indicate that copolymerization has taken place.[4] In the NMR spectrum (Figure 4) the two intense multiplets at 1.6 and 3.4 ppm can be assigned to the $-O-CH_2-\underline{CH_2-CH_2}-CH_2-O-$ and $-O-CH_2-\underline{(CH_2)_3}-CH_2-O-$ and to the $\underline{-CH_2}-CH_2-O-\underline{CH_2}-CH_2-$ protons, respectively. From the intensity of the weak signals at 2.4 ppm ($-CH_2-\underline{CH_2}-C(O)-O-$) and 4.1 ppm ($-CH_2-C(O)-O-\underline{CH_2}-CH_2-$) the content of ε-caprolactone units was estimated to about 5 mol %.

In the wide-angle x-ray diagram no reflexes were observed at the positions of the ε-caprolactone homopolymer but the somewhat broadened 020 and 110 reflexes at $2\theta = 19.65°$ and $2\theta = 24.15°$ indicate that the ε-caprolactone segments fit into the monoclinic unit cell of poly(tetrahydrofuran) with a concomitant widening of the lattice and decrease in crystallinity. The two endotherms observed in the DSC diagram (Figure 5) with maxima at 301 and 313 K can be attributed to the melting of crystalline, random, on alternating[20] copolymer segments (heat of fusion $\Delta H_m = 40$ J/g) and THF homopolymer segments (heat of fusion $\Delta H_m = 75$ J/g), respectively. This assumption is also confirmed by the shoulder observable in the intensity–temperature curve of the 020 x-ray reflex at 305 K (Figure 6). The IR spectrum (film from benzene on KBr plate) (Figure 7) of the molten copolymer (323 K) shows the $\nu(C{=}O)$ (1735 cm^{-1}) and $\nu(C-O-C)$ (small shoulder at 1165 cm^{-1}) stretching vibrations of the ε-caprolactone units superimposed on the poly(tetrahydrofuran) spectrum.

Poly(ether ester) of THF and γ-Butyrolactone. Here too, solubility of the polymer in ether and ethyl acetate in which the THF homopolymer is not soluble has been observed. In contrast to the previous copolymer, however, NMR spectroscopy indicates that γ-butyrolactone has been actually copolymerized in a lower proportion (<3%). This is also reflected in the IR spectrum of the copolymer by the weaker intensity of the $\nu(C{=}O)$ stretching vibration at 1735 cm^{-1} (Figure 8). The DSC diagram also shows two endothermic peaks at 301 and 321 K with heat of fusions $\Delta H_m \sim 9$ J/g and $\Delta H_m = 145$ J/g, respectively. Apart from the relatively low content of γ-butyrolactone steric considerations show that the ester units can be easier accomodated in the crystal lattice of the THF homopolymer and consequently the 020 and 110 wide-angle x-ray reflexes at $2\theta = 19.85°$ and $2\theta = 24.3°$ are less broadened than in the case of the ε-caprolactone copolymer. No significant break in the intensity–temperature curve of the 020 x-ray reflex could be observed for this copolymer.

We are currently testing the effectiveness of the catalytic system for other possible ring opening polymerizations. The results of these investigations and of systematic THF/ε-caprolactone and THF/γ-butyrolactone copolymerization experiments will be published later.

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A New Difunctional Anionic Initiator

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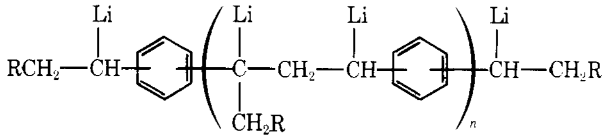
ABSTRACT: A new difunctional initiator for the preparation of 1,4-polyisoprene in hydrocarbon solvents has been obtained by the addition of *sec*-butyllithium to *m*-diisopropenylbenzene in the presence of 0.1 molecule of triethylamine per lithium site and subsequent reaction with 5 molecules of isoprene per lithium site. With this initiator, isoprene can be polymerized rapidly to an α,ω-dilithiopolyisoprene that has about the same microstructure as polymer obtained by initiation with a monoalkyllithium.

In one of several routes to ABA triblock copolymers from dienes and styrene, the diene is converted to an α,ω-dilithio-1,4-polydiene by initiation with a difunctional lithium carbanion followed by addition of styrene. This scheme has been employed by Fetters and Morton,[2] who used 1,4-dilithio-1,1,4,4-tetraphenylbutane to prepare the polydiene. The butane was obtained by reacting diphenylethylene with lithium in a hydrocarbon solvent containing a small amount of an aromatic ether. Later Karoly[3] described a similar scheme using 1,4-dilithio-1,4-dimethyl-1,4-diphenylbutane to make the polydiene. Karoly's butane was synthesized by reaction of α-methylstyrene with lithium in a hydrocarbon solvent using tetrahydrofuran as a promoter. In both dilithiobutane syntheses, the ether was necessary for the reaction. However, ether content was kept low enough to permit synthesis of polyisoprenes of relatively high cis-1,4 content.

Both compounds gradually lose solubility through association of alkyl lithiums, which leads to agglomerates of inactive initiator macromolecules. To prevent agglomeration, Fetters and Morton added enough isoprene to form polyisoprenes at each lithio site of sufficient length to ensure retention of solubility. Short polyisoprenes, of dp 5 or so, served this purpose. Karoly used this scheme also and so have we.

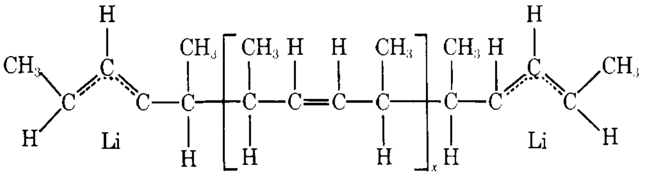
A third initiator that is free of ethers has been obtained by addition of *sec*-butyllithium to divinylbenzene in the presence of triethylamine. It is called DiLi-3[4] and is said to have the structure



R = *sec*-butyl; *n* = 0, 1, 2

DiLi-3 gives polyisoprene of high cis-1,4 content. However, its functionality is greater than 2 and in our hands was somewhat erratic in its batch to batch behavior. Polyisoprene made from it often had molecular weights quite different from those expected from the amounts of initiator used.

In connection with the synthesis of pivalolactone/diene triblock and block–graft copolymers,[5] which we have made and will report separately, we were interested in an anionic initiator that is exactly difunctional. Dilithio initiators are of general interest as is indicated by a recent study by Morton and co-workers[6] in which it was shown that lithium and 2,4-hexadiene react to form a difunctional initiator that has the formula



We have developed a dilithio initiator that is also effective in combining the features of difunctionality, good molecular weight reproducibility in isoprene polymerization, and high 1,4 content in resultant polyisoprenes. This initiator is formed by addition of *sec*-butyllithium to *m*-diisopropenylbenzene in the presence of a small amount of triethylamine followed by reaction with isoprene to improve solubility in hydrocarbon solvents. Since this is a complex molecule, we have adopted a code name for it. This name consists of "diplit", which denotes 1,3-bis(1-lithio-1,3-dimethylpentyl)benzene, and a number that denotes the size of the isoprene oligomer plus a second number to express equivalents of triethylamine. The composition we arrived at as a standard for isoprene polymerization is diplit 5.1 shown below.

Experimental Section

Materials. Solvents. As Morton and Fetters[7] have pointed out, it is necessary to provide solvents and monomers that are completely free of protonic materials if anionic polymerizations are to be successful. To ensure preparation of pure solvents, a Soxhlet extractor with a capacity of about 100 ml was modified by addition of a side port through which a stainless steel tube could be inserted through fittings made of Teflon, fluorocarbon resin. The extractor was attached to a large flask and a reflux condenser was sealed to the extractor. To the top of the reflux condenser was attached a T-tube. One side of the T-tube was connected to an argon cylinder through a valve and the other to a mercury filled bubbler. A stream of argon was passed through the T-tube to blanket the solvent and to flush with argon when the side port of the extractor was opened. The flask was filled ¾ full with solvent. In the case of tetrahydrofuran, sodium ribbon and diphenylethylene were added which caused the solvent to turn red because of formation of disodio-1,1,4,4-tetraphenylbutane. Solvent was kept under constant reflux in the closed extractor to assure that all protic materials would be washed into the flask where they would be removed by reaction with sodium. Complete removal of impurities was assured as long as the red color showed in the solvent in the flask. For cyclohexane, sodium ribbon was added along with a generous amount of a deep red solution prepared by adding 100 ml of $\sim$1.6 N *n*-butyllithium and 2.4 ml of diphenylethylene to 400 ml of cyclohexane.

Isoprene. Phillips Petroleum, Polymerization Grade isoprene was used. It was dried with calcium hydride and stored over calcium hydride. Just before use, butyllithium was added. The heat developed by the polymerization that ensued was used to distill unpolymerized monomer into the reactor or a reservoir from which the reactor was fed.

Triethylamine. Triethylamine was distilled twice. The second distillation, done just before use, was from butyllithium.

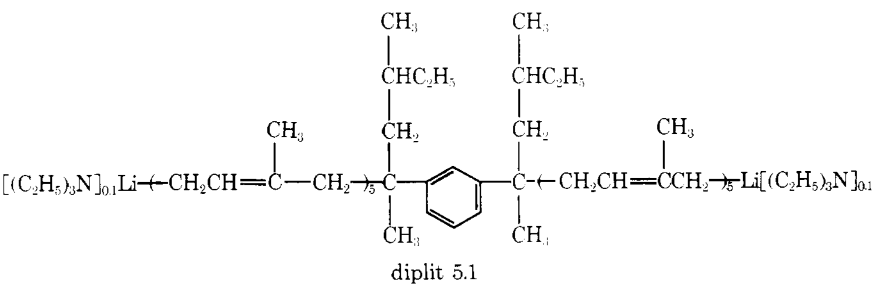
Butyllithium. *n*-Butyl- and *sec*-butyllithium were obtained from Foote Chemical Co. as 1.2–1.6 M solutions in hexane. Strength was determined by the Gilman double titration technique.[8,9]

***m*-Diisopropenylbenzene.** This compound was prepared in two steps from methyl magnesium bromide and dimethyl isophthalate. The first step was synthesis of 1,3-bis(1-hydroxyl-1-methylethyl)-benzene. A dry 5-l., three-necked flask was equipped with an efficient reflux condenser that had a T-tube attached at the top. One end of the T-tube was connected to a nitrogen source and the other to a bubbler. The flask was fitted with a motor-driven paddle stirrer made of Teflon and a dropping funnel. The flask was blanketed with nitrogen and then charged with 2.7 mol of methyl magnesium bromide dissolved in 2.5 l. of dry ether. As this solution was stirred, a mixture of 120 g of dimethyl isophthalate dissolved in 600 ml of dry ether was added dropwise to it from a dropping funnel over a 2-h period.

The resulting reaction mixture was poured with stirring over a mixture of 1 kg of ice, 200 ml of water, and 130 g of ammonium chloride. The ether layer was separated, the ether was removed by evaporation, and the solid so obtained was added to the aqueous layer. This aqueous layer was then neutralized, whereupon solid 1,3-bis(1-hydroxy-1-methylethyl)benzene precipitated. The solid was collected on a filter and then dissolved in 500 ml of benzene. The solution was heated under reflux using a Dean-Stark trap to remove water.

In the second step the bishydroxy compound was dehydrated by adding 30 g of *p*-toluenesulfonic acid to the above benzene solution and heating the resultant mixture under reflux for 2 h. After cooling, the solution was washed with water then with potassium carbonate solution and again with water. It was dried, the benzene was removed, and the yellow colored liquid that remained was distilled. The product amounted to 35 g (29% yield) boiling at 70–75 °C (1.5 mm).

1,3-Bis(1-lithio-1,3-dimethylpentyl)benzene. A dry, 200-ml bottle containing a metal magnetic stirring bar was flushed with dry argon and closed with a rubber septum. A hypodermic needle attached to an argon source was inserted into the septum and a slight positive argon pressure was maintained by use of a small mineral oil bubbler to provide back pressure in the argon line. A solution of 10 mmol of *sec*-butyllithium in 100 ml of cyclohexane was added to the bottle followed by addition of purified triethylamine. For 0.1 mol of amine per mol of alkyllithium, 0.14 ml of triethylamine was added. Next, the mixture was rapidly stirred and 0.05 mol of purified *m*-diisopropenylbenzene was added with a hypodermic syringe. This addition is usually made at room temperature but can be done at any temperature from 0 to 50 °C. As the addition of *sec*-butyllithium to *m*-diiso-



diplit 5.1

propenylbenzene proceeds, the solution turns red. The reaction mixture was allowed to stir overnight at room temperature after which time it had a deep red color.

The bifunctionality of the initiator was verified by NMR analysis. Decomposition of samples with water and with deuterium oxide gave products that had benzylic hydrogen and benzylic deuterium, respectively. Comparison of NMR absorption (Varian A60 NMR spectrometer) of benzylic protons at 2.5 to 3.0 ppm (tetramethylsilane as an internal standard) to absorption of aromatic protons at 6.9 to 7.2 ppm gave an integrated peak area ratio of 0.5 in the hydrogen case and 0.0 in the deuterium case. As a check, a comparison of total peak ratios for aliphatic protons from 0.5 to 3.0 ppm and aromatic at 6.9 to 7.2 ppm gave a value of 7.5.

The initiator solution was stabilized against agglomeration by adding isoprene via a hypodermic syringe. For diplit 5.1, there was added 0.5 mol for the size initiator sample described here. That the isoprene-stabilized initiator was bifunctional was established by carboxylating the initiator by reaction with carbon dioxide, converting the product to free acid, and titrating the free acid in tetrahydrofuran with 0.1 N tetrabutylammonium hydroxide in methanol. In this system, the end point is at pH 11.8–12. Neutral equivalent for the free acid was found to be 486, which corresponds to a composition containing 4.5 molecules of isoprene per lithio site. The combination of NMR data on unstabilized samples and titration data on isoprene-stabilized initiator indicate that trifunctional products claimed by Kamienski and Morrison[10] were not formed under the conditions used here.

Polyisoprene. A flame-dried, 2-l. reactor fitted with a sealed top, a T-tube for maintaining dry argon atmosphere, a stirrer, and a septum-stoppered inlet port was charged with 900 ml of highly purified cyclohexane and 120 ml (80 g) of purified isoprene. The reaction solution was heated to 50 °C and 64 ml of 0.1 N 1,3-bis(1-lithio-1,3-dimethylpentyl)benzene initiator solution was added. When the reaction mixture temperature reached 56 °C, the heating bath was removed and a cooling bath was applied to maintain the temperature at about 52 °C. After about 45 min, it was necessary to resume heating to keep the reaction temperature at 50–52 °C. Heating and stirring were continued for 2 h although polymerization was essentially complete in a much shorter time. Polymerizations with diplit 5.1 were conducted similarly.

With an initiator:isoprene ratio calculated to give a polyisoprene of $\overline{M}_n$ = 25 000 followed by carboxylation with CO_2, a product was obtained that had an $\overline{M}_n$ by GPC of 21 000. $\overline{M}_n$ by titration of the free acid using the procedure described for diplit 5.1 and calculated on the basis of two carboxylic groups per molecule was 21 410.

The infrared spectrum of polyisoprene made with diplit 5.1 contained the expected bands for 1,4 units and 3,4 units at 832 and 883 cm^{-1}, respectively. Comparison of peak areas indicated the microstructure of these polymers to be 92% 1,4 and 8% 3,4, the same as that of a control polymer made by initiation of isoprene with butyllithium.

GPC Determination. Molecular weight and polydispersity of polyisoprenes were determined on a Waters Model 200 Gel Permeation Chromatograph equipped with four Styragel columns arranged in a set to give a linear separation in molecular weight from 10^3 to 10^6. The eluting solvent was tetrahydrofuran. Calibrations were made using 272 and 17 M polybutadiene standards obtained from the Phillips Petroleum Co.

Results and Discussion

The use of 1,3-bis(1-lithio-1,3-dimethylpentyl)benzene as a difunctional initiator for preparing polyisoprenes with reactive ends is complicated by the need for a complexing agent, such as triethylamine, for rapid addition of *sec*-butyllithium to *m*-diisopropenylbenzene. Without the amine, addition is intolerably slow, and the product agglomerates through lithium bridge association complexes.

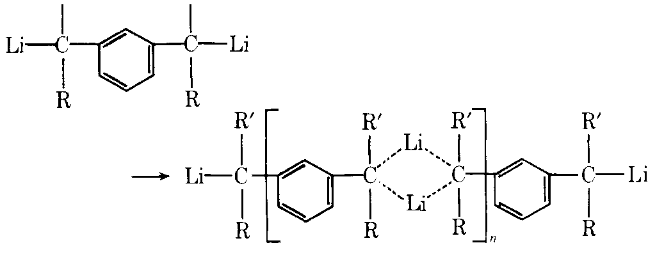


Table I
Characteristics of Polymers Made with Initiators of Varying Amine Content

Initiator	M_n by GPC × 10^{-3}	M_w/M_n	M_n of top 10% × 10^{-3}	Remarks
s-BuLi	18	1.24	37–58	Monomodal
Diplit 00	37	1.25	16–120	Monomodal
Diplit 03	22	4.70	260–600	Bimodal
Diplit 010	20	2.56	112–521	Bimodal
Diplit 01	26	2.77	160–300	Monomodal
Diplit 0.2	26	1.42	60–370	Monomodal
Diplit 0.1	25	1.23	49–122	Monomodal

The resulting polymer is insoluble and ineffective as a polymerization initiator.

The unsuitability of an initiator made without triethylamine, which is diplit 00, was demonstrated by attempted addition of *sec*-butyllithium to *m*-diisopropenylbenzene. Because addition in the absence of amine is very slow, the mixture was heated to 60 °C. As reaction took place, the solution turned a deep red as expected. However, a brown deposit also formed on the walls of the reaction vessel. To complete the addition, heating was continued for 5 h during which time a relatively large amount of insoluble brown product precipitated. When the organometallic in solution was used to initiate polymerization of isoprene in an amount calculated to give a M_n of 25 000, the resulting polyisoprene had an actual M_n of 37 000 as determined by GPC. It is believed that the higher than expected M_n is the result of loss of active initiator by agglomerization. When allowed to stand for a day or so, all of the bifunctional ingredient in the initiator was converted to insoluble agglomerate.

Although diplit 00 was so unstable that it had to be used immediately after preparation, the polyisoprene formed from it was of low dispersity as is shown in Table I. Furthermore, its molecular weight distribution curve did not have a large high molecular weight tail.

By using 3 equiv of amine per lithium site, agglomeration of the bislithio compound was reduced to a low level and a soluble, effective initiator (diplit 03) was obtained. However, polyisoprenes prepared using this compound had a bimodal molecular weight distribution and the very high dispersity of 4.70. The effect of high dispersity can be illustrated by noting that the top 10% of this polymer had a molecular weight range of 260 000–600 000 (Table I). The GPC curve for this polymer is shown in Figure 1.

Bimodality and high dispersity are indicative of more than one initiator specie. Though we have not identified additional initiators, Kamienski and Morrison[10] have said that organotrilithium initiators can be obtained by addition of 1,3-bis(1-lithio-1,3-dimethylphenyl)benzene to 1-(1-lithio-1,3-dimethylpentyl)-3-(1-methylethenyl)benzene in the presence of substantial amounts of triethylamine.

To demonstrate that bimodality was not associated with the polymerization method, initiation with *sec*-butyllithium in an amount designed to give an M_n of 25 000 was used as a control. This control polymer was monomodal, had a dispersity of 1.24, and the molecular weight range of the top 10% was only 37 000–58 000.

As diplit 03 aged, it deposited some insoluble material, which probably was a lithium bridge association agglomerate. It also lost active ingredient and gave polyisoprenes that, though lower in dispersity, were similar to those from unaged initiator in having bimodal molecular weight distributions. Dispersity of polyisoprenes made from initiator 52 days old was 2.11.

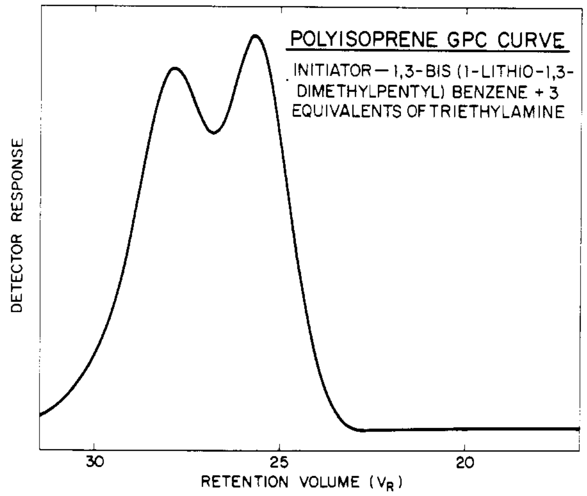


Figure 1.

Table II
Polyisoprenes of M_n = 25 000 Prepared Using Diplit 0.1

Initiator age, days	Initiator No.	Polyisoprene characteristics $M_n \times 10^{-3}$	M_w/M_n	M_n of top 10% × 10^{-3}
0	1	25	1.23	49–122
	2	23	1.31	49–167
1	2	27	1.34	90–249
2	1	27	1.25	54–128
	2	32	1.32	68–234
3	2	34	1.38	77–225
4	1	33	1.28	67–215
6	2	44	1.41	105–323
10	1	41	1.38	98–350
11	1	62	1.47	108–510
23	2	66	1.51	175–745

Increasing the amount of triethylamine gave initiators that produced polyisoprenes of somewhat lower polydispersity but which retained bimodal molecular weight distributions. Diplit 010 (Table I), for example, led to a polymer of polydispersity of 2.56 and a quite high molecular weight for the highest 10% of the sample.

As mentioned earlier, triethylamine is added to promote rapid addition of *s*-BuLi to the diisopropenylbenzene. It was found that the amount of amine could be reduced to 0.1 equiv without any great decrease in rate of addition of the organolithium compound to the double bond. Reduction in amine concentration was accompanied by a decrease in polydispersity. This behavior is illustrated in Table I for initiators containing from 1 to 0.1 equiv of triethylamine. Initiators with this range of amine content give polymers with monomodal molecular weight distributions. Diplit 0.1 behaves essentially as *sec*-butyllithium except, of course, for the desired attribute of giving α,ω-dilithiopolyisoprenes. This is illustrated in Table I, which shows that freshly made diplit 0.1 leads to a polyisoprene of predicted M_n, a dispersity of 1.23, and a maximum M_n of 122 000.

An important feature of an initiator from a convenience standpoint is stability over time. Stability studies on two different batches of diplit 0.1 are summarized in Table II. Both initiators gave polyisoprenes that were reasonably close to predicted molecular weight, were of low dispersity, and did not have an exceptionally high molecular weight tail. However, as they aged, the characteristics of both initiators worsened. Polyisoprenes made from initiator less than a month old were more than double the molecular weight of the original sample, had dispersities over 1.5, and contained an unusually high molecular weight fraction.

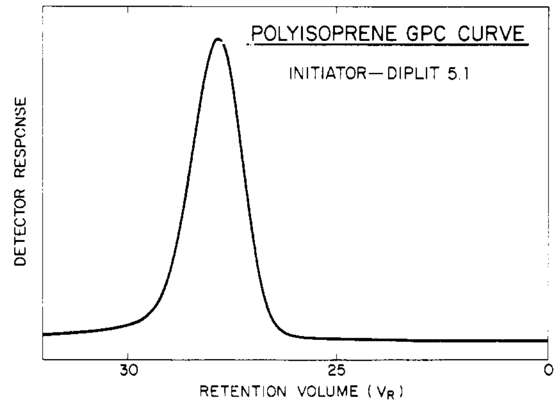


Figure 2.

Table III
Polyisoprenes of M_n = 25 000 Prepared Using Diplit 0.2

Initiator age, days	Polyisoprene characteristics $M_n \times 10^{-3}$	M_w/M_n	M_n of top 10% of 10^{-3}
0	26	1.42	60–370
1	27	1.37	61–250
2	28	1.37	65–250
3	32	1.37	83–350
7	47	1.47	120–500
32	85	1.69	267–1094

Table IV
Polyisoprenes of M_n = 25 000 Prepared Using Diplit 5.1

Initiator age, days	Polyisoprene characteristics $M_n \times 10^{-3}$	M_w/M_n	M_n of top 10% × 10^{-3}
0	23	1.31	48–136
1	23	1.35	50–214
2	23	1.35	50–168
3	24	1.33	50–168
6	23	1.31	49–176
16	24	1.24	48–140
30	24	1.24	48–146

Increasing amine content did not improve stability. Table III contains data for aging studies on diplit 0.2. Polyisoprenes made with 32 day old diplit 0.2 had even poorer characteristics than those made from the lower amine content material.

Stabilization of the initiator to prevent change with time has been accomplished by adding isoprene to form short oligomers on either side of the benzene nucleus. As with the Fetters and Morton and Karoly initiators, the diene oligomers improved solubility and prevented precipitation of inactive species. The size of the isoprene oligomers beyond that needed to maintain solubility is probably not critical. It was found that oligomers of dp 5 were satisfactory and polymerizations at various times up to 30 days with such a composition are shown in Table IV. Polymer made with 30 day old initiator was almost exactly the same as polymer made with freshly prepared initiator. Dispersity differences with time were not significant. However, dispersity decreased with age of initiator, which is an improvement. A typical GPC curve for these polymers is given in Figure 2.

Table V
Polyisoprenes of M_n = 50 000 Prepared Using Diplit 5.1

Initiator age, days	Polyisoprene characteristics $M_n \times 10^{-3}$	M_w/M_n	M_n of top 10% $\times 10^{-3}$
1	39	1.38	90–506
2	41	1.42	97–510
3	50	1.30	106–533
6	49	1.31	106–514
7	46	1.29	96–350

Table VI
Polymerization Time vs. Molecular Weight for Polyisoprenes of M_n = 25 000 Prepared with Diplit 5.1

Polymerization time at 60 °C, h	Polyisoprene characteristics $M_n \times 10^{-3}$	M_w/M_n	M_n of top 10% $\times 10^{-3}$
1	25	1.27	52–166
2	27	1.27	56–243
3	28	1.29	56–238
4	27	1.31	56–238

The relationship found to hold between initiator makeup and characteristics of polyisoprene of M_n = 25 000 also holds for higher molecular weight polymers. Data on the use of diplit 5.1 as the initiator in polymerizations calculated to give polyisoprenes of 50 000 molecular weight are given in Table V. Correspondence between calculated and actual M_n was within usual experimental variation. Polydispersity in all cases was well below 1.5.

In all these experiments, a polymerization time of 2 h was arbitrarily used. Though 2 h at 60 °C is known to result in high conversion of isoprene to polyisoprene, it was of interest to examine various polymerization times and relate the effect of polymerization time to differences in the product. We found very little difference in products prepared using shorter or longer polymerization periods. This is illustrated in Table VI which shows results obtained by GPC on polymerizations run at 60 °C for 1 to 4 h. Molecular weight is quite constant varying only from 25 000 to 27 000, which is within experimental error and dispersities ranged from 1.27 to 1.31.

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References and Notes

(1) Contribution No. 2334.
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Hypothesis about the Mechanism of Protein Folding[1]

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ABSTRACT: A three-step mechanism of protein folding, proposed in our previous paper, is applied here to postulate the nature of the intermediates in the folding of rubredoxin, ferricytochrome *c*, and lysozyme. Contact maps are calculated for these three proteins, and it is shown that they contain much information (such as the polarity of residues in contact regions) about the structure of the native protein. Elementary processes are described for the formation of contact regions. Based on these concepts, details of the pathways of folding these three proteins from the unfolded to the native structure are postulated, focusing on the formation of ordered backbone structures (such as α-helical, extended, and chain-reversal conformations) in step A of the three-step mechanism and on the formation of contact regions in response to medium- and long-range interactions in steps B and C. It was found that chain reversals can often play an important role in forming contact regions in step A (short-range interactions) and in step B (medium-range interactions) but not in step C.

In a previous paper,[3] a hypothesis was proposed for protein folding, wherein the globular structure of a native protein is thought to form by a three-step mechanism. It was also demonstrated[3] that such a three-step mechanism is necessary if the globular structure is to result from the folding process.

This proposed mechanism for the folding of a polypeptide chain to the globular structure of a native protein in a given medium involves the following three steps (which *may* proceed simultaneously): (A) Because of short-range interactions,[4] ordered backbone structures,[7] such as α-helical, extended, and chain-reversal conformations, are formed in a system at equilibrium under given conditions (e.g., above the denaturation temperature). (B) When these physical conditions are changed (e.g., by changing the temperature and/or solvent composition), so as to introduce medium-range interactions, the equilibrium is shifted, and small contact regions (defined in Figure 1 of ref 3 and in section III of ref 3), involving medium-range interactions, are nucleated among the amino acid residues both in the ordered and in the unor-