

# Chemistry of Polymer-Bound *o*-Benzyne. Frequency of Encounter between Substituents on Cross-Linked Polystyrenes

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**Abstract:** *o*-Benzyne was generated by oxidation of 1-aminobenzotriazole derivatives covalently bound to various polystyrene supports. When lead tetraacetate is employed as the oxidizing agent, in the absence of any other substrates, the intermediate is converted to a mixture of isomeric aryl acetates. This reaction is not observed for monomeric 1-aminobenzotriazoles, where dimerization is the predominant pathway. The results are explained by a low frequency of encounter between the polymer-bound intermediates which allow the relatively slow acetate formation to compete with the encounter-controlled dimerization process. Delayed trapping of the intermediate by a diene demonstrated a surprisingly long lifetime for the intermediate. When iodobenzene diacetate was used as oxidizing agent, no acetates were formed, and a rather complex series of reactions eventually resulted in intrapolymeric coupling of the benzyne. From the delayed trapping experiments, conducted under these two different sets of conditions, it can be concluded that the frequency of encounter between the intermediates bound to a 2% cross-linked polystyrene resin must lie between  $2.6 \times 10^{-2}$  and  $1.1 \times 10^{-3} \text{ s}^{-1}$ .

## Introduction

Use of cross-linked polystyrene resins as covalent supports for synthetic reagents has increased steadily since the pioneering work of Merrifield and his group.<sup>1</sup> One feature of this technique which has attracted particular interest is the possibility that functional groups attached to an insoluble polymer might be less prone to react with one another relative to independent small molecules with the same functional groups in solution. Such a "pseudodilution" effect could, in principle, enhance the utility of many reagents. Remarkably, the most common experience<sup>2,3,6</sup> has been that polymer substituents are capable of reacting quite extensively with one another. While there have been a few encouraging counterexamples,<sup>4,5,7</sup> the factors governing such reactions remain to be clearly defined. So far, experimental attention has been concentrated primarily on the effects of polymer morphology<sup>3,6</sup> and extent of functionalization (the effective concentration of reactive functional groups along the polymer backbone). On the other hand, the actual kinetics of intrapolymeric reactions have been largely ignored.

From the kinetic standpoint, the most important factor governing intrapolymeric reaction must be the frequency of encounters between reactive substituents. This encounter frequency has a fundamental significance equivalent to the diffusion-limited rate of collisions between monomeric reagents in solution. For polymer substituents this rate is limited not simply by diffusion, but rather by the potentially more restricted conformational motions of the polymer backbone. Despite the wealth of knowledge concerning many other aspects of polymer dynamics, there have been no measurements of the encounter frequency for substituents on any true macromolecules. The problem is particularly complicated for the cross-linked resins since the reactive substituents are likely to be distributed over a range of sites with widely variable mobility. Nonetheless, even a crude measure of this fundamental property would be of considerable value in attempting to analyze and predict the behavior of synthetically useful reagents.

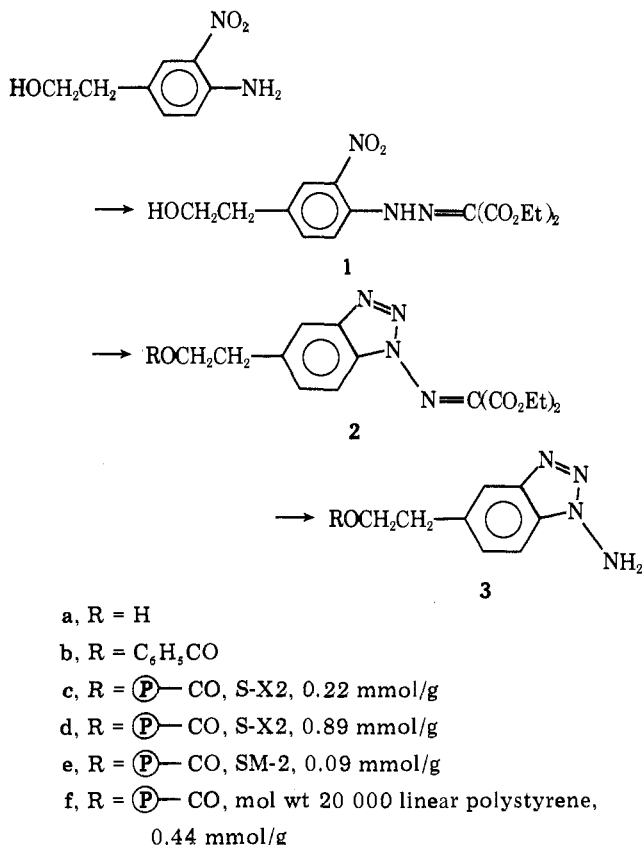
Our research has focused on the chemistry of *o*-benzyne (1,2-dehydrobenzene) covalently bound to a polystyrene support.<sup>7</sup> While monomeric benzyne undergoes very rapid dimerization in solution, this pathway was found to be greatly retarded for the polymer-bound analogue. Using the method of Campbell and Rees,<sup>8</sup> benzyne was generated by lead tetraacetate (LTA) oxidation of a 1-aminobenzotriazole deriv-

ative. Under these conditions dimerization was completely suppressed relative to a rather slow reaction with monomeric reagents in solution. More recently, it was found that these heterogeneous side reactions could be avoided by the use of an alternative oxidizing agent, iodobenzene diacetate (IBD). Under these conditions the reactive intermediates persist for even longer periods of time and are ultimately destroyed by intrapolymeric coupling. This fortuitous juxtaposition of very slow intrapolymeric coupling with more rapid heterogeneous reactions has provided a means to estimate the actual frequency of encounter between the polymer substituents. The qualitative details of these reactions will first be discussed, beginning with synthesis of the precursors, before considering the more general quantitative conclusions.

## Results and Discussion

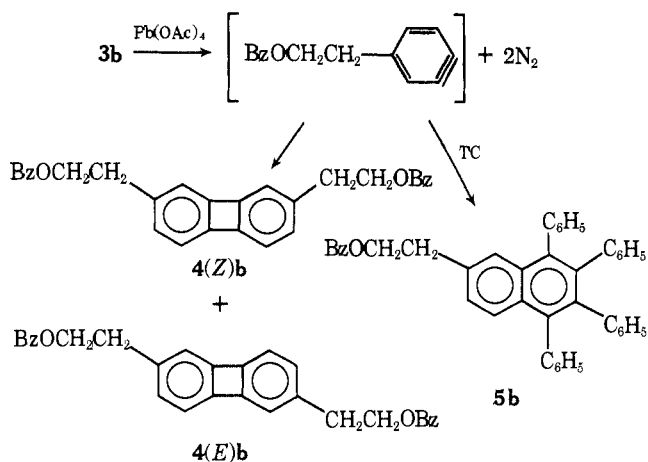
**Synthesis of the Precursors.** The diazonium salt of 2-nitro-4-( $\beta$ -hydroxyethyl)aniline was condensed with diethyl malonate to obtain hydrazone **1**. Catalytic reduction of the nitro group followed by a second diazotization yielded the amino-protected 1-aminobenzotriazole **2a** ( $R = H$ ). Each of the esters **2b-f** was prepared via conventional Schotten-Baumann procedure. The final step in the sequence, deprotection of the amino group, presented some problems. Simple acid- or base-catalyzed hydrolysis resulted in nonspecific cleavage of both imino and ester functions. The necessary selectivity was ultimately provided by the use of hydroxylamine in pH 5 buffered solution. (With the more highly cross-linked SM-2 polymer much longer reaction times were required and some ester hydrolysis resulted nonetheless.)

The polymer supports included two different macroreticular, divinylbenzene cross-linked resins, "Bio-beads" SM-2 and S-X2 (20 and 2% cross-linked, respectively) and a soluble, linear polystyrene of molecular weight 20 000. The monomeric benzoyl derivative, **3b**, was also prepared for control experiments. Oxidation of the precursors was carried out with samples suspended or dissolved in 1,2-dichloroethane. In the case of the 2% cross-linked polymer (S-X2) these conditions provided good swelling of the matrix. In order to optimize the speed of mixing of reagents, the entire reaction vessel was immersed in a thermostated ultrasonic bath. The progress of the reaction was monitored by volumetric determination of evolved gases. Two different oxidizing reagents were employed, lead tetraacetate (LTA) and iodobenzene diacetate (IBD).



Since the two provide very different results, the experiments will be described separately.

**Reactions with Lead Tetraacetate (LTA).** In control experiments, the chemistry of the monomeric derivative, **3b**, exactly paralleled that described by Campbell and Rees<sup>8</sup> for the parent 1-aminobenzotriazole. Reaction with an equimolar amount of LTA provided the two isomeric biphenylenes **4(E)b** and **4(Z)b** in 68% yield. (<sup>1</sup>H NMR at 270 MHz indicated that both isomers were present in roughly equal amounts.) The high yield of biphenylenes from this reaction, in contrast to other methods of benzyne generation, can be attributed to the fact that LTA oxidation of the aminotriazole is very rapid, and consequently high steady-state concentrations of benzyne are achieved. When the reaction was repeated in the presence of a slight excess of tetraphenylcyclopentadienone (TC), the usual Diels-Alder adduct, **5b**, was isolated in 80% yield.

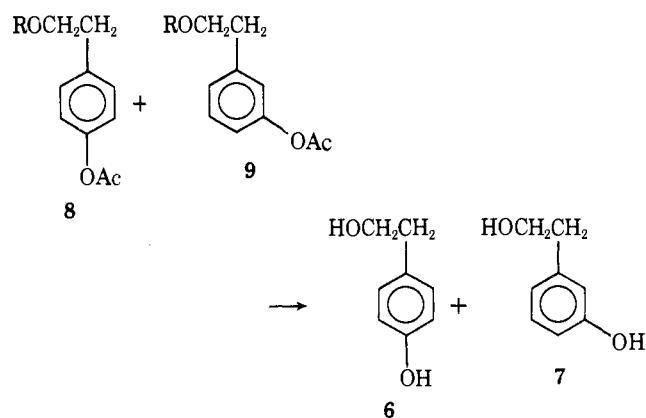


Oxidation of the polymer-anchored precursors **3c-f** in the presence of TC gave similarly high yields of Diels-Alder adduct. In each case, following treatment of the polymeric products with methylmagnesium bromide, the corresponding

alcohol **5a** was isolated in greater than 90% yield based on N<sub>2</sub> and CO evolved. The rate of the oxidation process was slowest for the more highly cross-linked resin **3e**. Figure 1 shows the progress of typical experiments involving the 2% cross-linked resin **3c**.

In the absence of TC, LTA oxidation of the polymer-anchored aminobenzotriazoles provided very different results from the monomeric analogue. With cross-linked resins **3c-e**, no detectable amount of the biphenylene diols **4(E)a** or **4(Z)a** could be isolated following treatment of the reaction products with methylmagnesium bromide. (Control experiments with authentic samples of these diols demonstrated that a yield of as little as 0.3% would not have escaped detection.) The diols were, however, obtained in yields as high as 25% from reaction of the soluble polymer **3f**. Apparently, a significant fraction of these dimers are the result of interpolymeric coupling. Thus, LTA oxidation of a 5% solution of **3f** resulted in rapid gel formation, indicating that multiple interpolymer linkages had been established.

The fact that no coupling products were obtained from the cross-linked resin precursors is particularly interesting in view of the fact that Crowley, Harvey, and Rapoport had demonstrated earlier<sup>6</sup> that extensive intrapolymeric reactions can occur with other S-X<sub>2</sub> supported reagents where the extent of functionalization was even lower than those employed in our experiments. It was of obvious importance to discover the ultimate fate of benzyne residues generated in the absence of TC. The first clue was provided by infrared (IR) spectra of polymer samples following reaction and removal of all soluble reagents. In addition to a strong band at 1720 cm<sup>-1</sup> corresponding to the benzoyl esters, and a weak absorption at 1750 cm<sup>-1</sup> attributable to a small amount of residual iminomalate, a new, moderately strong band appeared at 1760 cm<sup>-1</sup> indicating a new ester functionality. Following the usual treatment with methylmagnesium bromide, all of these bands disappeared, and from the soluble fraction *m*- and *p*-β-hydroxyethylphenols, **6** and **7** were isolated in a combined yield of 85% from the cross-linked precursors (65% from the linear polymer **3f**).



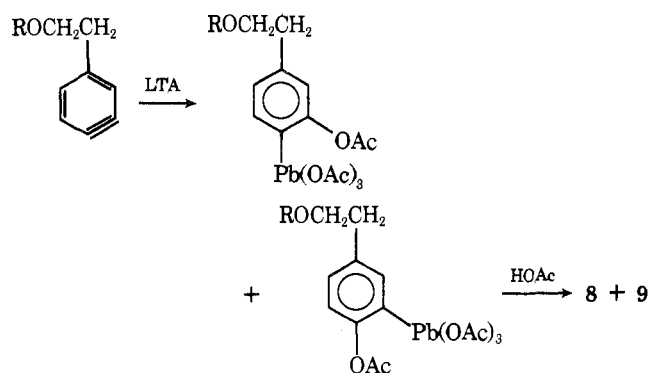
The IR evidence suggests that these phenolic alcohols are derived from the corresponding polymer-bound acetates, **8** and **9**. Addition of acetic acid or acetate ion to the triple bond of benzyne could account for such products. (Two equivalents of acetic acid is generated during the oxidation.) Alternatively, LTA might be involved. For example, "oxylumbation" of benzyne followed by acetolysis of the C-Pb bond would provide the same overall result.<sup>9</sup>

The important point is that no such products are formed from LTA oxidation of monomeric aminobenzotriazoles. Their prominence for the polymeric reagents must somehow be related to suppression of the coupling reaction. (The Diels-Alder reaction with TC demonstrates that the same intermediate is

Table I. Delayed Trapping Experiments<sup>a</sup>

sample	oxidizing agent (*)	<i>t'</i> , s	<i>X</i> <sub>a</sub> ( <i>t'</i> ), %	<i>X</i> <sub>b</sub> ( <i>t'</i> ), %	$\tau_p$ , s
3b	LTA	0	100	80	
3b	LTA (30)	45	0	0	(<5)
3c	LTA	0	100	99	
3c	LTA (30)	70	0	10	52 ± 3
3c	LTA (30)	50	0	13	27 ± 3
3c	LTA (40)	55	0	11	24 ± 3
3d	LTA	65	50	69	35 ± 3
3d	LTA	180	11	22	65 ± 6
3d	LTA (130)	130	0	19	58 ± 4
3e	LTA	0	100	99	
3e	LTA (70)	95	0	30	70 ± 8
3e	LTA (150)	220	0	16	103 ± 5
3e	LTA (90)	210	0	0	(<120)
3f	LTA (70)	85	0	0	(<15)
3b	IBD	0	100	90	
3d	IBD	0	100	90	
3d	IBD (1500)	1800	0	10	800 ± 80
3d	IBD (1800)	1800	0	4.5	820 ± 60

<sup>a</sup> (\*), approximate time at which N<sub>2</sub> evolution ceased; *t'*, time at which TC was added; *X*<sub>a</sub>(*t'*), amount of unreacted precursor remaining at *t'*; *X*<sub>b</sub>(*t'*), yield of Diels-Alder adduct.



involved in either case.) The most obvious hypothesis is that acetate formation is too slow to compete with dimerization for monomeric benzyne derivatives but becomes important for the polymeric counterparts owing to a much slower coupling rate, the consequence of a low encounter frequency. Consistent with this description, it was found that the lifetime of polymer-anchored benzyne dramatically exceeds that of the monomeric analogues.

A series of delayed trapping experiments was performed as follows. LTA oxidation of the precursors was carried out in the usual way, the extent of reaction being followed manometrically. At some point after a large fraction of the nitrogen had evolved excess TC was added. (In some instances the oxidation was allowed to go entirely to completion prior to addition of TC.) The yield of Diels-Alder adduct was determined following cleavage of the esters. Results are reported in Table I. The important qualitative result is that, for the cross-linked polymers, the isolated yield of Diels-Alder adduct consistently exceeded the percent of unreacted aminobenzotriazole present at the time when TC was added (except for very long delay times). In other words, a significant fraction of benzyne generated early in the reaction persists to be trapped following delayed addition of TC. This persistence amounts to many seconds, in contrast to the microseconds required for dimerization of monomeric benzyne.<sup>10</sup> In each case, **6** and **7** were the only other products. Thus, formation of **8** and **9** ultimately limits the lifetime of the intermediate under these conditions.

The lifetime of benzyne on the soluble polymer sample, **3f**, was insufficient to be reflected in delayed trapping experiments. As might have been anticipated, this material displays

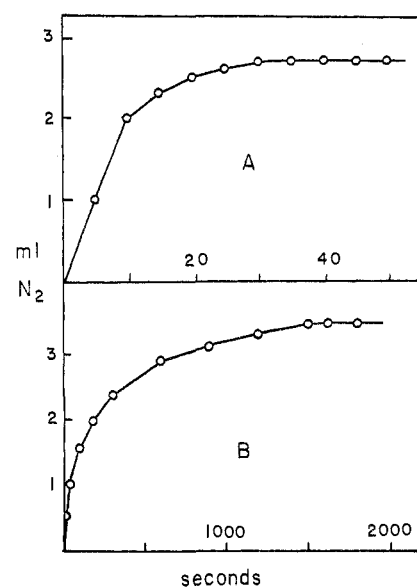


Figure 1. Typical reaction profiles for oxidation of sample 3d with Pb(OAc)<sub>4</sub>, A, and with PhI(OAc)<sub>2</sub>, B.

reactivity patterns intermediate between those of the resins and monomeric derivatives.

Since intrapolymeric processes play no role in any of the reactions yet described for the cross-linked precursors, a measure of the rate of disappearance of benzyne under these conditions would constitute an upper limit for the encounter frequency. We will return to this point later on. Under the circumstances it was of obvious interest to see if an alternative method for generating benzyne might circumvent formation of the aryl acetates and result in yet a longer lifetime for the intermediate. Following unsuccessful attempts to prepare other benzyne precursors in practical yield, we returned our attention to the aminobenzotriazole derivatives and their reactions with a different oxidizing agent.

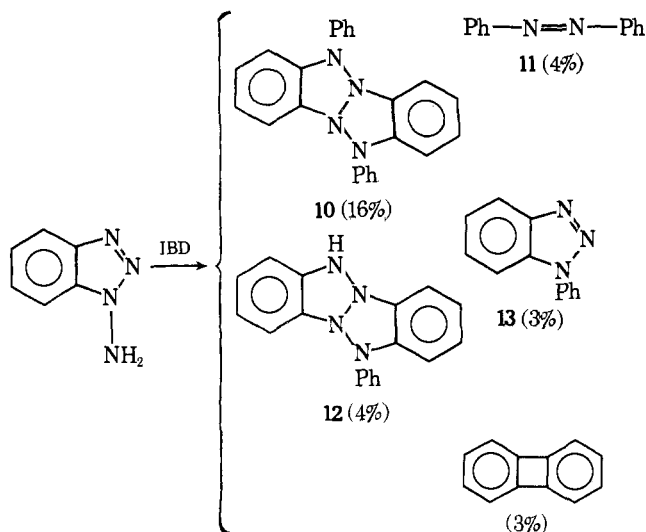
**Reactions with Iodobenzene Diacetate (IBD).** Campbell and Rees<sup>11</sup> had reported that oxidation of 1-aminobenzotriazole by IBD proceeded more slowly than LTA, and yielded a complex mixture of nitrogen-containing products among which only **10–13** were isolated and characterized. On reinvestigating this reaction, we discovered that biphenylene was also formed in 3% yield. Another important point, apparently missed by

Table II. Elemental Analyses of IBD Generated Products

sample <sup>a</sup>	% C	% H	% N
i	79.54	6.79	5.98 ± 0.3
ii	86.62	6.53	0.7 ± 0.1
iii	82.47	6.8	2.0 ± 0.3
iv	60.33	6.57	6.05
v	53.93	5.62	31.46

<sup>a</sup> (i) **3d**, (ii) **3d** following reaction with IBD and TC, (iii) **3d** following reaction with IBD alone, (iv) products of ester cleavage of iii, (v) **3a**.

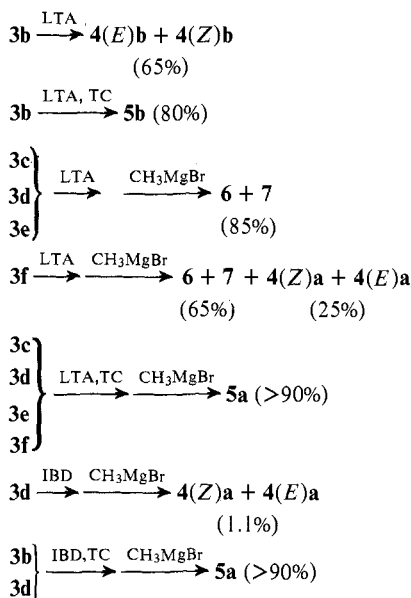
the original investigators, is that when the reaction is carried out in the presence of excess TC, the Diels–Alder adduct (1,2,3,4-tetraphenyl-naphthalene) is formed in excellent yield (98%). Thus, despite the complexity, this reaction is apparently a good source of benzyne. The low yield of biphenylene is not surprising in view of the fact that the reaction is slow and the steady-state concentration of intermediate must be quite low. One can only speculate as to the origin of the curious heterocyclic products. These may be derived from reaction of benzyne with various oxidation intermediates which still retain nitrogen. It may be relevant that IBD has been successfully employed to generate aminonitrene-like intermediates under very similar conditions, and that these intermediates are sufficiently long lived to be trapped by an olefin.<sup>12</sup>



Oxidation of the polymer-bound precursors with IBD provided substantially the same results. In the presence of TC, Diels–Alder adduct was obtained in high yield. When the reaction was run in the absence of diene, cleavage of the ester with methylmagnesium bromide provided a complex mixture of soluble products. Among these were the two isomeric biphenylene diols, **4(E)a** and **4(Z)a** (identified by comparison with authentic samples in gas chromatography and mass spectrometry). Significantly, these products were even obtained from the cross-linked resin **3d** in about 1.1% yield, the first evidence for intrapolymeric coupling of benzyne intermediates on these materials.

While it was not possible to identify the other components in this mixture (at least eight compounds), circumstantial evidence suggests that they may be derivatives of the same nitrogen heterocycles **10–13** characterized by Campbell and Rees.<sup>11</sup> Gas chromatography of the acetylated reaction mixtures showed that the same products were obtained from both monomeric and resin-bound precursors, **3b** and **3d**, respectively. Nitrogen content of the mixture was determined at three different stages of the experimental sequence. First, it was noticed that 20% less N<sub>2</sub> was liberated in those experiments

Table III. Summary of Products and Yields



conducted in the absence of TC than when it was present. The residual nitrogen was accounted for by combustion analyses of polymers following the reaction. Table II lists analyses of (i) a sample of **3d**, (ii) a sample of **3d** following reaction with IBD in the presence of TC, and (iii) a sample of **3d** reacted with IBD alone. The small quantity of nitrogen in (ii) is presumed to be due to about 2.5 mol % iminomalonnate-protected aminobenzotriazole, **2d**, which is known to contaminate these samples. (It is unreactive toward the oxidizing agents.) Taking this impurity into account, the nitrogen content of (iii) represents about 25% of that originally present in the aminobenzotriazole functions of **3d**. Finally, sample (iii) was treated with methylmagnesium bromide and the soluble fraction, (iv), subjected to combustion analysis. This mixture contained about 20% less nitrogen than an equal weight of **3a**. Thus of the total 0.89 mmol of aminobenzotriazole functions in 1 g of **3d**, about one-fourth are converted to other nitrogen-containing products, but only in the absence of TC. By analogy with the monomeric aminobenzotriazole, it seems likely that these products, in addition to the biphenylene diols, are derived from intrapolymeric reactions.

IBD oxidation of the soluble polymer, **3f**, was accompanied by gel formation, although the yield of biphenylenes was no higher than for the monomeric precursor. Since gel formation implies creation of sufficient cross-links to generate a semi-infinite network, it can be concluded that a minimum of 2 equiv of aminobenzotriazole residues per polymer molecule, or 23% of the total precursors, was involved in these interpolymeric couplings. (Gel formation was suppressed when the reaction was run in the presence of TC.)

Despite the much longer times required for the IBD oxidations (see Figure 1), delayed trapping experiments again succeeded in establishing the persistence of the intermediate. In fact, Diels–Alder adduct could be isolated from experiments where TC was added as much as 5 min after N<sub>2</sub> evolution had ceased (see entries in Table I). This represents a substantial increase in lifetime relative to the LTA oxidations. The result is consistent with the fact that the lifetime was limited by acetate formation in the LTA reactions whereas no acetate is formed with IBD. Formation of biphenylene diols with IBD indicates that over the longer time interval intrapolymeric coupling ultimately does occur.

The experiments described above (summarized in Table III) represent two limiting conditions for reaction on the cross-

linked resins. With LTA no coupling is observed and the rate of acetate formation therefore constitutes an upper limit for the frequency of encounter between benzyne residues. (Benzyne dimerization is known to be collision controlled in the gas phase.<sup>10</sup>) With IBD some, if not all, of the products are the result of intrapolymeric coupling. Therefore, the slower rate of disappearance of the intermediate under these conditions constitutes a lower limit for the encounter frequency. It remains to evaluate these rates or, equivalently, to evaluate the lifetime of the intermediate under the two different sets of conditions.

Before pursuing such quantitative details, it is important to review some areas of uncertainty surrounding these reactions and see how they may influence our conclusions. For example, it could be argued that benzyne per se need not be involved in any of these reactions. Perhaps some "masked" form of the aryne functionality is actually responsible for the formation of biphenylenes, Diels–Alder adducts, and aryl acetates. This possibility cannot be ruled out except by direct spectroscopic observation of the intermediate, which has not so far been practical despite the relatively long lifetime. The most serious problem created by this circumstance would be if biphenylene formation from this undefined intermediate were slower than encounter controlled. In view of the striking differences between products formed from monomeric and polymeric precursors with LTA this does not seem likely. Furthermore, even if the dimerization were somewhat slower than for benzyne itself, this process is clearly very fast for the monomeric analogue yet much slower for the polymer analogue (delayed trapping experiments were unsuccessful for both the monomeric and the soluble polymer precursors). It is therefore unlikely that our upper limit for the encounter frequency could be too low. There is no ambiguity relating to the lower limit inasmuch as the IBD reactions clearly give rise to intrapolymeric coupling products.

#### Kinetic Analysis of the Delayed Trapping Experiments.

Delayed trapping provides a means to evaluate the quantity of intermediate present at any time during an experiment. One might be tempted to derive the relevant rates from analysis of this data. Unfortunately, this cannot be done in a rigorous manner. One reason is that the overall rate law depends upon mass transport of soluble reagents to reactive sites along the polymer. It is not possible to characterize the kinetics of such a process given our ignorance of the detailed morphology of the polymer. There is also a more fundamental problem. The extent of cross-linking is likely to be important in determining the accessibility and mobility of polymer substituents. Since the coupling reactions which occur during the course of the IBD reactions increase the extent of cross-linking, the results must be very complex.

These problems forbid a proper kinetic analysis. However, in the present situation even an approximate quantitative result would clearly be of value. Accordingly, a purely empirical approach was devised based on a parameter  $\tau_p$ , called the persistence time of the intermediate to distinguish it from the true kinetic lifetime. Both definition and measurement of  $\tau_p$  are directly derived from details of the delayed trapping experiments.

Figure 2 shows a schematic diagram of a reaction profile representing the fraction of aminobenzotriazole residues,  $X_a(t)$ , which remains unreacted at any time  $t$  during an experiment. (This profile is obtained in practice from the gas evolution curves.) Suppose that TC were added to the mixture at time  $t'$ , and that Diels–Alder adduct was ultimately isolated in a yield of  $X_b(t')$ . To whatever extent intermediates generated earlier in the experiment had persisted until  $t'$ ,  $X_b(t')$  will be found to exceed  $X_a(t')$ . The difference,  $X_b(t') - X_a(t')$ , is a measure of the amount of intermediate present on the polymer at  $t'$ . We define  $\tau_p$  as the time elapsed since an amount

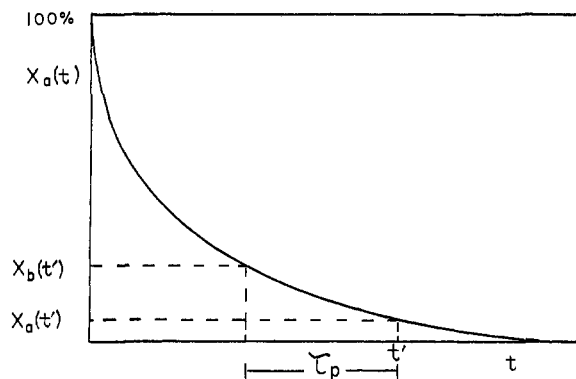


Figure 2. Schematic reaction profile illustrating the measurement of  $\tau_p$  from results of a delayed trapping experiment.  $X_a(t)$  is the percent unreacted precursor remaining at time  $t$ , and  $X_b(t')$  is the yield of Diels–Alder product from addition of TC at the time  $t'$ .

of precursor equal to  $X_b(t') - X_a(t')$  still remained unreacted on the polymer. In other words, this is the minimum amount of time, according to the reaction profile, required for generation and survival of the quantity of intermediate ultimately trapped by TC at  $t'$ .  $\tau_p$  is determined graphically from the gas evolution profiles as indicated in Figure 2.

The last column of Table I reports values of  $\tau_p$  for each of the delayed trapping experiments. Errors represent the operational precision for determining reaction profiles and yields. There are, in addition, somewhat larger random errors from one experiment to the next for any given precursor. Most likely this is due to the difficulty in exactly reproducing such parameters as the mixing rate. Taking these factors into account,  $\tau_p$  for **3d** is taken to be  $53 \pm 15$  s with LTA and  $810 \pm 80$  s with IBD. If we accept these as approximations to the true lifetimes, then upper and lower limits for the encounter frequency of reactive substituents on this material would be given by their reciprocals:  $2.6 \times 10^{-2}$  and  $1.1 \times 10^{-3} \text{ s}^{-1}$ , respectively. For a solution-phase reaction, this would correspond to an encounter-limited bimolecular reaction rate in a typical nonviscous solvent at concentrations of about  $10^{-11}$  M. The term "pseudodilution" is therefore a reasonably apt descriptive of the situation. (Experiments described here involved typically about 0.1 mmol of reagent suspended in a few milliliters of solvent.)

While the encounter frequency will undoubtedly vary with the extent of functionalization, our measurements are obviously too approximate to reflect this detail. It is strictly fortuitous that the upper and lower boundaries established by these experiments happen to be so close. The results may be of some general use in predicting or interpreting behavior of other polymer-bound reagents, particularly inasmuch as 2% cross-linked polystyrene resins are the most widely used supports. It is to be hoped that more systematic and versatile methods for determining encounter frequencies will be forthcoming. This parameter should be of prime importance in the rational design of solid-phase reagents and certainly warrants greater attention.

#### Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer. Spectra of the polymer samples were obtained as KBr pellets. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Bruker HX-270 spectrometer and all chemical shifts are relative to tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories Inc. Gas chromatographic separations were performed on a Perkin-Elmer Model 3920 using a  $\frac{1}{8}$  in. by 6 ft column packed with 5% OV-101 on 60/80 Anachrom ABS. High-resolution mass spectra were recorded

on a double-focusing AEI Model MS-9. An ultrasonic cleaning bath, Cole-Parmer Model 8845-30, was used to maintain rapid mixing rates during oxidation of the precursors.

**Reagents and Solvents.** Lead tetraacetate (LTA) (Eastman Chemicals) was recrystallized from glacial acetic acid and dried under reduced pressure. Iodobenzene diacetate (IBD) (Aldrich Chemical Co.) was recrystallized from benzene. 1,2-Dichloroethane was distilled from  $P_2O_5$  and stored over molecular sieves. Tetracyclone<sup>13</sup> (TC) was recrystallized from triethylene glycol.

**2-Nitro-4- $\beta$ -hydroxyethylaniline.** 4- $\beta$ -Hydroxyethylaniline<sup>14</sup> (2.4 g, 18 mmol) dissolved in 12 mL of acetic anhydride was treated with 2.5 mL of  $HNO_3$  while cooling in an ice bath. Cold water (50 mL) was added and the resulting precipitate was filtered, washed, and recrystallized from methanol to yield 3.5 g (75%) of 2-nitro-4- $\beta$ -acetoxyethylaniline: IR ( $CHCl_3$ ) 3375 (m), 1740 (s), 1700 (m), 1510 (s), 1340 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.05 (s, 3 H), 2.27 (s, 3 H), 2.95 (t,  $J = 6$  Hz, 2 H), 4.29 (t,  $J = 6$  Hz, 2 H), 7.51 (dd,  $J = 9$ , 2 Hz, 1 H), 8.11 (d,  $J = 2$  Hz, 1 H), 8.7 (d,  $J = 9$  Hz, 1 H). This material was dissolved in 25 mL of methanol and treated with 12 mL of 20% KOH in methanol. Solvent was evaporated and the red residue treated with 10 mL of cold water to obtain bright orange crystals. The product was recrystallized from ether (mp 85–86 °C). Analytical and spectral data were in good accord with the desired structure. IR ( $CHCl_3$ ): 3610 (m), 3520 (m), 4300 (m), 1640 (s), 1520 (s), 1340 (s)  $cm^{-1}$ .  $^1H$  NMR (acetone- $d_6$ ): 2.69 (t,  $J = 6$  Hz, 2 H), 3.3 (broad, 3 H), 3.65 (t,  $J = 6$  Hz, 2 H), 7.03 (d,  $J = 9$  Hz, 1 H), 7.33 (dd,  $J = 9$ , 2 Hz, 1 H), 7.88 (d,  $J = 2$  Hz, 1 H). Anal. Calcd for  $C_8H_{10}N_2O_3$ : C, 52.73; H, 5.54. Found: C, 52.62; H, 5.44.

**Diethyl Mesoxalate 2-Nitro-4- $\beta$ -hydroxyethylphenylhydrazone (1).** 2-Nitro-4- $\beta$ -hydroxyethylaniline (2 g, 11 mmol) was dissolved in 10 mL of concentrated HCl and then diluted with an additional 20 mL of water. To this was added 1.5 g of sodium nitrite in 7 mL of water while cooling in an ice bath. After stirring for 5 min, the mixture was filtered and the pale yellow solution of diazonium salt was added dropwise to 2 g (12.5 mmol) of diethyl malonate in 40 mL of water at 5 °C. Sodium acetate (8 g) was added in small portions during the course of the reaction. After stirring for 1 h the precipitate was filtered and dried. The product (3.2 g, 82.5%, mp 90–91 °C) was characterized by the following properties: IR ( $CHCl_3$ ) 3610 (m), 3400 (m), 1720 (s), 1625 (m), 1510 (s), 1340 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.41 (m, 6 H), 1.64 (broad, 2 H), 2.88 (t,  $J = 7$  Hz, 2 H), 3.96 (t,  $J = 7$  Hz, 2 H), 4.54 (m, 4 H), 7.61 (dd,  $J = 8$ , 2 Hz, 1 H), 8.07 (d,  $J = 8$  Hz, 1 H), 8.15 (d,  $J = 2$  Hz, 1 H). Anal. Calcd for  $C_{15}H_{19}N_3O_7$ : C, 50.97; H, 5.42. Found: C, 50.79; H, 5.44.

**Diethyl (5- $\beta$ -Hydroxyethylbenzotriazol-1-yl)iminomalonate (2).** 1 (3.2 g) in 50 mL of ethyl acetate containing 0.5 g of 10% Pd/C was hydrogenated at atmospheric pressure (4 h) to obtain 2.6 g (97%) of diethyl mesoxalate 2-amino-4- $\beta$ -hydroxyethylphenylhydrazone (mp 69–70 °C): IR ( $CHCl_3$ ) 3620 (m), 3490 (m), 3350 (m), 1720 (s), 1530 (m)  $cm^{-1}$ ;  $^1H$  NMR (acetone- $d_6$ )  $\delta$  1.29 (m, 4 H), 2.7 (t,  $J = 7$  Hz, 2 H), 3.7 (t,  $J = 7$  Hz, 2 H), 4.24 (m, 4 H), 5.5 (broad), 6.59 (dd,  $J = 8$ , 2 Hz, 1 H), 6.74 (d,  $J = 8$  Hz, 1 H), 7.1 (d,  $J = 8$  Hz, 1 H). Anal. Calcd for  $C_{15}H_{21}N_3O_5$ : C, 55.70; H, 6.54. Found: C, 55.93; H, 6.64.

The hydrogenation product was then dissolved in 30 mL of methanol and treated with 2 g of sodium nitrite in 15 mL of water. This homogeneous solution was added dropwise over a 45-min period to 50 mL of 4 N HCl cooled in an ice bath. After 15 min the mixture was filtered. The precipitate was dried and recrystallized from benzene-petroleum ether to obtain yellow needles (mp 78–79 °C): IR ( $CHCl_3$ ) 3600 (m), 1740 (s), 1620 (m), 1240 (s), 1040 (m)  $cm^{-1}$ ;  $^1H$  NMR (acetone- $d_6$ )  $\delta$  1.4 (m, 6 H), 2.87 (broad), 3.05 (t,  $J = 6$  Hz, 2 H), 3.85 (t,  $J = 6$  Hz, 2 H), 4.41 (m, 4 H), 7.71 (d,  $J = 8$  Hz, 1 H), 7.83 (d,  $J = 8$  Hz, 1 H), 7.98 (s, 1 H). Anal. Calcd for  $C_{15}H_{18}N_4O_5$ : C, 53.87; H, 5.43. Found: C, 53.76; H, 5.35.

**Functionalized Polymers 2c–f.** The polymers, "Bio-Bead" resins S-X2 and SM-2 (Bio-Rad Laboratories), and linear polystyrene (20 000 mol wt, Polysciences, Inc.), were partially carboxylated by the procedure of Letsinger et al.<sup>16</sup> (In each case, extent of functionalization was established by titration with standardized base.) These materials were next converted to the corresponding acid chlorides by treatment with refluxing thionyl chloride. (IR spectra showed strong absorption at 1770  $cm^{-1}$ .)

The acid chloride derivatives (1 g) were suspended (or dissolved in the case of 2f) in a mixture of 1 mL of dry pyridine and 15 mL of benzene and treated with an excess of the amino-protected alcohol,

1 (5 h at room temperature). Formation of the ester was evidenced by the appearance of IR absorptions at 1750 and 1720  $cm^{-1}$ .

**Benzyne Precursors 3c–f.** Deprotection of the aminotriazoles was accomplished by treating 4 g of the resin sample, 2c, 2d, or 2e, with a solution of hydroxylamine hydrochloride (3.5 g) and sodium acetate (0.5 g) in a mixture of benzyl alcohol, ethanol, and water in volumetric proportions 1:2:3. Progress of the reaction (45–50 °C) was monitored by IR analysis of polymer aliquots, in particular disappearance of the 1750- $cm^{-1}$  band and appearance of N–H stretching absorptions at 3350 and 3200  $cm^{-1}$ .

The linear polymer 2f (1 g) was dissolved in a solution of hydroxylamine hydrochloride (0.8 g) and sodium acetate (0.2 g) in water-ethanol-tetrahydrofuran (2:3:3). The polymer product was recovered by precipitation with methanol.

**Reactions with LTA and IBD.** In a typical experiment, a sample of precursor (3c–f, 0.25 g) was suspended in 3 mL of 1,2-dichloroethane in a 40-mL reaction flask immersed in an ultrasonic cleaning bath. The bath was maintained at 25 °C by means of an external thermostat. A solution of the oxidizing agent (LTA or IBD, threefold excess) dissolved in 2 mL of 1,2-dichloroethane was added rapidly from a pressure-equalizing dropping funnel and the volume of evolved gas was measured on a 10-mL buret. (Depending upon the particular experiment, TC was added either at the beginning of the experiment or after some appropriate delay; see text.)

Following completion of the reaction, polymer samples were filtered, washed thoroughly with solvent, and dried. The sample was then suspended in 5 mL of dry THF and treated with 1.5 mL of 2 M methylmagnesium bromide in ether. The mixture was stirred for 10 h. Water (2 mL) was added and the soluble products were recovered by continuous extraction with ethyl acetate. Further purification was accomplished by preparative thin layer chromatography on silica gel. The relevant analytical properties of each product are summarized below.

**1,2,3,4-Tetraphenyl-6- $\beta$ -hydroxyethylnaphthalene (5a):** mp 213–214 °C; IR ( $CHCl_3$ ) 3630 (m), 3480 (b), 1600 (m), 1480 (m), 1240 (s)  $cm^{-1}$ ; NMR ( $CDCl_3$ )  $\delta$  2.94 (t,  $J = 6$  Hz, 2 H), 3.9 (t,  $J = 6$  Hz, 2 H), 6.83 (m, 10 H), 7.2 (m, 10 H), 7.29 (dd,  $J_1 = 9$ ,  $J_2 = 2$  Hz, 1 H), 7.48 (d,  $J = 2$  Hz, 1 H), 7.63 (d,  $J = 9$  Hz, 1 H); mass spectrum  $m/e$  476.209 ( $M^+$ , calcd for  $C_{36}H_{28}O$ , 476.214).

***p*- and *m*- $\beta$ -Hydroxyethylphenols (6 and 7).** The mixture of these two compounds gave a positive ferric chloride test. As their bisacetyl derivatives, they could be separated by gas chromatography. IR and mass spectra were obtained on the mixture of the two diols. IR ( $CHCl_3$ ): 3600 (m), 3610 (m), 2950 (s), 1600 (m), 1100 (s), 1010 (s), 800 (m)  $cm^{-1}$ . Mass spectrum:  $m/e$  138.066 (81%,  $C_8H_{10}O_2$ ), 120.057 (12%,  $C_8H_8O$ ), 108.058 (95%,  $C_7H_8O$ ), 107.050 (100%,  $C_7H_7O$ ). (These data are in good accord with known<sup>15</sup> fragmentation patterns for the  $\beta$ -hydroxyethyl groups.)  $^1H$  NMR ( $CDCl_3$ ): para  $\delta$  7.07 (d,  $J = 8$  Hz, 2 H), 6.76 (d,  $J = 8$  Hz, 2 H), 3.85 (t,  $J = 7$  Hz, 2 H), 2.83 (t,  $J = 7$  Hz, 2 H); meta  $\delta$  7.15 (t,  $J = 8$  Hz, 1 H), 6.76 (d,  $J = 8$  Hz, 1 H), 6.69 (overlapping d and s, 2 H), 3.85 (t,  $J = 7$  Hz, 2 H), 2.83 (t,  $J = 7$  Hz, 2 H).

**2,6-Bis( $\beta$ -hydroxyethyl)biphenylene (4(E)a) and 2,7-Bis( $\beta$ -hydroxyethyl)biphenylene (4(Z)a).** These two isomers could be cleanly separated by fractional recrystallization from ether-petroleum ether. The less soluble isomer melted at 174–177 °C while the other melted at 125–128 °C. Spectral properties did not permit unambiguous distinction between the two. IR ( $CHCl_3$ ): 3600 (m), 1600 (m), 1100 (s)  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.67 (6,  $J = 7$  Hz, 4 H), 2.92 (b, 2 H), 3.73 (t,  $J = 7$  Hz, 4 H), 6.6 (m, 6 H), differs slightly in chemical shift between the two isomers). Mass spectrum of bisbenzoyl derivatives:  $m/e$  224.082 (100%, calcd  $M^{2+}$  for  $C_{30}H_{22}O_4$ , 224.083).

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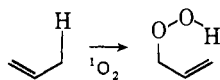
## Chemistry of Singlet Oxygen. 30. The Unstable Primary Product of Tocopherol Photooxidation<sup>1</sup>

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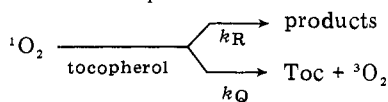
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**Abstract:**  $\alpha$ -Tocopherol (vitamin E) reacts with singlet molecular oxygen both by a quenching process and by irreversible reaction to give products, and this scavenging action may be one mode of its biological antioxidant function. Final reaction products such as  $\alpha$ -tocopherol quinone and  $\alpha$ -tocopherol quinone epoxide have been reported and a mechanism involving endoperoxide intermediates has been proposed by other workers. We have investigated the photooxidation of  $\alpha$ -tocopherol at low temperature and identified the primary product as the modestly stable *hydroperoxydienone* (**6**). The structure of **6** has been characterized by IR, UV, <sup>1</sup>H and <sup>13</sup>C NMR, and mass spectroscopy. On decomposition of **6**,  $\alpha$ -tocopherol quinone (**1**) and the quinone epoxide (**2**) are formed; reduction of the intermediate with triphenylphosphine gives **1** as sole product.

Lipid peroxidation is a significant pathological process which alters membrane activity and function. Singlet molecular oxygen (<sup>1</sup>O<sub>2</sub>) is believed to be involved in some cases in peroxidation of biological lipids;<sup>3,4</sup> it can be produced under the influence of light and a sensitizing pigment, or in a variety of nonphotochemical processes involving oxygen, peroxides, or superoxide.<sup>3,5</sup> Although many of the tests by which it has been detected in biological systems are not sufficiently specific to distinguish singlet oxygen unequivocally from other oxidizing species such as hydroxyl radical, halogens, or alkoxy radicals, the evidence is highly suggestive that <sup>1</sup>O<sub>2</sub> does occur as a pathological byproduct of certain enzymatic processes. Once formed, <sup>1</sup>O<sub>2</sub> is known to be capable of reaction with unsaturated lipids (such as fatty acids or cholesterol) to yield peroxides according to an "ene" mechanism as shown below.<sup>3,5,6</sup>

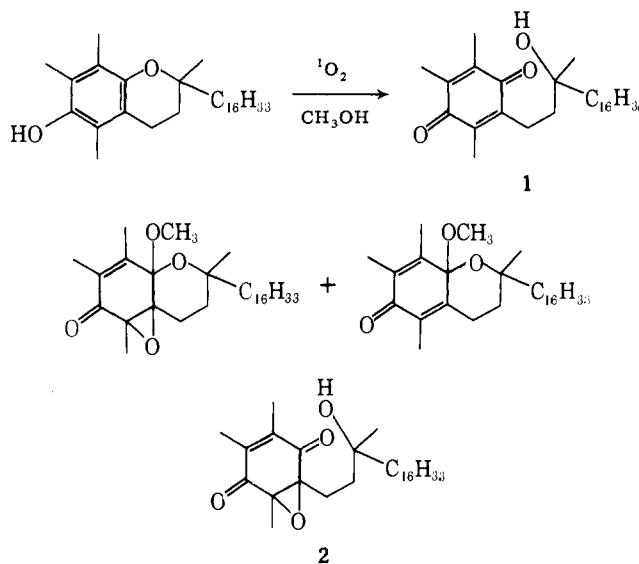


Tocopherols (vitamin E) act as biological antioxidants. Previous attention has centered on their importance as radical chain terminators,<sup>7,8</sup> and this is clearly an important mode of their antioxidant function.<sup>3,4</sup> However, it was recently demonstrated that tocopherols are capable of highly efficient singlet oxygen scavenging, both by a quenching process and by irreversible reaction to form products.<sup>9-15</sup>



Quenching tends to predominate, with the ratio of the two processes dependent on solvent polarity and ranging from 14:1 in CH<sub>3</sub>OH to about 120:1 in less polar solvents. Rate constants for the reaction, determined by us and by other investigators, are summarized in Table I. The overall reaction efficiency is such that  $\alpha$ -tocopherol at a concentration as low as 10<sup>-5</sup> M can intercept 50% of the <sup>1</sup>O<sub>2</sub> in nonpolar solvents. It has been proposed that singlet oxygen scavenging may be an additional protective biological role of tocopherol.<sup>9-15</sup>

The products of tocopherol photooxidation were reported by Grams et al.<sup>10,11</sup> to be a mixture of tocopherol quinone (**1**) and the quinone epoxide (**2**), along with methanol adducts.



These authors suggested<sup>10,11</sup> that the products derive from several endoperoxide intermediates **3-5** which result from 1,4

