Characterization of Organic Substrates Bound to Cross-linked Polystyrenes by ^{13}C NMR Spectroscopy

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The ^{13}C NMR spectra of a wide variety of organic substrates bound to 2% cross-linked polystyrenes may be obtained routinely, provided the resins can be sufficiently swollen. The ^{13}C chemical shifts of polymer-bound trityl alcohol, polymer-bound monotrityl ethers of the symmetrical diols $HO(CH_2)_nOH$ (n=2, 4, 6, 7, 9 and 10), and some related intermediates in the solid phase synthesis of insect pheromones are presented. ^{13}C shift additivity correlations, differing little from those in free trityl ethers, are drawn.

The determination of the structure of organic substrates bound to cross-linked polystyrenes is a problem of great interest to workers involved in solid phase peptide synthesis,[1] organic synthesis on solid phases,[2] and functionalized polymers for use as chemical reagents.[3,4] Chemical methods of analysis, such as functional group analysis, elemental analysis, and removal of the organic substrate from the polymer can be time-consuming, inaccurate and destructive, while simple physical methods such as IR and ESR spectroscopy give limited information on the exact structure of the polymer-bound substrate.[3,5]

^{13}C NMR spectroscopy has been applied to the characterization of a wide variety of insoluble bulk materials,[6–10] but there have been limited reports concerning the ^{13}C NMR spectra of organic substrates bound to cross-linked polystyrene.[11] However, two very recent publications,[12,13] concerned with the use of ^{13}C NMR spectra in the determination of the chloromethylation levels of cross-linked polystyrenes, prompt us to report our findings on the ^{13}C NMR spectra of a wide variety of organic substrates bound to 2% cross-linked polystyrenes. Our interest in the synthesis of insect pheromones on cross-linked polystyrenes[2,14–16] has led us to prepare a series of polymer-bound monotrityl ethers of symmetrical diols[14–16] and more complex polymer-bound synthetic intermediates. The final products of these syntheses were characterized by removal of the synthetic product from the polymer,[14–16] but the structure of the polymer bound intermediates or their purity was not adequately determined. ^{13}C NMR spectroscopy allows characterization of these insoluble polymer-bound organic substrates for the first time.

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EXPERIMENTAL

Carbon-13 NMR spectra were determined in the Fourier mode using a Bruker HFX-270 spectrometer at 67.89 MHz. (It is worth noting that good spectra may be obtained using lower field strength spectrometers.) A Nicolet 1180 computer was used to acquire data. In general, a spectral width of 15 kHz was observed in 16 K data points using an approximate pulse angle of 60° and averaging 2–4 K acquisitions. In some cases more acquisitions were obtained to enhance the signal-to-noise of low intensity peaks, and delays of 10–15 s between pulses were used when integration was desired. Samples were contained in 10 mm o.d. tubes. Solvent induced swelling of 0.75 g of polymer in 2–2.5 ml of deuterochloroform generally produced an adequate sample volume of the appropriate slurry consistency. However, when the solid polymer bead size was small a greater weight of polymer per unit volume of solvent was required. Internal referencing was achieved using the centre peak of deuterochloroform ($\delta = 77.0$ ppm).[17]

RESULTS AND DISCUSSION

General features

As noted by Manatt *et al.*,[12] solvent swollen cross-linked (1–2%) polystyrenes studied as slurries exhibit relatively narrow ^{13}C NMR signals, and only trivial differences in chemical shifts exist between soluble and solvent swollen, insoluble polystyrenes. At the outset of our studies we invoked the additional premise that segmental motion[18] of side chain substituents attached to the backbone polymer will result in sharply defined

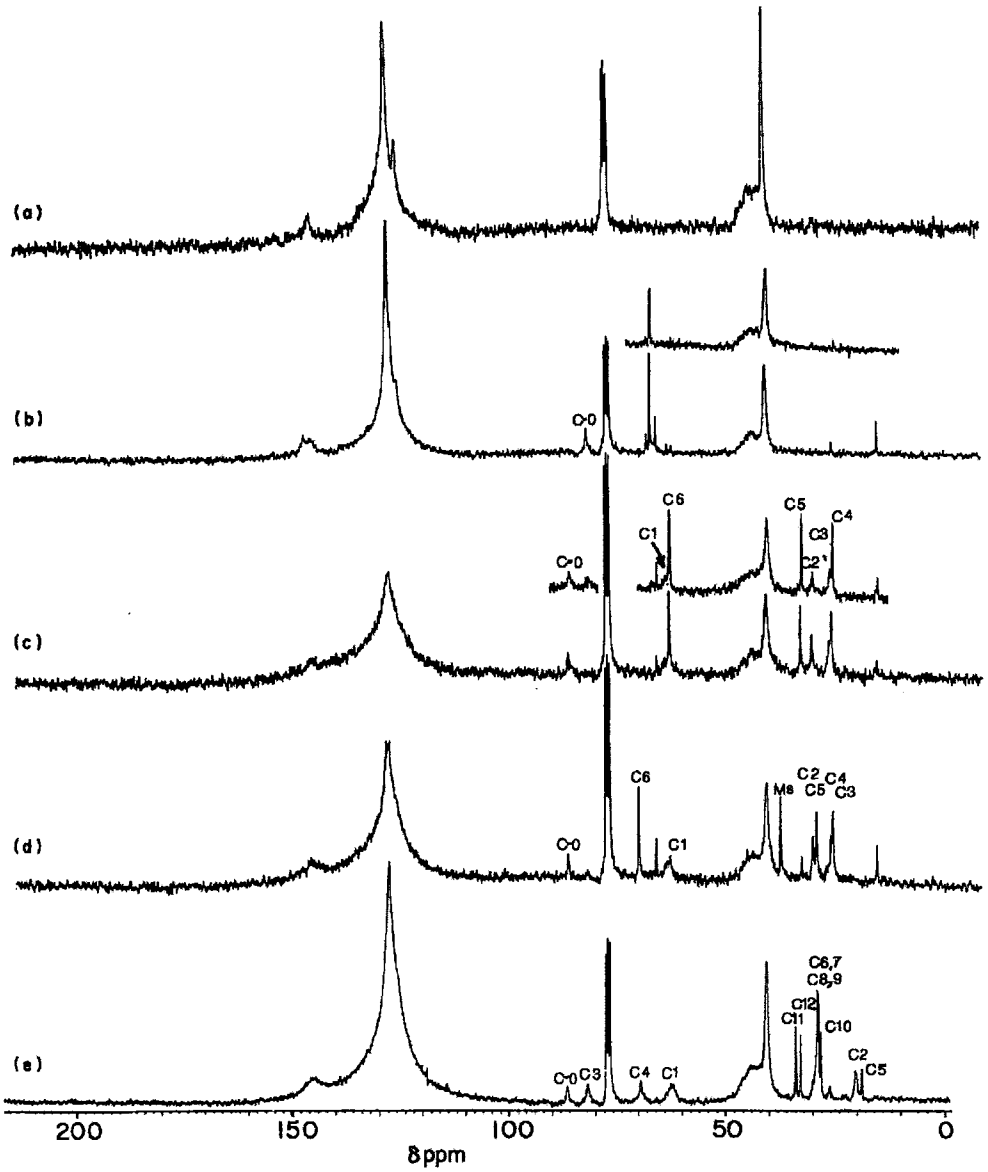

Figure 1. The ^{13}C NMR spectra, determined at 67.89 MHz, of solvent (deuterochloroform) swollen slurries of (a) Eastman 2% divinylbenzene cross-linked polystyrene, (b) polystyrene bound trityl alcohol; inset shows the same spectrum after solvent evaporation and resuspension, (c) the polymer-bound monotrityl ether of hexanediol **1**; inset is the spectrum obtained using a pulse delay of 10 s, (d) the polymer-bound methylsulphonate derivative **2** of **1** and (e) the polymer-bound C_{12} bromoalkyne **3**. The side chain carbon atoms are numbered from the trityl ether anchoring site, C—O refers to the trityl carbinol carbon and Ms to the methylsulphonate methyl carbon.

^{13}C NMR signals for the more mobile portions of the substituent molecules. In addition, our observations indicate that resonances of the carbon atoms close to the polymer binding site are broadened relative to those associated with portions of the side chains considered to be more freely rotating. Clearly, this indicates increasing T_1 and T_2 values for the carbon atoms of the side chain substituents with distance from the polymer backbone. Furthermore, we expected that trace materials (not necessarily polymer-bound) would exhibit the normal line widths of solution spectra. Our qualitative view is substantiated by the very recent detailed analysis of the molecular dynamics of polymer chains in solution provided by Levy *et al.*[19] However, while qualitatively valid, the simple model of isotropic motion in polymer side chains cannot be quantitatively applied in the analysis of relaxation and nuclear Overhauser parameters,[19] but can clearly aid in the differentiation between molecular sites involved in free or restricted motion. Most significant from an assignment point of view are the obvious broad lines (relatively shorter T_2 values) generally associated with the first three carbon atoms of the side chain substituents.

Figure 1 shows a montage of spectra arising from a sequence in a polymer-bound synthesis. In the 2% cross-linked polystyrene spectrum (Fig. 1(a)) ^{13}C NMR signals characterizing the quaternary aromatic carbons (145.8 ppm), the *ortho* and *meta* carbons (128.0 ppm), the *para* carbons (125.7 ppm) and the backbone methylene and methine carbons (40.4 and 43.0 ppm) are observed. The spectrum of polymer-bound trityl alcohol, prepared according to published procedures,[15] is shown in Fig. 1(b). The characteristic broad line at 81.9 ppm is attributed to the quaternary carbon atom in the triphenylcarbinol group and that at 147.0 ppm to the α-carbons in the phenyl ring (corresponding carbons in trityl alcohol 79.4 and 149.2 ppm).[20] The sharp resonances at 67.9, 67.0, 65.8 and 15.2 ppm must be attributed to impurities. The presence of these impurities prompted us to adhere strictly to our published procedure for the preparation of polymer-bound trityl alcohol.[15] Impurities were observed in some preparation batches when the benzophenone was stirred overnight with polymer-bound phenyllithium. In fact, we suggest that optimization of reaction yields can be achieved by monitoring the ^{13}C NMR spectra of the products. Some impurities were also removed by solvent evaporation and resuspension to provide spectra with zero or reduced intensities at 15.2, 65.8 and 67.9 ppm. Off-resonance spectra and correlations with literature data suggest that the 'impurity peaks' arise from solvent shifted or polymer-bound ethylbenzene (15.2 ppm, literature,[21] 15.8 ppm), benzyl alcohol (66.9 ppm, literature,[22] 64.5 ppm) and two tertiary aliphatic alcohol functions (67.8 and 65.7 ppm), but not reaction solvents,[15] such as *N,N,N',N'*-tetramethylethylenediamine (δ 57 and 46 ppm).[23]

The spectrum of the polymer-bound monotrityl ether of hexanediol **1** shown in Fig. 1(c) is characteristic of many of the polymer-bound substrate species studied. Notably, the polystyrene resonances are broadened compared to those in straight polystyrenes,

Ⓟ—Tr—O—$(CH_2)_6$OR — **1** R = H; **2** R = OSO_2Me

Ⓟ—Tr—O—$(CH_2)_2C{\equiv}C(CH_2)_8Br$ — **3**

Ⓟ—Tr—O—$(CH_2)_2C{\equiv}CH$ — **4**

Ⓟ—Tr—O$(CH_2)_6C{\equiv}C(CH_2)_2CH_3$ — **5**

Ⓟ—Tr—O$(CH_2)_6CH{=}CH(CH_2)_3CH_3$ — **6**

Ⓟ—Tr—O$(CH_2)_6C{\equiv}C(CH_2)_2C{\equiv}C(CH_2)_3CH_3$ — **7**

where Ⓟ denotes polystyrene backbone

and the β-substituent shift (+4.2 ppm) compared to the polymer-bound trityl alcohol quaternary carbon characterizes ether formation. The motional properties and their effects on the relaxation behaviour of the side chains clearly produce two distinct groups of resonances; low intensity, short T_1 (~0.1–0.5 s) at 26.1, 30.0 and 64.0 ppm, and higher intensity, longer T_1 (~2–3 s) at 25.7, 32.6 and 62.9 ppm). (T_1 estimates are derived from consideration of the intensity effects observed in the spectra using different acquisition delays.) Chemical shift correlations with hexanediol, the monotrityl ether of hexanediol[24] (Table 1), along with the qualitative relaxation considerations, establishes the order of the shifts given in Table 1. Chemical shift additivity is illustrated in the methylsulphonate derivative **2**, as shown in Fig. 1(d). Typical β- and γ-substituent shifts of +7.1 and −3.6 ppm are noted. The very broad resonance, 63.1 ppm, and the low intensity signals at 81.9 and 32.4 ppm, suggest the presence of the unreacted polymer-bound monotrityl ether of hexanediol and polymer-bound trityl alcohol. The commonly occurring 'impurities' were also observed in the unevaporated sample.

Figure 1(e) shows the ^{13}C spectrum of a polymer-bound C_{12} bromoalkyne **3** derived using an alternative synthetic precursor, the monotrityl ether of ethylene glycol. Confirmation of the assignments given in Table 1 is obtained by comparison with the spectrum of the

Table 1. ^{13}C chemical shifts of selected substrates in polymer-bound syntheses

Carbon position[a]	Compound 1[b]	2	3[c]	4	PTrOH[d]
1	64.0	63.2	61.9	61.8	—
2	30.0	29.8	20.3	20.0	—
3	26.1	(25.2)	81.8	81.8	—
4	25.7	(25.7)	69.6	69.3	—
5	32.6	29.0	18.8	—	—
6	62.8	69.8	28.7	—	—
7	—	—	28.7	—	—
8	—	—	28.9	—	—
9	—	—	28.9	—	—
10	—	—	28.1	—	—
11	—	—	32.7	—	—
12	—	—	33.9	—	—
Ms[e]	—	37.2	—	—	—
Carbinol carbon	86.2	86.2	86.5	86.6	81.9

[a] Side chain numbered from the ether anchoring site, δ ppm with respect to TMS.
[b] ^{13}C shifts in the monotrityl ether of hexanediol δ 63.5, 30.0, 26.1, 25.6, 32.7 and 63.0 ppm, trityl group δ 86.4, 144.5, 128.7, 127.7 and 128.8 ppm.
[c] cf. ^{13}C shifts in 12-bromo-3-dodecyne-1-ol, 61.4, 23.2, 82.6, 76.4, 18.7, 28.7, 28.6, 28.9, 28.9, 28.1, 32.8 and 33.7 ppm.
[d] Polymer-bound trityl alcohol.
[e] The methyl resonance of the mesylate group.

Table 2. ^{13}C chemical shifts of the polymer-bound monotrityl ethers of the symmetrical diols $HO(CH_2)_nOH$

	Carbon position[a]									
n	1	2	3	4	5	6	7	8	9	10
2[b]	61.8	69.3	—	—	—	—	—	—	—	—
4	63.4	26.6	29.9	62.7	—	—	—	—	—	—
6	64.0	30.0	26.1	25.7	32.6	62.8	—	—	—	—
7	63.5	30.0	26.2	29.2	26.6	32.6	62.8	—	—	—
9	63.5	30.0	26.2	25.7	29.4	29.3	29.4	32.7	62.9	—
10[c]	63.6	30.1	26.2	29.4	29.4	29.4	29.4	25.7	32.7	62.8

[a] Side chain numbered from the trityl ether anchoring site. δ ppm with respect to TMS.
[b] For $n=2$ mesylate derivative, principal component shifts δ C-2: 71.3, C-1: 60.8 and Me: 37.5 ppm.
[c] δ ^{13}C ppm in the monotrityl ether of decanediol: phenyl carbons δ144.6, 128.8, 127.6 and 126.8 ppm, carbinol carbon 86.4 ppm, methylenes 63.7, 30.1, 26.3, 29.4, 29.5, 29.5, 29.4, 25.8, 32.8 and 63.0 ppm.

analogous polymer-bound trityl ether 4 of 1-butyne-4-ol (61.8, 20.0, 81.8 and 69.3 ppm), cf. the ^{13}C shifts in 1-butyne-4-ol, 60.8, 22.7, 81.5 and 70.1 ppm. It is unfortunate that the lines at 81.8 and 61.8 ppm are so similar in shift to those of characteristic carbons in unreacted polymer-bound trityl alcohol and its glycol ether (81.8 and 61.9 ppm), since this precludes estimation of the synthetic purity of the polymer-bound species.

Symmetrical diol derivatives

The ^{13}C chemical shifts of the polymer-bound monotrityl ethers of the symmetrical diols $HO(CH_2)_nOH$, where $n=2$, 4, 6, 7, 9 and 10, along with the mesylate for the $n=2$ case, are given in Table 2. (The data for $n=6$ are reproduced from Table 1 for convenience.) Generally, spectra exhibit line intensities associated with the motional properties described above. For the $n=2$ case a broader higher field methylene (61.8 ppm) is assigned to the C-1 carbon by analogy with the corresponding carbon in the ethyl ether of glycol.[25] In the case of some synthetic batches the spectra of earlier members of the series also exhibited resonances attributable to approximately 30% unreacted polymer-bound monotrityl alcohol (81.7 ppm). In addition, the mesylate of the $n=2$ ether, while exhibiting the characteristic methyl group at 37.5 ppm, also showed the presence of up to 30% unreacted alcohol. The methylene resonances of the mesylate derivative were sharper than in the precursor alcohol implying greater motional freedom, but unusual additivity shifts of −0.9 and +2 ppm are noted for the β- and γ-positions, respectively. For $n=4$ the terminal C-4 methylene resonance is more intense than other lines in the spectrum, while the signal of C-1 is very broad, consistent with segmental motion, and by analogy with the $n=6$ case shown in Fig. 1. For $n=7$, 9 and 10 spectra similar to that of $n=6$ are also observed and assignments follow from additivity relationships. No evidence for unreacted precursors was obvious in the spectra of $n=7$, 9 or 10. Assignments for the C_{10} chain were derived by comparison with the monotrityl ether of decanediol.[24]

Limiting factors

In efforts to procure spectra for other samples, including the C_{12} alkyne 5 and the C_{12} alkene 6, a distinct problem arose. The swelling volume of the polymer beads was clearly the dominant factor contributing to the quality of the results. Attempts to increase the solvent swelling using the alternative solvents pyridine or methylene chloride were not successful. In some cases standing in chloroform for a prolonged period (1 week) increased the swelling volume, resulting in favourable spectra (for example, in the case of the C_{16} dialkyne 7) compared with those obtained for 'freshly prepared' samples. The failure to obtain clearly interpretable results in some cases may also arise from the possibility that there are fewer side chain substituents per unit volume of polymer, or that motional freedom is inhibited by intramolecular bonding contributions or modifications in the stereochemistry of the side chains.[19] Clearly the initial size of the dry polymer beads in these cases is smaller than in all other examples studied, and swelling by solvent is reduced by at least a factor of two. It is apparent that systems of this kind should be studied using solid-state NMR methods.[10] It is of some interest to note that the synthetic criterion for determining the best condition for reactions of polymer bound substrates also relies on maximizing solvent swelling volumes.

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