2-Butene CSI Addition Product

The NMR spectrum of the addition product of 2,3-dimethyl-2-butene and CSI showed peaks at 0.84 and 1.4 ppm downfield from TMS. Each of these appeared as a pseudo-doublet and are assigned as follows: The doublet at 0.84 ppm is assigned to the 2 methyl groups on the #4 carbon atom (alpha to the nitrogen atom). The other psuedo-doublet (1.4 ppm downfield from TMS) is assigned to the 2 methyl groups on the #3 carbon atom.

Synthesis of 2,3-Dimethyl-2-Butene/CSI Hydrolysis Product

The solid addition product was isolated by simple flash evaporation of the reaction mixture followed by washing with several portions of methylene chloride. Hydrolysis of this to give the desired structure was done using 100 mL of 2.5-molar sodium hydroxide solution. The NaOH was slowly added (under an inert atmosphere) via a separatory funnel. The reaction is quite fast and violent, resulting in a great deal of frothing. An infrared spectrum of the product [taken as a KBr pellet on the IBM IR32] is shown in Figure 15 with peaks summarized in Table 12.

TABLE 12. INFRARED SPECTRUM OF 2,3-DIMETHYL-2-BUTENE/CSI HYDROLYSIS PRODUCT

wavenumber	% Transmittance	Assignment	Reference
3192.6	55.7	NH	(44)
2984.7	59.0	CH	(44)
2970.7	59.0	CH_3	(44)
2926.9	58.8	CH_3	(44)

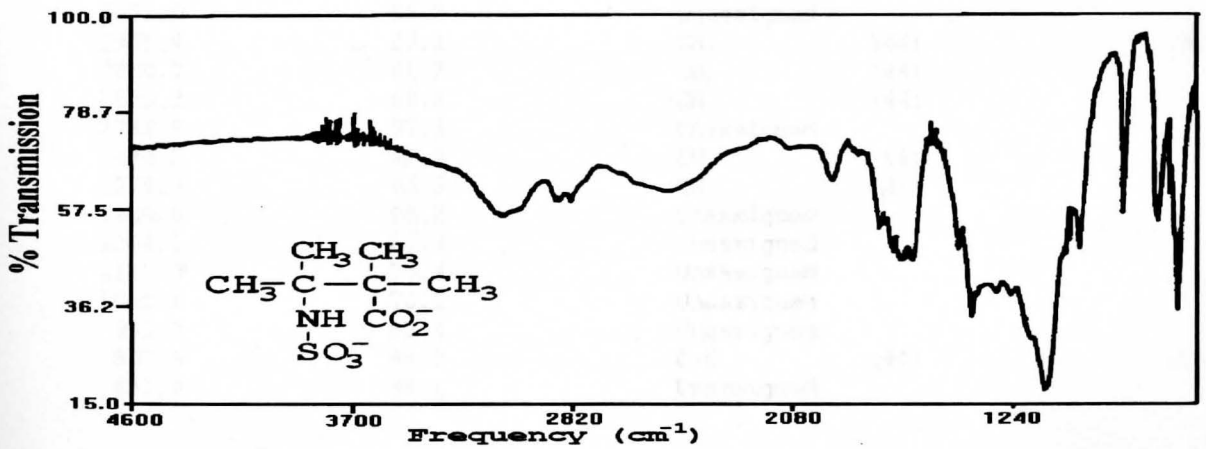


Figure 15. INFRARED SPECTRUM OF 2,3-DIMETHYL-2-BUTENE/CSI HYDROLYSIS PRODUCT

An NMR spectrum of the hydrolysis product of the 2,3-dimethyl-2-butene/CSI compound was taken using deuterium oxide as the solvent, and showed peaks at 2.02 ppm,

1.87 ppm, 1.78 ppm, and 1.73 ppm. All were of approximately equal area and overlapped. Assignment was not possible.

Synthesis of 2-Methyl-2-Pentene CSI Addition Product

The next material that was studied was 2-methyl-2-pentene, which served as a model for polyisoprene, differing by only one methylene group. The 2-methyl-2-pentene that was used came from Chemical Samples Company (no catalog number, m.w. 84.16, density 0.6863 g/mL, m.p. -135.07 °C, b.p. 67.29 °C). The infrared spectrum of this material is shown in Figure 16 and summarized in Table 13. The amount used was 15.00 mL, corresponding to 0.1223 moles of the pentene. This was reacted with the CSI under the same conditions as in the general case to give a product that decomposed at 55-57 °C. An infrared study revealed the spectrum shown in Figure 17 with peaks summarized in Table 14.

TABLE 13 INFRARED SPECTRUM OF 2-METHYL-2-PENTENE

wavenumber	% Transmittance	Assignment	Reference
3031.0	96.8	Unassigned	
2965.4	23.1	CH_3	(44)
2930.7	41.2	CH_3	(44)
2875.3	48.2	CH_2	(44)
2732.0	97.3	Unassigned	
1448.2	42.8	CH_3	(44)
1378.3	46.9	CH	(44)
1305.0	86.2	Unassigned	
1208.1	83.3	Unassigned	
1121.3	76.8	Unassigned	
1062.4	70.1	Unassigned	
985.3	83.4	Unassigned	
907.6	84.8	C-C	(44)
831.9	38.1	Unassigned	

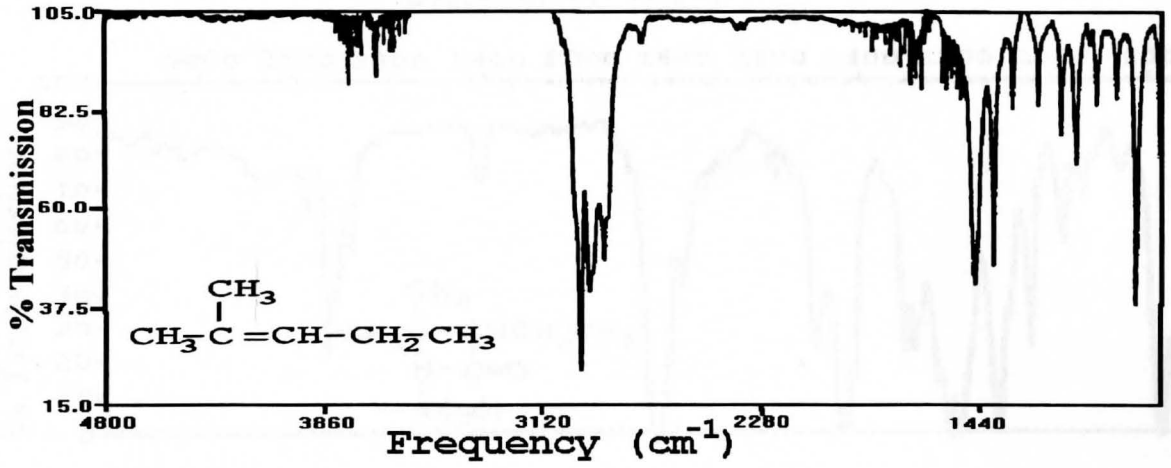


FIGURE 16. INFRARED SPECTRUM OF 2-METHYL-2-PENTENE

TABLE 14. INFRARED SPECTRUM OF 2-METHYL-2-PENTENE CSI ADDITION PRODUCT

wavenumber	Assignment	Reference
3140	Unassigned	
3000	CH stretch	(44)
2950	CH_3	(44)
2938	CH_2	(44)
1815	C=O	(4,31,44)
1788	C=O	(4,31,44)
1494	Unassigned	
1425	S=O	(4,31,44)
1410	Unassigned	
1296	Unassigned	
1290	Unassigned	
1195	S=O	(4,31,44)
1103	Unassigned	
1020	Unassigned	
990	Unassigned	

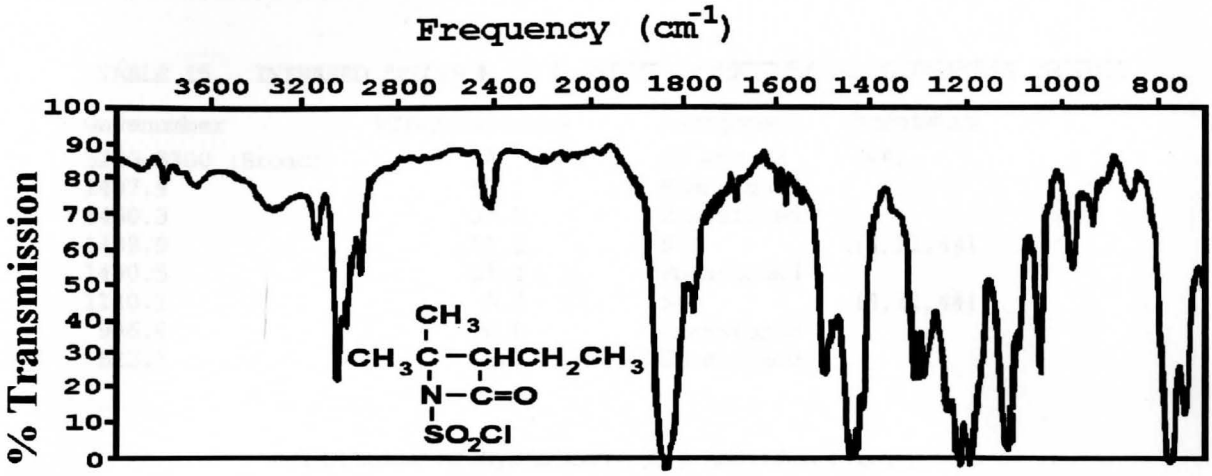


Figure 17. INFRARED SPECTRUM OF 2-METHYL-2-PENTENE CSI ADDITION PRODUCT

Synthesis of 2-Methyl-2-Pentene/CSI Hydrolysis Product

Addition of an excess of NaOH to the 2-Methyl-2-Pentene addition product resulted in a white crystalline material with the infrared spectrum given in Figure 18 and briefly summarized in Table 15.

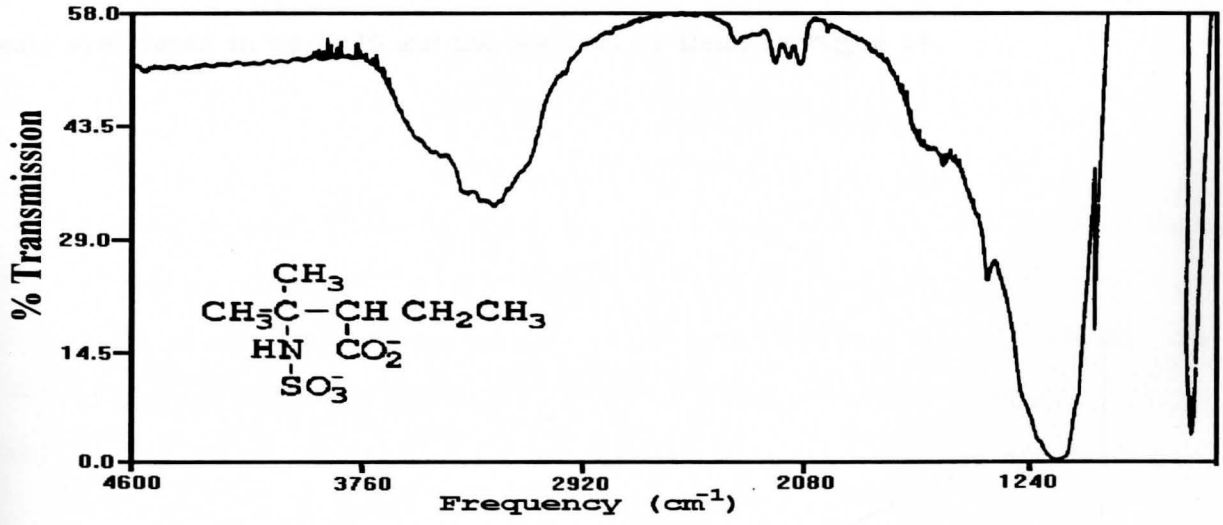


Figure 18. INFRARED SPECTRUM OF 2-METHYL-2-PENTENE HYDROLYSIS PRODUCT

TABLE 15. INFRARED SPECTRUM OF 2-METHYL-2-PENTENE/CSI HYDROLYSIS PRODUCT

wavenumber	%Transmittance	Assignment	Reference
3200-3300 (Broad)	33	NH and CH	(44)
1497.9	37.1	Unassigned	
1460.3	33.1	Unassigned	
1439.9	31.2	S=O	(4,31,44)
1400.5	23.1	Unassigned	
1140.1	0.4	S=O	(4,31,44)
996.4	16.9	Unassigned	
622.1	3.7	Unassigned	

Synthesis of Cyclohexene CSI Addition Product

The reaction of cyclohexene using 0.115 moles of CSI and 0.148 moles of cyclohexene was also studied. After a long period of time (2 days) the cyclohexene and the CSI were found to react to give a pale yellow (almost white) crystalline material. This was found to be soluble in benzene, acetone and methanol. The theoretical yield is 25.70 grams and the actual yield was 4.0 grams (15.6%). Later experiments increased this to a 35.2% yield. No literature melting point was reported. Upon keeping the reaction mixture in the freezer at -10 to -15°C for 2 months, it was noted that the amount of crystals increased, increasing the yield to 40.3%. An infrared spectrum of the neat cyclohexene (Chemical Samples Co. #5706, m.w. 82.15, m.p. -103.5 °C, b.p. 82.98 °C, density 0.8102 g/mL) was taken using a 0.025-mm solution cell on the IBM IR32. The peaks are listed in Table 16 and the spectrum is shown in Figure 19.

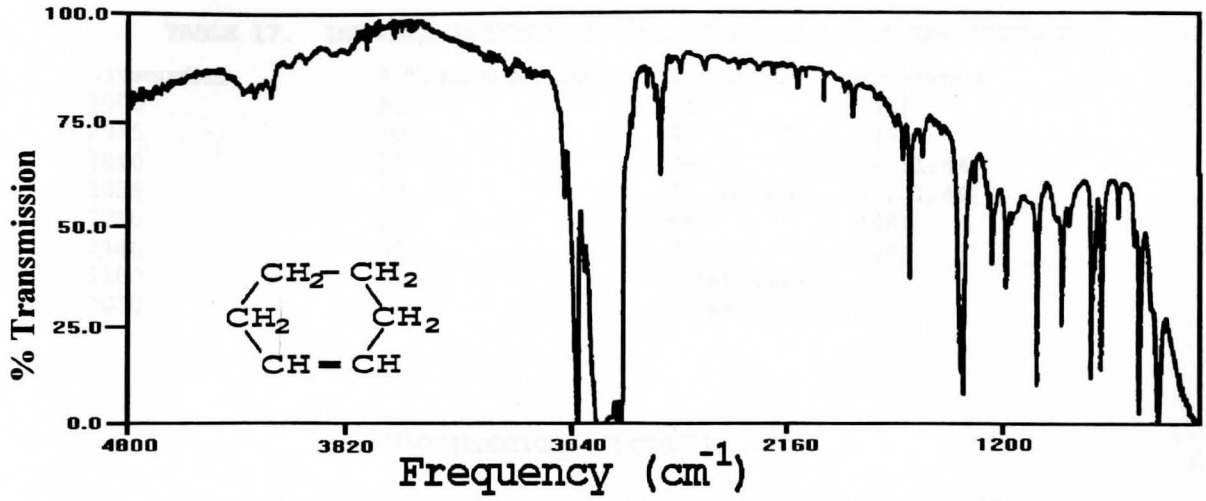


FIGURE 19. INFRARED SPECTRUM OF CYCLOHEXENE

TABLE 16. INFRARED SPECTRUM OF CYCLOHEXENE

wavenumber	% Transmittance	Assignment	Reference
3062.9	26.2	CH	(44)
3024.3	0.0	CH	(44)
3022.8	0.0	CH	(44)
2984.7	17.8	CH	(44)
2929.3	0.0	CH_2	(44)
2910.9	0.0	CH_2	(44)
2906.1	0.2	CH_2	(44)
2902.7	0.3	CH	(44)
2900.8	0.5	CH	(44)
2858.4	0.4	CH	(44)
2839.1	0.0	Unassigned	
1653.7	22.8	C=C	(44)
1447.8	9.2	CH	(44)
1437.6	5.1	Unassigned	
1321.9	30.4	Unassigned	
1265.0	28.1	Unassigned	
1036.9	20.3	Unassigned	
916.8	9.7	C=C	(44)

The NMR spectrum of the cyclohexene revealed peaks which are assigned as follows: (1). 5.45 ppm assigned to the CH=CH protons, (2). 1.90 ppm assigned to CH_2 protons alpha to the double bond, (3). 1.55 ppm assigned to the protons beta to the double bond. The infrared spectrum of the cyclohexene/CSI addition product, obtained using a PE 700A, is summarized in Table 17 and shown in Figure 20.

TABLE 17. INFRARED SPECTRUM OF CYCLOHEXENE CSI ADDITION PRODUCT

wavenumber	% Transmittance	Assignment	Reference
3000	51	CH	(44)
2945	68	CH	(44)
1840	23	C=O	(4,31,44)
1435	29	CN and S=O	(4,31,44)
1210	23	S=O	(44)
1140	35	S=O	(44)
1100	46	Unassigned	
1030	70	Unassigned	

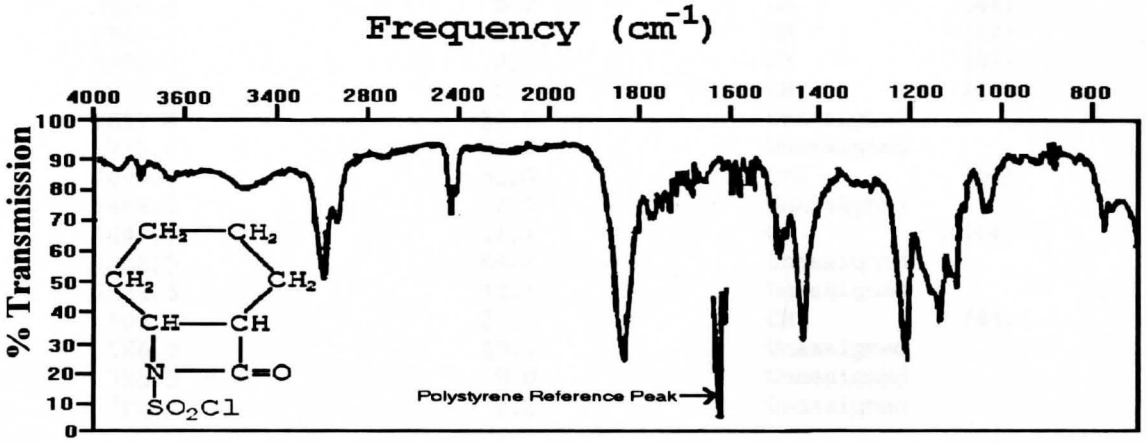


FIGURE 20. INFRARED SPECTRUM OF CYCLOHEXENE CSI ADDITION PRODUCT

Synthesis of Cyclooctene CSI Addition Product.

CSI (10.00 mL) was reacted with 0.154 moles of cis-cyclooctene (Columbia Carbon Company, #13349, m.w. 110.20, m.p. -12 °C, b.p. 138 °C, density 0.8472 g/mL). The theoretical yield was 22.3 grams compared with an actual yield of 19.9 grams, for an 89% yield. The melting point of this addition product was found to be 62-63 °C. This compound was soluble in benzene, acetone, o-xylene, carbon disulfide, and carbon tetrachloride. Also obtained were 4 grams of a viscous liquid of unknown composition. The infrared spectrum of the cis-cyclooctene taken on the IBM IR32 using the 0.025-mm solution cell under neat conditions is shown in Figure 21 and is summarized in Table 18.

An NMR spectrum of neat cyclooctene was obtained and revealed 3 major peaks: (1). 5.47 ppm assigned to CH=CH protons, (2). 2.11 ppm assigned to CH_2 protons alpha to the double bond, (3). 1.50 ppm assigned to CH_2 protons beta to the double bond. An infrared spectrum of the addition product taken 15 minutes after the addition of the CSI to the cyclooctene revealed the major peaks listed in Table 19 and shown in Figure 22.

TABLE 18. INFRARED SPECTRUM OF CYCLOOCTENE

Wavenumber	% Transmittance	Assignment	Reference
3015.1	0.8	CH vinyl	(44)
2926.4	0.0	CH_2	(44)
2905.6	0.0	CH	(44)
2902.7	0.0	CH	(44)
2856.9	0.0	CH_3	(44)
2682.4	52.9	Unassigned	
1711.6	80.9	Unassigned	
1645.0	81.6	C=C	(44)
1466.1	2.7	Unassigned	
1449.1	11.1	CH	(44)
1358.5	64.2	Unassigned	
1242.3	48.3	Unassigned	
893.2	27.6	CH	(44)
766.3	43.7	Unassigned	
750.9	0.0	Unassigned	
702.2	6.2	Unassigned	

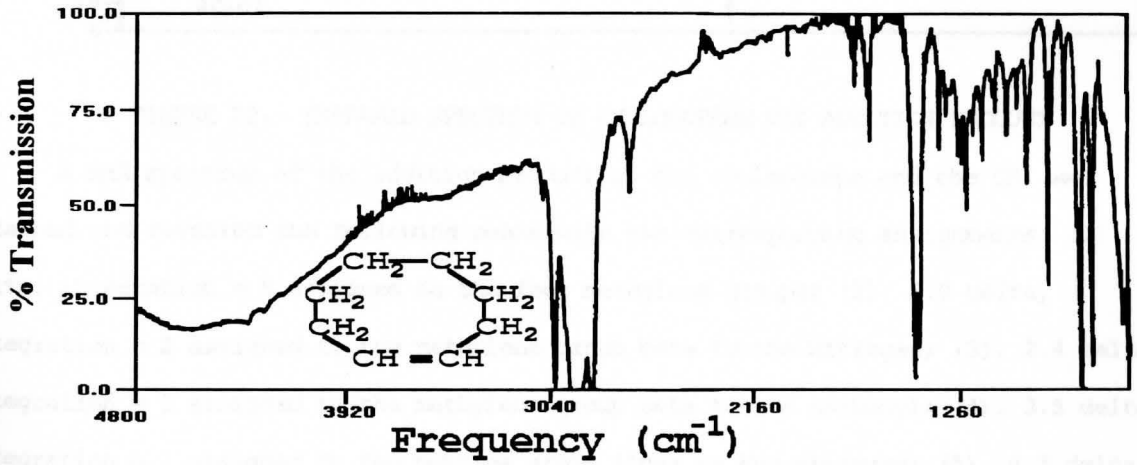


FIGURE 21. INFRARED SPECTRUM OF CYCLOOCTENE

TABLE 19 INFRARED SPECTRUM OF CYCLOOCTENE/CSI ADDITION PRODUCT

wavenumber	% Transmittance	Assignment	References
3150	44	CH	(44)
3005	3	CH	(44)
2950	29	CH_2	(44)
2350	<0	Unassigned	
1860	22	C=O	(4,31,44)
1455	<0	S=O	(4,31,44)
1310	<0	S=O	(44)
1240	1	Unassigned	
1150	35	S=O	(4,31,44)
943	42	CN	(44)

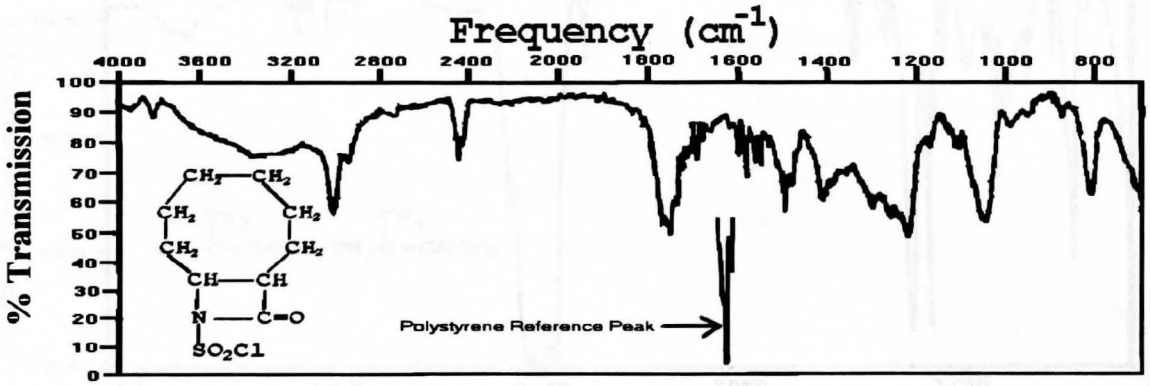


FIGURE 22. INFRARED SPECTRUM OF CYCLOOCTENE CSI ADDITION PRODUCT

A NMR spectrum of the addition product of the cyclooctene and the CSI was obtained and revealed the following peaks with the corresponding assignments: (1). 1.5 delta, integration = 8 assigned to the four methylene groups; (2). 2.0 delta, integration = 2 assigned to the methylene group beta to the nitrogen; (3). 2.4 delta, integration = 2 assigned to the methylene group beta to the carbonyl; (4). 3.5 delta, integration = 1 assigned to the methine group alpha to the nitrogen; (5). 4.3 delta, integration = 1 assigned to the methine group alpha to the carbonyl group.

Synthesis of Cis-2,6-Dimethyl-2,6-Octadiene CSI Addition Product

The same reaction was run using cis-2,6-dimethyl-2,6-octadiene (Chemical Samples Company, b.p. 168 °C, M.W. 138.25, density 0.775 g/mL). This compound served as a dimer model for cis-polyisoprene. The octadiene (13.00 mL) was reacted with 10.00 mL of the CSI in methylene chloride. The infrared spectrum of the starting material taken on the IBM IR32 showed the peaks summarized in Table 20 and Figure 23.

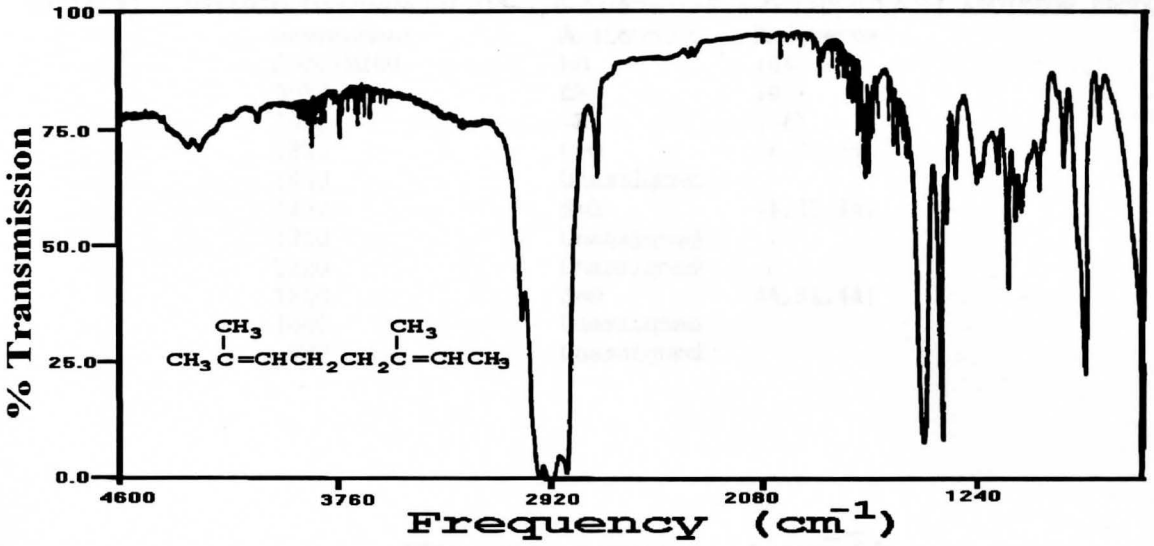


FIGURE 23. INFRARED SPECTRUM OF CIS-2,6-DIMETHYL-2,6,OCTADIENE

TABLE 20. INFRARED SPECTRUM OF CIS-2,6-DIMETHYL-2,6-OCTADIENE

wavenumber	% Transmittance	Assignment	Reference
2967.4 [part of]	0.0	CH	(44)
2960.6 [this peak]	0.5	CH_3	(44)
2923.5-2906.1	0	CH_2	(44)
2860.3	1.2	Unassigned	
2728.7	65.1	Unassigned	
1449.7	7.4	CH	(44)
1375.4	7.4	Unassigned	
1347.9	54.7	Unassigned	
1312.2	64.3	Unassigned	
1230.3	63.5	Unassigned	
1208.6	64.8	Unassigned	
1145.4	65.3	Unassigned	
1109.7	40.6	Unassigned	
1078.8	55.0	Unassigned	
1053.7	57.0	Unassigned	
984.8	61.6	Unassigned	

The addition product of the reaction of cis-2,6-dimethyl-2,6-octadiene and CSI was a solid that decomposed at 124 °C. The theoretical yield was 12.79 grams compared with 3.44 grams actual yield (26.9%) for the reaction of 0.115 moles CSI and 0.073 moles of the octadiene material. The CSI is in excess due to the difunctionality of the octadiene. This product was found to be soluble in acetone and dimethyl sulfoxide, and partially soluble in carbon disulfide. The following peaks were found in the infrared spectrum (Table 21, Figure 24).

TABLE 21. INFRARED SPECTRUM OF CIS-2,6-DIMETHYL-2,6-OCTADIENE/CSI ADDITION PRODUCT

wavenumber	Assignment	Reference
2900-3100	NH	(44)
3050	CH	(44)
2952	CH_3	(44)
1820	C=O	(4,31,44)
1490	Unassigned	
1430	S=O	(4,31,44)
1310	Unassigned	
1220	Unassigned	
1110	S=O	(4,31,44)
1040	Unassigned	
930	Unassigned	

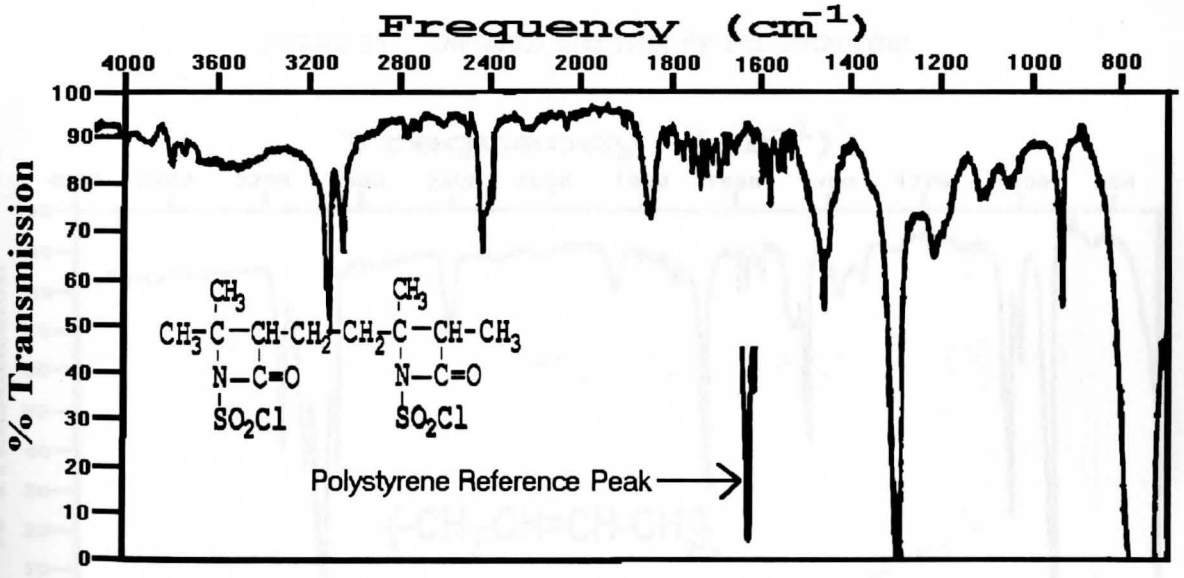


FIGURE 24. INFRARED SPECTRUM OF 2,6-DIMETHYL-2,6-OCTADIENE CSI ADDITION PRODUCT

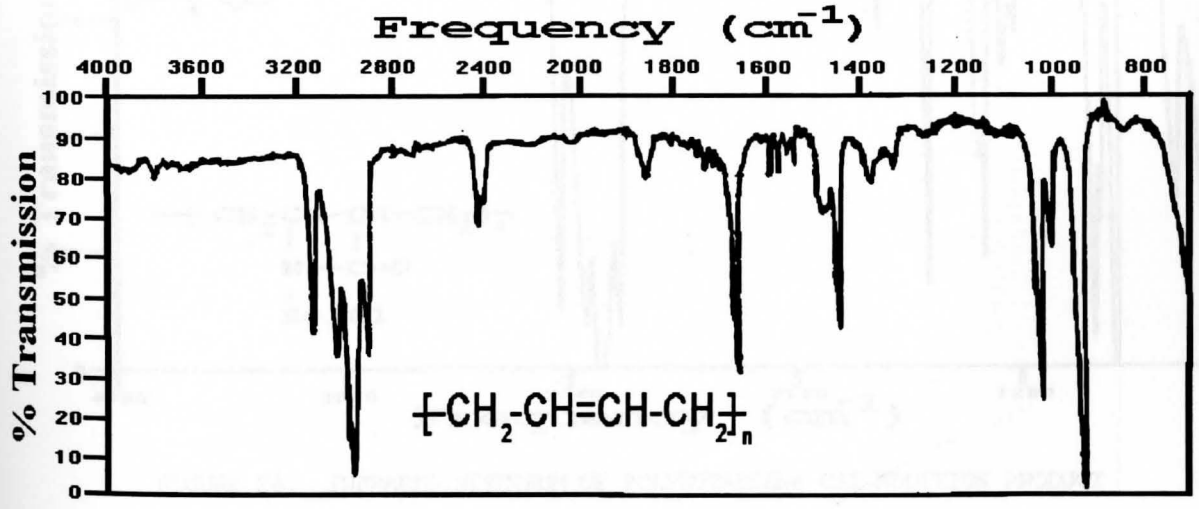
Synthesis of Polybutadiene CSI Addition Product

Another material studied was a 2,000 molecular weight polybutadiene (Aldrich). A sample weighing 6.0070 grams corresponding to 0.1112 moles of double bonds, was reacted with an excess of CSI in methylene chloride to give a yield of 66.2%. The actual yield was 10.50 grams compared to a theoretical yield of 15.87 grams. This addition product was found to decompose at 215 °C, and was soluble in dimethyl sulfoxide. The infrared spectrum of the polybutadiene, obtained using a PE 700A, had the following peaks (Table 22, Figure 25).

TABLE 22 INFRARED SPECTRUM OF POLYBUTADIENE

wavenumber	% Transmittance	Assignment	Reference
3125	42	Unassigned	
3030	36	CH vinyl	(44)
2967	5	CH	(44)
2904	36	Unassigned	
1860	80	Unassigned	
1665	32	C=C	(44)
1480	71	Unassigned	
1445	45	CH	(44)
1380	79	C=C	(44)
1330	83	Unassigned	
1020	25	Unassigned	
1000	64	CH	(44)
925	3	Unassigned	

FIGURE 25. INFRARED SPECTRUM OF POLYBUTADIENE



The NMR spectrum of the same material revealed only 2 peaks; one at 2.00 delta assigned to the methylene groups, and one at 5.26 delta assigned to the methine groups. After reacting the polybutadiene with CSI, an infrared spectrum was taken using the PE 700A and revealed the following peaks (Table 23, Figure 26).

TABLE 23 INFRARED SPECTRUM OF POLYBUTADIENE CSI ADDITION PRODUCT

wavelength	% Transmittance	Assignment	Reference
3448	13	Unassigned	
3333	12	Unassigned	
3226	7	Unassigned	
3125	7	Unassigned	
3058	18	Unassigned	
2976	10	CH_3	(44)
2545	55	Unassigned	
2400	23	Unassigned	
2340	34	Unassigned	
1790 [broad]	42	C=O	(4,31,44)
1670	40	C=C	(44)
1575	8	Unassigned	
1429	0	S=O	(4,31,44)
1300	0	Unassigned	
1230	3	Unassigned	
1105	5	Unassigned	
1020	25	Unassigned	
945	8	Unassigned	

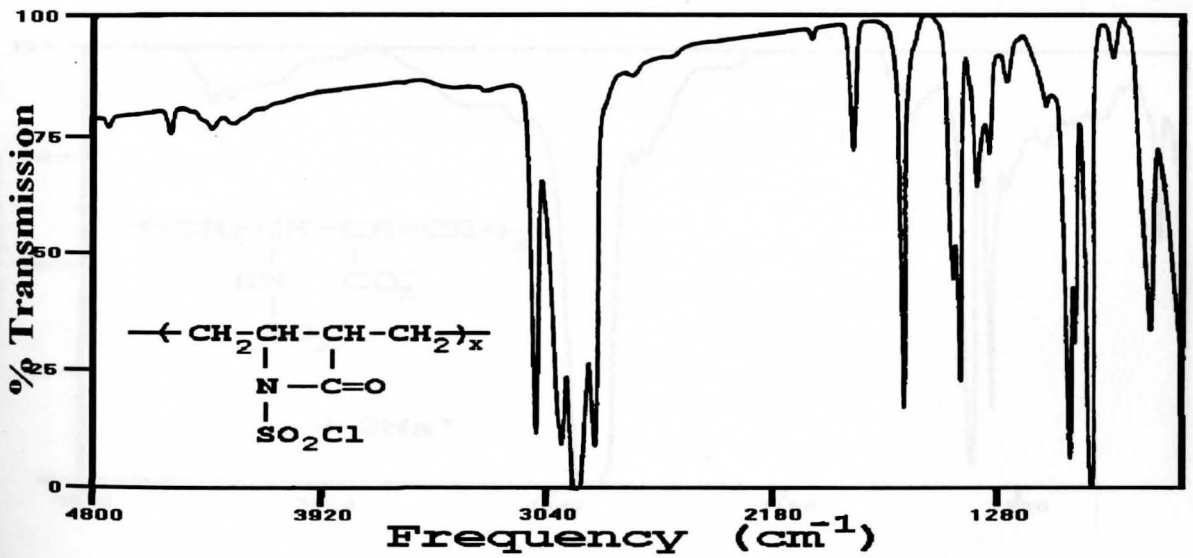


FIGURE 26. INFRARED SPECTRUM OF POLYBUTADIENE CSI ADDITION PRODUCT

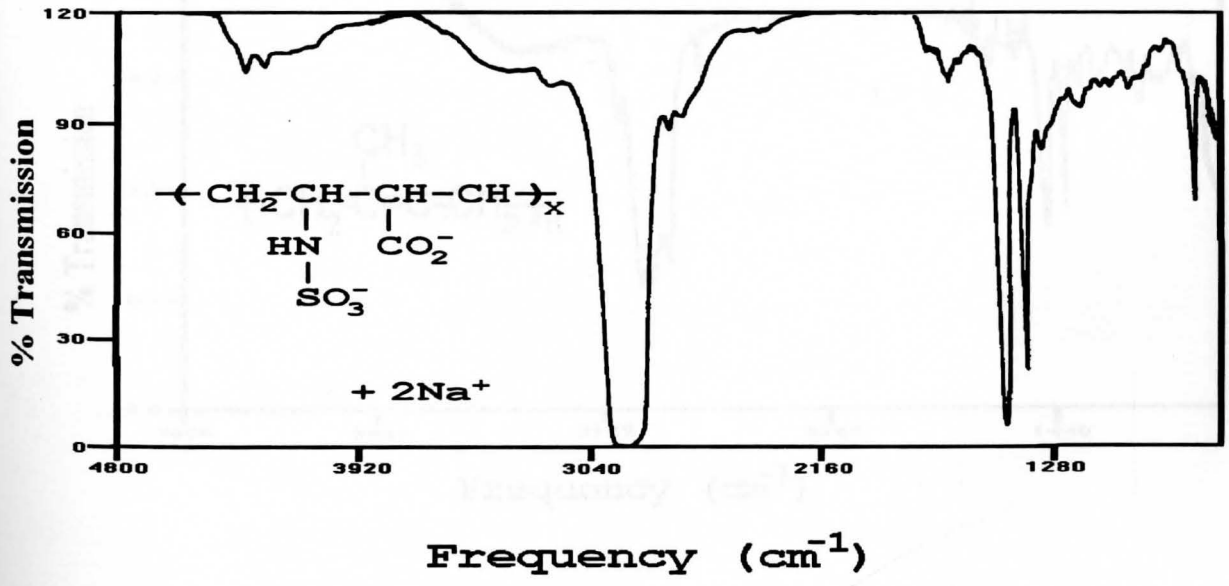
Synthesis of Polybutadiene CSI Hydrolysis Product

The polybutadiene intermediate was isolated and hydrolyzed under the conditions given earlier. An infrared spectrum of this product was obtained (Figure 27) and revealed the peaks listed in Table 24.

TABLE 24 INFRARED SPECTRUM OF POLYBUTADIENE HYDROLYSIS PRODUCT

wavelength	Assignment	Reference
3074.9	NH	(44)
2972.7	CH_2	(44)
2918.7	CH	(44)
2845.4	Unassigned	
1828.7	Unassigned	
1639.7	Unassigned	
1457.4	Unassigned	
1446.8	CH	(44)
1373.5	SO_2	(4,31,44)
1346.5	Unassigned	
995.4	CH	(44)
968.4	Unassigned	

FIGURE 27. INFRARED SPECTRUM OF POLYBUTADIENE CSI HYDROLYSIS PRODUCT



Synthesis of Polyisoprene CSI Addition Product

Polyisoprene (200,000 weight-average molecular weight) was reacted with the CSI; 5.99 grams of the polyisoprene were used with 0.115 moles of the CSI. An infrared spectrum of this polyisoprene material (Natsyn 410) revealed the following major peaks (Table 25, Figure 28).

TABLE 25 INFRARED SPECTRUM OF POLYISOPRENE

wavelength	% Transmittance	Assignment	Reference
2964.0	6.6	CH_3	(44)
2855.5	8.1	CH	(44)
1664.3	17.2	C=C	(44)
1376.9	10.9	C=C	(44)
1308.4	17.6	Unassigned	
1246.2	18.0	Unassigned	
1128.0	17.4	Unassigned	
1083.6	17.6	C=C	(44)
1037.8	17.7	Unassigned	

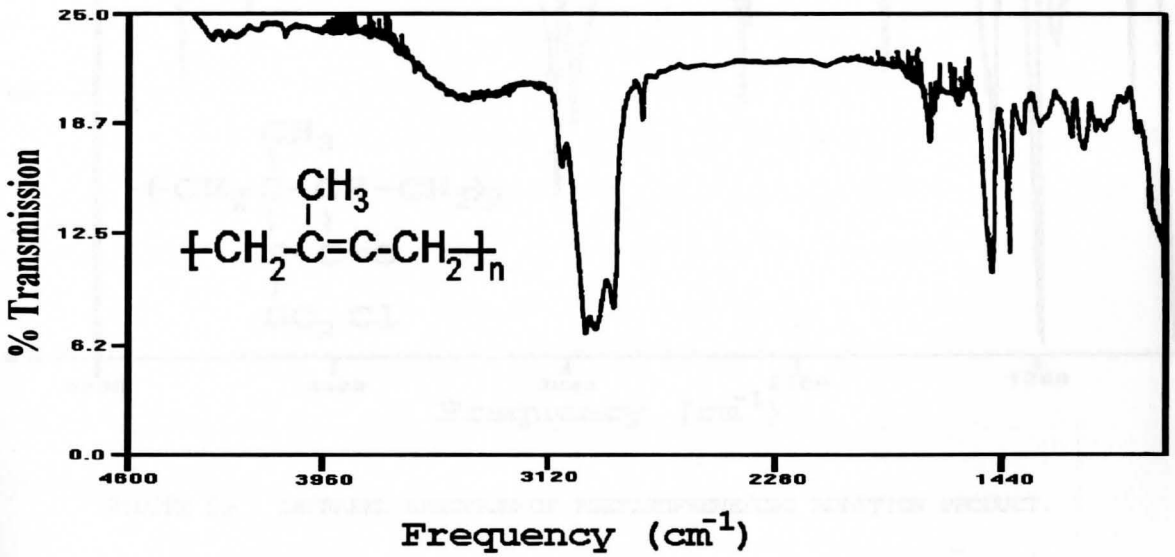


FIGURE 28. INFRARED SPECTRUM OF POLYISOPRENE

The polyisoprene material and the methylene chloride were mixed together, and allowed to set overnight. The apparatus was assembled and the reaction proceeded as described earlier. Then, CSI and KCl were added, and the mixture was allowed to react overnight. The following morning the methylene chloride was flash evaporated and the addition product was isolated. The infrared spectrum is as follows (Table 26, Figure 29).

TABLE 26 INFRARED SPECTRUM OF POLYISOPRENE CSI ADDITION PRODUCT

wavelength	Assignment	Reference
3150-3316	Unassigned	
3055.6	Unassigned	
2985.2	Unassigned	
2968.8	CH_3	(44)
1807.0	CH_2	(44)
1441.0	C=O	(4,31,44)
1406.8	S=O	(4,31,44)
1625.5	Unassigned	
1195.1	Unassigned	
1176.2	O=S=O	(4,31,44)

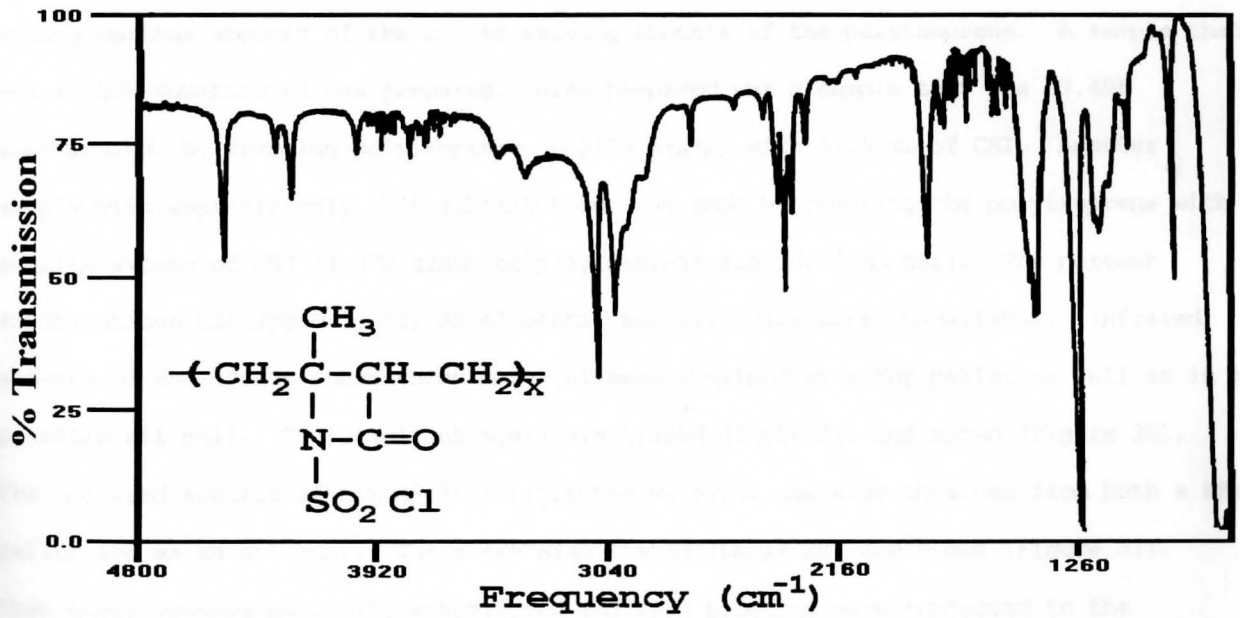


FIGURE 29. INFRARED SPECTRUM OF POLYISOPRENE/CSI ADDITION PRODUCT.

The cycloaddition product was usually a white to off white material. This may be isolated by filtration, but was not very stable and readily air oxidized to a dark brown product of unknown composition. It was found that this change was due to air oxidation by running the reaction and allowing it to set for several weeks under normal lighting conditions. The air slowly leaked into the flask around the joints and turned the portion of the product close to the joints brown. The whole of the product was exposed to normal room lighting, but only the portions near the neck of the flask turned brown. Hence, a photodecomposition of the addition product is not indicated, but instead an oxidation seems to occur.

Synthesis of Partially Substituted Polyisoprene/CSI Addition Products and Their Hydrolysis

Polyisoprene samples with various degrees of substitution were prepared by simply adding various amounts of the CSI to varying amounts of the polyisoprene. A sample that was 49.50% substituted was prepared. Also prepared was a sample that was 37.49% substituted, by reacting polyisoprene, 6.2626 grams, with 3.00 mL of CSI. Another sample with approximately 100% substitution, was made by reacting the polyisoprene with a large excess of CSI (4.872 grams of polyisoprene and 10.00 mL CSI). The percent substitutions are approximate, as elemental analysis data were unavailable. Infrared spectra of the 37.49% substituted material were obtained as a KBr pellet as well as in a paraffin oil mull. The resultant peaks are listed (Table 27) and shown (Figure 30). The infrared spectra of the 49.5% substituted material was also obtained from both a KBr pellet and as an oil mull. These are also listed (Table 28) and shown (Figure 31). Then these various partially substituted addition products were subjected to the standard hydrolysis procedure.

TABLE 27. INFRARED SPECTRUM OF 37.49% SUBSTITUTED POLYISOPRENE/CSI HYDROLYSIS PRODUCT

wavenumber	Assignment	Refenence
2900-3100 (very broad)	NH and CH	(44)
2955.3	CH_3	(44)
2930.2	CH_2	(44)
2856.0	CH_2	(44)
1455.5	Unassigned	
1450.7	Unassigned	
1402.4	S=O	(4,31,44)
1129.5	Unassigned	
1070.6	Unassigned	

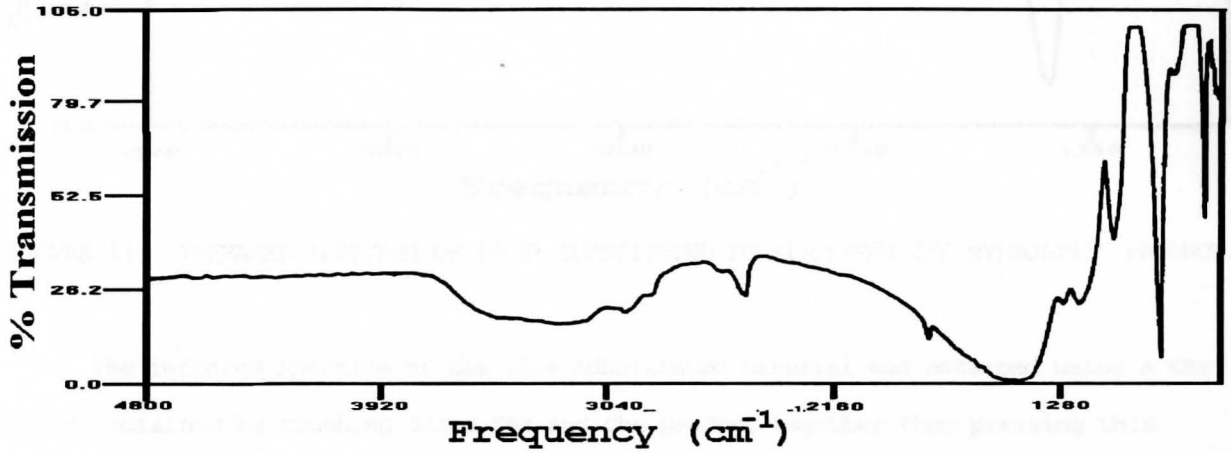


FIGURE 30. INFRARED SPECTRUM OF 37.49% SUBSTITUTED POLYISOPRENE CSI HYDROLYSIS PRODUCT

TABLE 28. INFRARED SPECTRUM OF 49.5% SUBSTITUTED POLYISOPRENE CSI HYDROLYSIS PRODUCT

Wavenumber	Assignment	Reference
2700-3100(very broad)	NH and CH	(44)
1561.6	CO_2	(44)
1417.9	C-N, S=O	(4,31,44)
1378.3	CN and CH	(44)
1257.7	Unassigned	
1176.7	Unassigned	
1107.3	Unassigned	
1075.4	Unassigned	
874.8	C=C	(44)
830.5	C-C	(44)

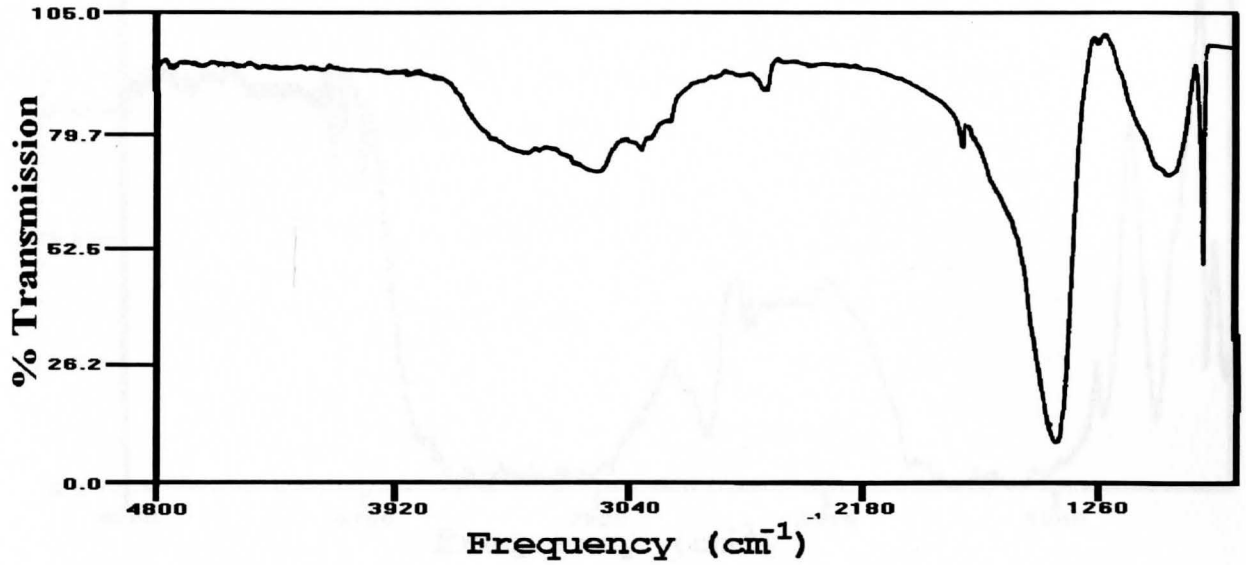


FIGURE 31. INFRARED SPECTRUM OF 49.5% SUBSTITUTED POLYISOPRENE CSI HYDROLYSIS PRODUCT.

The infrared spectrum of the 100% substituted material was obtained using a KBr pellet (obtained by crushing dried KBr and the product together then pressing this material). The resulting pellet was then placed in the FTIR and revealed the following peaks (Table 29, Figure 32).

TABLE 29. INFRARED SPECTRUM OF 100% SUBSTITUTED POLYISOPRENE HYDROLYSIS PRODUCT

wavenumber	% Transmittance	Assignment	Reference
3458.6 TO 2818.1	0.0	NH and CH	(44)
2504.4	4.9	Unassigned	
2125.8	17.7	Unassigned	
1773.3	1.8	Unassigned	
1067.7	6.9	C=O	(44)
888.3	7.3	CH	(44)
874.3	10.9	Unassigned	

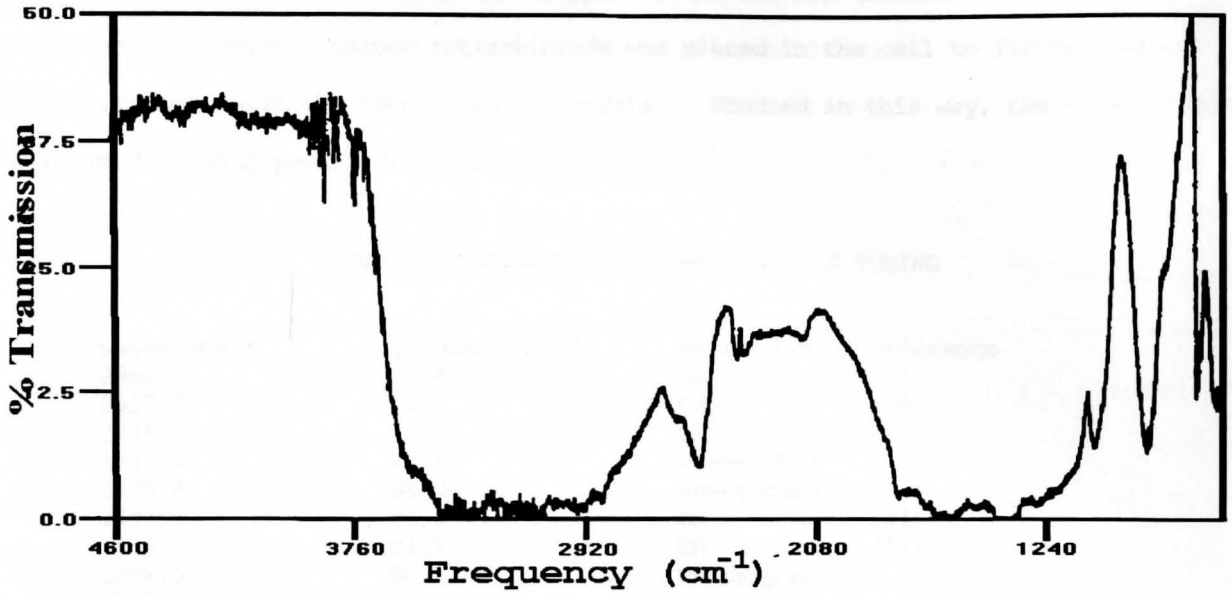


FIGURE 32. INFRARED SPECTRUM OF 100% SUBSTITUTED POLYISOPRENE/CSI HYDROLYSIS PRODUCT.

The effect of water on the partially-substituted hydrolysis products was noted in a rather crude but quite effective way. Approximately 0.1 gram of each material was placed in separate test tubes. Approximately 10 mL of distilled water was then added to each, and the test tubes were then stoppered. These were then allowed to stand overnight and each was then visually inspected, and any changes noted.

TABLE 30. WATER SOLUBILITY OF SUBSTITUTED POLYISOPRENE HYDROLYSIS PRODUCTS

Approximate degree of substitution	Effect of Water
37.5%	None
49.5%	Visibly swells
100%	Dissolves

Synthesis of Tubing CSI Addition Product

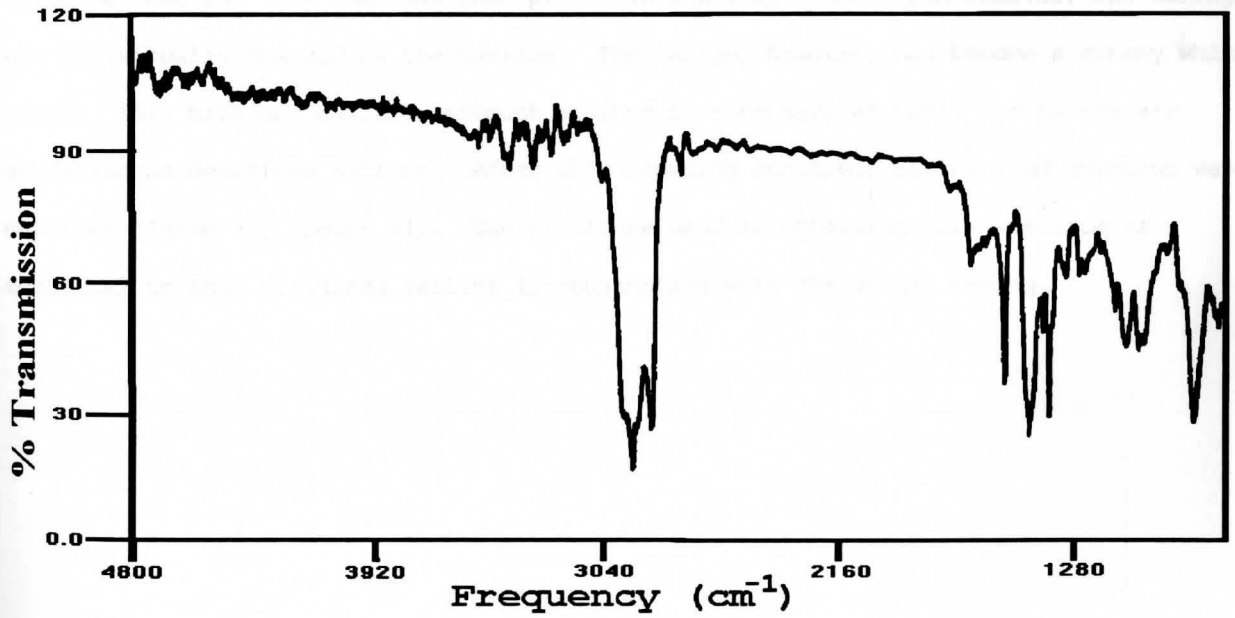
An infrared spectrum of virgin latex tubing in contact with the IBM circular reflectance cell was obtained. It was found that, by the most extraordinary coincidence, the diameter of the circular reflectance cell crystal is essentially identical to the inside diameter of the tubing samples. Therefore, the tubing samples

were simply sliced down one side and wrapped around the ATR (Attenuated Total Reflectance) crystal. Carbon tetrachloride was placed in the cell to further insure good contact between the sample and the crystal. Studied in this way, the virgin tubing gave the following peaks (Table 31, Figure 33).

TABLE 31. INFRARED SPECTRUM OF VIRGIN TUBING

wavenumber%	Transmittance	Assignment	Reference
2956.8	80.8	CH_3	(44)
2917.7	50.1	CH_2	(44)
2849.7		CH_2	(44)
1539.4	74.6	Unassigned	
1463.3	84.0	Unassigned	
1457.4	84.8	CH	(44)
1436.2	81.8	CH	(44)
1399.5	88.1	Unassigned	
1375.9	89.7	Unassigned	
1321.9	93.6	Unassigned	
834.3	89.8	CH_3	(44)

FIGURE 33. ATR INFRARED SPECTRUM OF VIRGIN LATEX TUBING



Synthesis of the tubing/CSI addition product was drastically different from the synthesis of the other materials. A length of tubing approximately 6 inches long was placed over the bottom end of a 25-mL burette. A Hoffman clamp was then placed at the bottom end of this length of tubing. A small quantity of glass wool was placed in the burette, and dried KCl (approximately 0.1 gram) was added to the burette. This was then filled with methylene chloride, and half of the methylene chloride was drained through the tube. The bottom clamp was closed before the top clamp to keep the piece of tubing full of the solvent. In this manner, the surface was not only cleaned, but pre-swelled as well. The burette was refilled to about 20 mL total volume. At this point, about 5 mL of the CSI was added to the burette. After leaving this set for about 10 minutes, the top clamp and then the bottom clamps were opened. The flow rate was not determined but could be estimated from the burette readings to be about 3 mL per minute. Just before the last 5 mL could flow through the tube, the clamps were closed (since the last few mL were presumed to have the greatest contamination from the air).

The sample was removed from the burette and quickly placed in a beaker full (200 mL in a 250 mL beaker) of methylene chloride. In this way, all unreacted materials could be removed. The tube was then placed in a drying oven. Upon removal, the tubing was not visually changed on the outside. The inside, however, had become a creamy white color. This presumed addition product browned in room air, probably due to the air oxidation as described earlier. After this browning occurred, an infrared spectrum was obtained (Table 32, Figure 34). The procedure used in obtaining this spectrum is identical to that discussed earlier in conjunction with the virgin tubing.

TABLE 32 INFRARED SPECTRUM OF OXIDIZED TUBING/CSI ADDITION PRODUCT

wavenumber	% Transmission	Assignment	Reference
3575.9 to 3092.2	73.8	CH and NH	(44)
2965.5	77.8	CH_3	(44)
2917.7	61.0	CH_2	(44)
2849.7	65.3	CH_2	(44)
1707.2	78.7	Unassigned	
1540.0	80.7	CO_2	(4,31,44)
1472.8	79.8	Unassigned	
1462.8	79.8	CH	(44)
1170.0 [broad]	73.3	S=O	(4,31,44)
1037.6	75.0	Unassigned	
886.8	76.7	Unassigned	

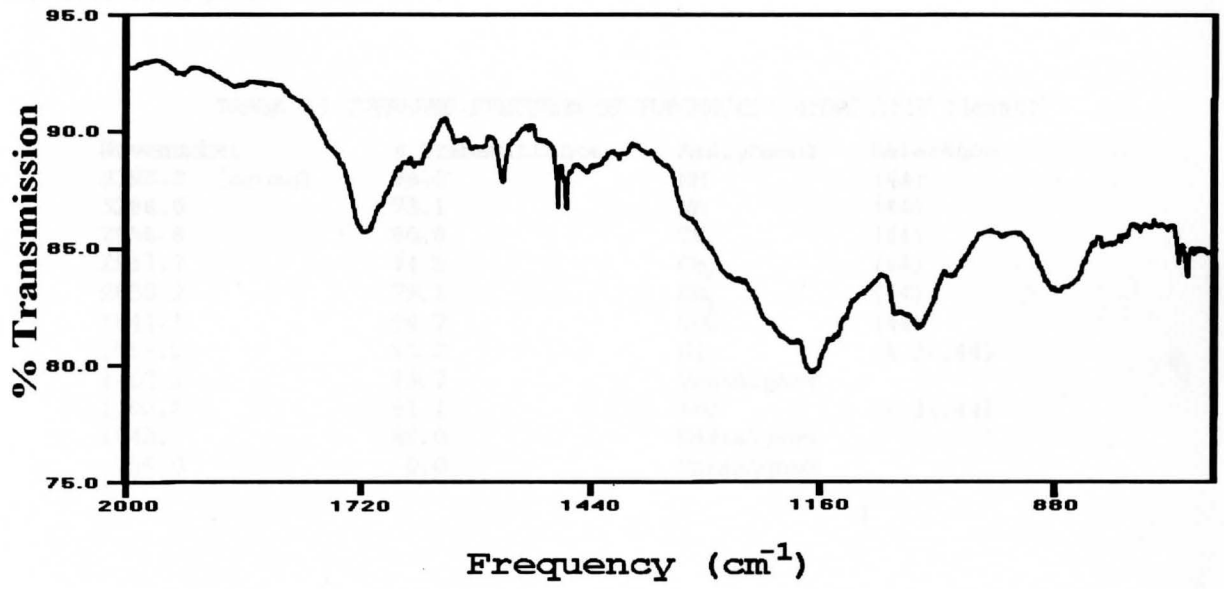


FIGURE 34. INFRARED SPECTRUM OF OXIDIZED TUBING/CSI ADDITION PRODUCT.

Synthesis of Tubing CSI Hydrolysis Product

The above-described synthesis of the tubing/CSI addition product was repeated, however, this time the product was quickly placed into a beaker containing sodium hydroxide solution (as described earlier). Then, the NaOH solution and tubing were rapidly heated to provide the desired final product without the sample decomposing to the brown product just described. The effort was successful, as the tubing this time had a white inside and the product did not decompose. This material was characterized by placing it in the circular reflectance cell, which was then filled with carbon tetrachloride. When obtained in this manner, the infrared spectrum (Figure 35) revealed the following peaks (Table 33).

TABLE 33 INFRARED SPECTRUM OF TUBING/CSI HYDROLYSIS PRODUCT

Wavenumber	% Transmittance	Assignment	Reference
3393.0 [broad]	89.0	NH	(44)
3286.6	73.1	NH	(44)
2956.8	86.8	CH_3	(44)
2917.7	74.8	CH_2	(44)
2850.2	79.1	CH_2	(44)
1641.1	84.7	C=C	(44)
1559.2	85.2	CO_2	(4,31,44)
1463.2	83.7	Unassigned	
1102.5	81.1	S=O	(4,31,44)
1042.7	80.0	Unassigned	
750.0	0.0	Unassigned	

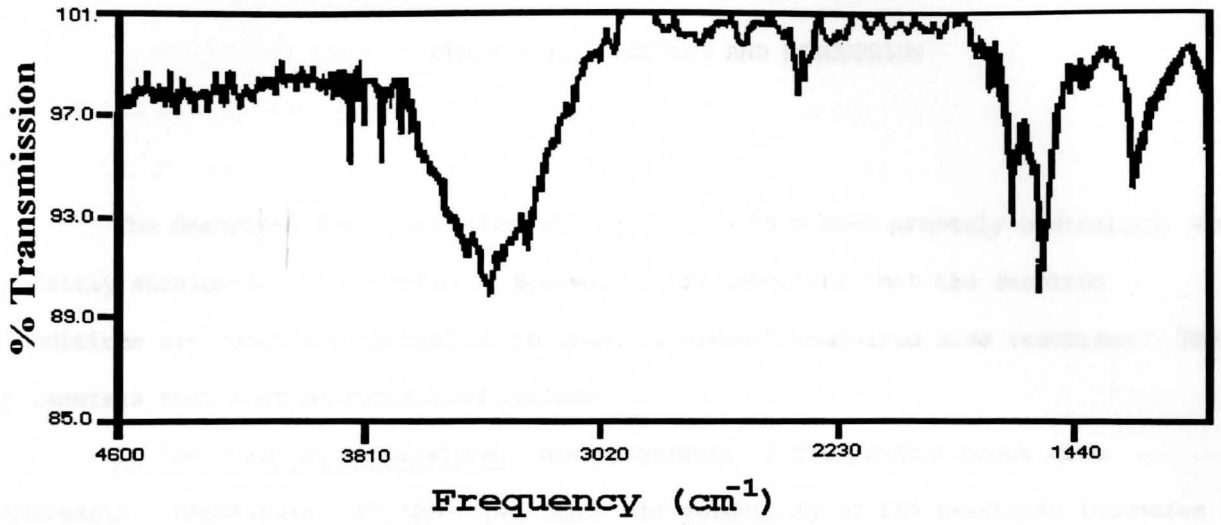


FIGURE 35. INFRARED SPECTRUM OF TUBING CSI HYDROLYSIS PRODUCT

CHAPTER III RESULTS AND DISCUSSION

The described syntheses, when all conditions have been properly controlled, are a fairly straightforward reaction. However, it is important that the reaction conditions are carefully controlled in order to prevent undesired side reactions. The parameters that must be controlled include:

1. The reaction temperature. Rearrangements of the product occur with increasing temperature. On the other hand, the solubility of the reactants increases with increasing temperature. Therefore, the best temperature that satisfies both requirements is zero degrees Celsius.

2. The effect of age. Elapsed time since the initial opening of the bottle of CSI is very important. Its highly reactive nature may result in increasing amounts of impurities in subsequent reactions. Even if the bottle is open for less than one minute, this may be enough time for the contents to react with air constituents - decreasing purity with each reaction. While the bottle is open, a large quantity of white fumes are emitted, confirming this reactivity. It is worthy of note that this effect of age was observed even though the bottle was thoroughly flushed with dry nitrogen gas every time it was used.

3. Addition of dry KCl. Without the addition of dry KCl, any sulfur trioxide present will react with the unsaturated materials to give a variety of products that are orange and gelatinous. These byproducts are impossible to purify and were not further investigated. The amount of KCl required is not very great, but an excess of it was always used (about 0.5 grams). Presumably, the amount of SO_3 present is only a trace amount, hence the low requirement. Very low yields were obtained without its addition. While addition of the KCl is important, its presence allows for possible side reactions of its own (by liberating Cl_2, however, this may be removed by proper purging and is present in only trace amounts).

4. Proper purging. Proper purging of the reaction system with an unreactive gas is imperative. This removes all traces of moisture, atmospheric oxygen, and liberated Cl_2. The addition product in this reaction is a ß-lactam which is highly oxygen sensitive. Upon exposure it readily reacts with oxygen to give a dark brown product. To avoid difficulties in isolating this lactam without exposing it to atmospheric oxygen and moisture, later addition products were not isolated. Instead, the hydrolysis was carried out on the unopened flask. In this way, the integrity of the lactam was not compromised, and the final product could be isolated without concern about lactam decomposition.

5. Dryness. The dryness of all glassware is critical. The glassware was all flame dried before assembly and then again after assembly to insure dryness. Any water in the reaction vessel could give rise to a variety of products, increasing side reactions and decreasing product purity. In general, all equipment was thoroughly dried, as was the KCl. Therefore, the reaction conditions described are an absolute requirement for good yields of the desired products.

Concerning the reaction itself, a few comments are in order:

1. The reaction with CSI appears to be exothermic. All reactions carried out without ice water baths liberated a large amount of heat, often enough to cause the methylene chloride to reflux.

2. The reaction is, so far as could be determined, spontaneous. Infrared spectra of the systems usually lacked the CSI peaks immediately after addition of the CSI. The ring systems that were studied (cyclohexene, cyclooctene) appear to react more slowly. The ring systems and higher molecular weight polymers showed very slow reaction rates (the exact values being undetermined).

3. The observations are consistent with the accepted mechanism of a 4- centered 2-π antarafacial reaction, using the Woodward Hoffman rules and notation (32, 33).

4. Strained and hindered systems seem to be especially prone to hydrolysis and decomposition. This effect appears to decrease with decreasing strain.

5. Hydrolysis of the low molecular weight products occurs readily, while the higher molecular weight polymers require heating to reflux.

6. Impurities appear to be always orange in color, though the structure of these impurities was not further studied.

Synthesis of the desired compounds requires great care, but can be done successfully. However, analysis represents some difficulties that should also be discussed:

1. The products of these reactions are multifunctional and this makes infrared analysis difficult. For example, the region of 2900 cm^{-1} to 3700 cm^{-1} can be assigned to both the NH and CH stretching, the region from 1400 cm^{-1} to 1500 cm^{-1} can be assigned to both the CN and S=O stretching, etc. The assignments made here are consistent with those that are available in the literature (4, 31, 42, 43). Elemental analysis would be useful in characterizing the samples, however, this was not done.

General conclusions drawn from the present work:

By proper selection of the degree of substitution, synthesis of a polymer with the desired degree of solubility is possible. Using this methodology, one could fine tune the solubility of the polymer to the desired amount for a particular end use. As was shown by Sederel, et al (4), the blood compatibility of these polymers directly depends on the sulfamate and carboxylic content. However, the bulk flexibility also affects this compatibility. Therefore, optimum conditions may require a trade off.

Though the purpose of this research was not to determine blood compatibility, it was shown that this reaction is successful with pre-made latex tubing. By analogy with the work of Sederel et al (4), this is a very promising material that should possess exceptional biocompatibility. By using a simple procedure of flushing the CSI down the inside of the tubing (or possible total immersion of the tubing to react both inside and outside), followed by hydrolysis with sodium hydroxide, this reaction may be used to improve blood compatibility. Since the tubing is present as a crosslinked unsaturated polymer, the stiffness of the tubing may be altered (by changing the degree of crosslinking) to be essentially the same as the vein (or artery) that is being replaced. Of course, cracking of the surface and the bulk material itself must be avoided.

Therefore, the two main parameters, stiffness and degree of substitution, that determine blood compatibility may be altered to give the optimum values. Since, as the blood compatibility of the polymer increases, the tissue compatibility increases, this reaction could be run on the outside of the tubing to provide an even better (more biocompatible) implant.

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