Reaction of living polyTHF with amines:
4. Primary amines

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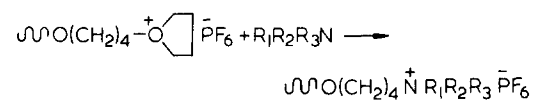
Cationic living polyTHF reacts with primary amine rapidly under ambient conditions. When the amine is in excess the main product is a polymer possessing a terminal secondary amine ligand, and near quantitative conversion is achieved at ten fold excess. The proportion of mono- and disubstituted polymer formed at a given reagent ratio is insensitive to the nature of the amine. Surprisingly, therefore, it is found that the form of the un-neutralized amine product is dependent on the primary amine used, that from aniline exists as the free secondary amine whilst those from cyclohexylamine and n-butylamine exist as the acid salt. A hypothesis is put forward to explain these observations.

Keywords Polytetrahydrofuran; cation; polymer amine; gel permeation chromatography; ^1H nuclear magnetic resonance; Menschutkin reaction

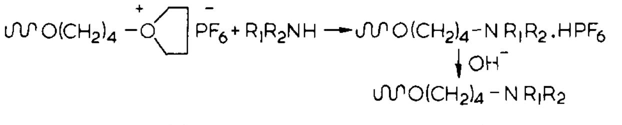
INTRODUCTION

This paper is part of a series of publications describing the reactions of 'living' polymer cations, exemplified by polytetrahydrofuran (polyTHF), with amines. The first two papers[1,2] were concerned with the reaction of living polyTHF with tertiary amines, equation (1), in which


(1)

quaternary ammonium salts were formed. It was found that the rate of reaction was controlled by the nucleophilicity of the amine, the reaction of pyridine and aliphatic amines such as triethylamine being complete within a minute or so at −10°C in contrast to the extremely slow addition of acridine. Most of these polymer salts were found to behave in an anomalous manner on styragel gel permeation chromatography columns, owing to adsorption by their ionic terminal groups[1]; this behaviour is described in the texts of these communications.

Part 3 in the series[3] examined the reaction of living polyTHF with secondary amines to form polymers possessing terminal tertiary amine groups (equation (2)). With certain amines (e.g. diethylamine) the reaction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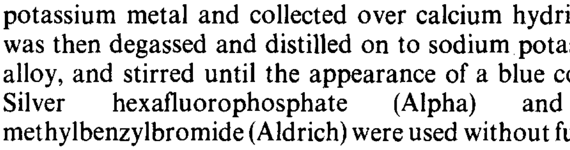
proceeded rapidly, but with other less basic amines (e.g. carbazole) the polymer tertiary amine could only be prepared efficiently by first converting the secondary amine to its alkali metal salt. The materials thus produced, possessing non-ionic terminal groups, were found to behave normally on g.p.c. columns; they could, however, be treated subsequently, either with an alkyl or polystyryl halide or with further polyTHF, to yield quaternary ammonium salts which, again, displayed anomalous g.p.c. behaviour.

Reaction between living polyTHF and primary amines should, in principle, proceed in a similar manner to produce polymers with secondary amine terminal groups (equation (3)). The conditions under which this product is optimized are examined here.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EXPERIMENTAL

Materials

Tetrahydrofuran (THF) was dried successively over potassium hydroxide and calcium chloride, distilled from potassium metal and collected over calcium hydride. It was then degassed and distilled on to sodium potassium alloy, and stirred until the appearance of a blue colour. Silver hexafluorophosphate (Alpha) and *p*-methylbenzylbromide (Aldrich) were used without further purification.

The amines (aniline, cyclohexylamine and n-butylamine) were distilled and stored over molecular sieves.

Synthesis of amine terminated polyTHF

The general vacuum techniques employed have been described previously[4−7]. The apparatus used (*Figure 1*)

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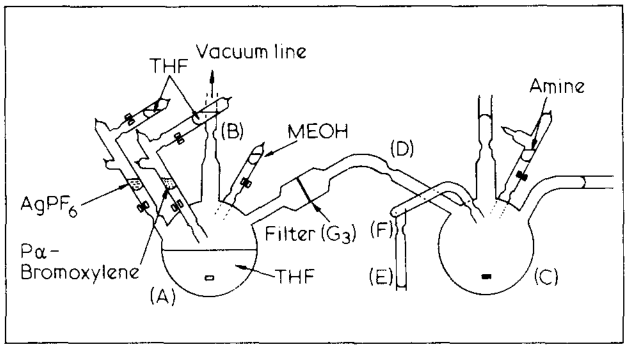


Figure 1 Apparatus used for the preparation of living polyTHF under vacuum and subsequent reaction of the product with amine or methanol

was connected to a vacuum line and degassed. The required volume of THF was then distilled into the reaction flask A and the apparatus sealed off at B. After cooling to $-10^\circ C$ *p*-methylbenzyl bromide and silver hexafluoro phosphate were added to generate the initiator at a concentration of about 10^{-2}M.

Following polymerization at $-10^\circ C$, the THF solution was cooled to $-78^\circ C$ and most of the solution filtered from silver bromide into the reaction vessel C. The apparatus was then divided by sealing at D. The living polymer in A was terminated with methanol in order to act as the low molecular weight control and, simultaneously, a second sample of living polymer solution was removed into tube E which was then sealed at F. The amine was then added to the third portion remaining in C, and both C and E held at $-10^\circ C$ for the required period before methanol was introduced into each to terminate any polymerization. The polymer sample in E was then used as the high molecular weight control.

Excess amine was removed from the aminated material by pumping for 12 h under high vacuum, and the polymer secondary amine was then generated by dissolving in THF and neutralizing with potassium hydroxide or potassium carbonate.

The low molecular weight oligo THFs (DP ~ 2) were prepared by initiating at $-50^\circ C$ and allowing a polymerization time of 1 hour at this temperature. Under these conditions all the initiator is consumed.

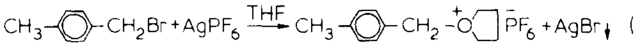
Characterization of products

Gel permeation chromatography (g.p.c.). The products were examined by g.p.c. using a Waters Associates ALC/GPC 301 equipped with a differential refractometer detector thermostatically controlled at 25°C, and a u.v. detector. The columns were microstyragel with porosities ranging from 10^2 to 10^5 Å. Molecular weights were determined with reference to polystyrene standards.

Nuclear magnetic resonance (n.m.r.). ^{1}H n.m.r. spectra of the oligo THFs were recorded on a Varian HA100 or on a Varian ER390 spectrometer. 10% solutions were prepared in deuterochloroform and spectra were obtained at ambient temperature, the chemical shifts being measured relative to tetramethylsilane as internal reference.

RESULTS AND DISCUSSION

Living polyTHF of narrow polydispersity may be conveniently prepared by reacting an alkyl bromide such as *p*-methylbenzyl bromide which possesses a weak C–Br bond, with silver hexafluorophosphate at $-10^\circ C$ in THF[9] (equations (4) and (5)). Under these conditions initiation (equation (4)) is faster than propagation and,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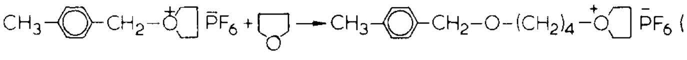
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since transfer reactions are negligible, polymers with narrow molecular weight distributions result. At $-10^\circ C$ the molecular weight increases linearly at about 3600 per hour. Difunctional living polyTHF has also been prepared in this manner by using a xylylene dibromide as initiator[10].

In the following discussion on the reaction of living polyTHF with primary amine, it is initially assumed that the reaction proceeds according to equation (3), and this assumption is subsequently confirmed by ^{1}H n.m.r. analysis. Experiments were carried out using methods similar to those described previously[3]. In order to check whether reactions of living polymer with the amine was complete, the mixture was allowed to remain undisturbed for some time after addition of the amine. Thus any unreacted living polymer could be resolved as a high molecular weight fraction in the product and could be recognized by comparing its g.p.c. trace with those of control samples of living polymer terminated with methanol at the beginning and end of the reaction period.

The reaction of living polyTHF with primary amines yields directly the acid salt of the secondary amine (equation (3)) and, in this form, the product should not be subject to any further electrophilic attack. However, the generated acid may equilibrate between the polymer secondary amine and any unreacted primary amine present (equation (6)). Clearly the position of this equilibrium depends on the relative basicities of the two

$$\sim\!\sim O(CH_2)_4NHR.HPF_6 + RNH_2 \rightleftharpoons \sim\!\sim O(CH_2)_4NHR + RNH_2.HPF_6 \quad (6)$$

amines involved, and this in turn could control the course of further reaction with living polyTHF since secondary amine is released which can undergo further alkylation (equation (2)) and the amount of free primary amine available is correspondingly reduced. The nature of the amine ligand must also influence the value of the equilibrium constant and so three primary amines were chosen to study this reaction with living polyTHF; n-butylamine, cyclohexylamine and aniline.

Initial experiments were designed to determine the relative proportions of the reagents necessary to produce polyTHF terminated with secondary amine in high yield. Reactions were carried out at various molar ratios, *r*, of amine to living polyTHF, the reaction products neutralized and their g.p.c. traces compared with those of their controls. A typical series of traces resulting from such an experiment with aniline is shown in *Figure 2*. The product trace shows two peaks with the larger corresponding closely to the low molecular weight control. This correspondence is strong evidence that termination is rapid relative to propagation. The minor peak at about double the molecular weight of the major component is attributable to the tertiary amine formed by an attack of a second living polyTHF molecule on a free polymer secondary amine, and is therefore confirmation of the presence of the equilibrium shown in equation (6).

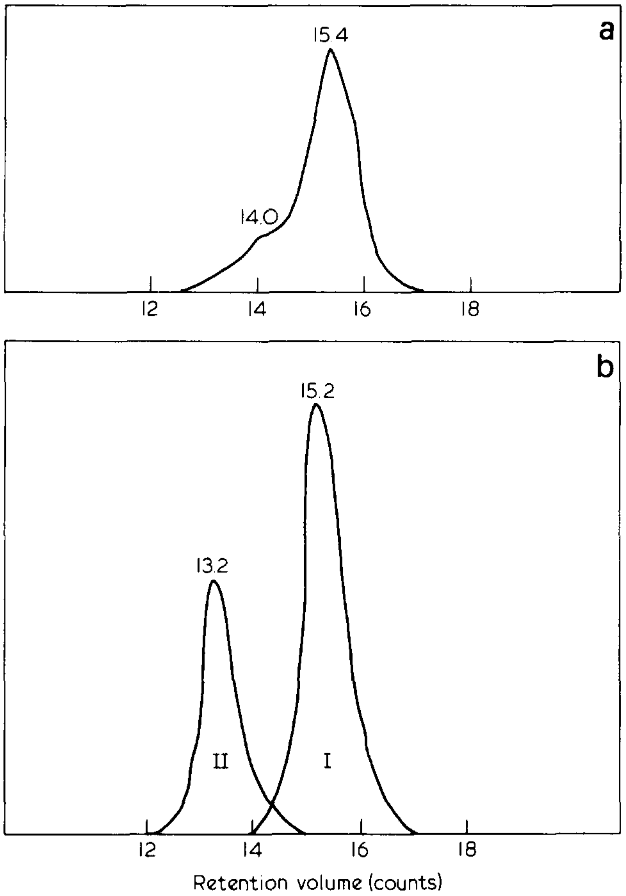


Figure 2 G.p.c. traces (differential refractometer detector) of (a) neutralized product of 3 h reaction of living polyTHF with aniline at a molar ratio of 1 : 1.2; (b) living polyTHF terminated with methanol at (I) time of mixing (low mol wt. control), and (II) 3 h later (high mol. wt. control)

The relative peak areas of the two products derived from traces similar to those given in *Figure 2* are listed in *Table 1* for the three amines at different relative concentrations of reagents. The efficiencies of formation of the polymer secondary amine are seen to be comparable at constant reagent ratio, *r*, for all three amines, although those derived from aniline may be marginally higher than the other two. It is apparent, however, that quantitative conversion is approached only by using a substantial excess of amine and, for this reason, preparative scale synthesis of secondary amine terminated polyTHF should always be carried out at $r \geq 10$.

When reactions were conducted with the three amines at $r = 10$ and samples of product also analysed prior to neutralization, the situation was found to be more complex (*Table 2*). With aniline, the g.p.c. traces were the same as those of the neutralized product, the peaks having the same symmetrical shape and eluting consistently close to the position of the low molecular weight control and independent of the amount of sample injected on to the columns. In contrast, however, whereas the neutralized products resulting from n-butylamine and cyclohexylamine gave traces similar to those obtained with aniline, without neutralization they gave peaks which were asymmetric with steep high molecular weight edges and elongated low molecular weight tails. Moreover the peak positions were at significantly longer elution times than the low molecular weight controls and moved to even longer times when the amount of sample injected was reduced, as shown in *Table 2*.

The latter behaviour is very similar to that observed in traces of quaternary ammonium salts prepared from tertiary amine and polyTHF[1,2], and has been ascribed to specific interaction of those terminal ionic groups with polar ligands on the crosslinked polystyrene column matrix[1]. It may therefore be taken as indicating that the products before neutralization are at least partially in the form of acid salts, as anticipated by equation (3). The difference from the aniline product, which is presumably present as the free secondary amine without treatment with alkali, is best explained on the basis of the equilibrium shown in equation (6), which for n-butylamine and for cyclohexylamine lies well over to the left and for aniline lies well over to the right.

Table 2 also demonstrates that the neutralized amine product elutes at a time marginally but consistently longer than the low molecular weight control (see also *Figure 2*). This trend was also observed with tertiary amine terminated polyTHF and to about the same degree[3], and so a similar cause probably obtains in both systems. Two hypotheses were put forward previously in explanation; namely, that the terminal amine groups weakly interacted with the polar ligands on the column, and that these groups induced a tighter conformation of the polymer coil than the methoxy terminated derivative. Either or both these explanations could equally well apply to secondary amine terminated polyTHF.

Confirmation of the structures proposed above was obtained from ^1H n.m.r. studies carried out on THF oligomers of DP ~ 2 terminated with each of the three amines at $r = 10$. Their spectra were recorded under a variety of conditions; the species obtained directly from the reaction were examined before and after exchange with D_2O, they were then neutralized, again equilibrated with D_2O and finally protonated with trifluoroacetic acid. The effects of all these operations on significant peaks of the resulting spectra are listed in *Table 3*.

It is apparent that the aniline product responded differently to these treatments than did the other two. This reaction product absorbed at 3.10δ, 3.80δ and 6.60δ signalling the presence of the $-CH_2-NH-Ph$ ligand and there was no evidence of any protonated material, the absorptions remaining unchanged after neutralization.

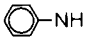
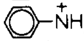
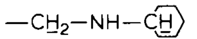
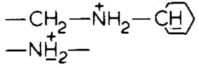
Table 1 Relative amounts of adducts as a function of molar ratio *r* of reagents

$r = \frac{\text{amine}}{\text{polyTHF}}$	Primary amine	Monoadduct (%)	Diadduct (%)
1	Aniline	78	22
	Cyclohexylamine	75	25
	n-butylamine	68	32
2	Aniline	80	20
	Cyclohexylamine	80	20
	n-butylamine	78	22
5	Aniline	92	8
	Cyclohexylamine	85	15
	n-butylamine	84	16
10	Aniline	98	3
	Cyclohexylamine	96	4
	n-butylamine	96	4

Table 2 Effect of injection concentration on elution maxima of g.p.c. traces of living polyTHF terminated with primary amines, before and after neutralization

Terminating agent	Not neutralized			Low *MW* control elution max (cm)	Neutralized (KOH)		
	Injection concn (g cm^{-3})	Elution max (cm)	Peak shape		Injection concn (g cm^{-3})	Elution max (cm)	Peak shape
Aniline	0.047 0.027 0.010 0.0058	16.65 16.70 16.65 16.65	symm	16.60	0.050 0.022 0.010	16.65 16.70 16.70	symm
n-Butylamine	0.051 0.028 0.013 0.0055	16.8 16.95 17.05 17.35	asymm	16.60	0.066 0.046 0.016	16.80 16.80 16.80	symm
Cyclohexylamine	0.050 0.026 0.011 0.0051	16.4 16.8 17.2 17.4	asymm	16.20	0.075 0.029 0.012	16.45 16.5 16.45	symm

Table 3 ^1H n.m.r. peaks from the reaction products of oligo THF with amines

Terminating agent	Peaks (ppm) (TMS)	Assignment	Before neutralizing		After neutralizing		
			Product	D_2O Exchange	Product	D_2O Exchange	CF_3COOH
Aniline	3.10	$-C\underline{H}_2-NH-$	x	x	x	x	–
	3.50	$-CH_2-\overset{+}{N}H_2-$	–	–	–	–	x[a]
	3.80	$-N\underline{H}-$	x	–	x	–	–
	6.60		x	x	x	x	–
	7.10		–	–	–	–	x
	9.25	$-\overset{+}{N}\underline{H}_2-$	–	–	–	–	x[b]
n-butylamine	0.95	$-N\underline{H}-$	–	–	x[c]	–	–
	2.90	$-C\underline{H}_2-NH-C\underline{H}_2-$	–	–	x	x	–
	3.15	$-C\underline{H}_2-\overset{+}{N}\underline{H}_2-C\underline{H}_2-$	x	x	–	–	x
	8.70	$-\overset{+}{N}\underline{H}_2-$	x	–	–	–	x[b]
Cyclohexylamine	1.10	$-NH-$	–	–	x	x	–
	2.60		–	–	x	–	–
	2.95		x	x	–	–	x
	9.15	$-\overset{+}{N}\underline{H}_2-$	x	–	–	–	x[b]

[a] Signal coincident with $-OC\underline{H}_2-$ peak presence inferred from integral value

[b] Disappears on further exchange with D_2O

[c] Signal coincident with $-CH_2-C\underline{H}_3$ peak, presence inferred from integral value

Protonation only occurred after addition of trifluoroacetic acid, with the three peaks being shifted to 3.50δ, 9.25δ and 7.10δ respectively. D_2O exchange reactions then confirmed the lability of the two amine protons.

The products derived from the two aliphatic amines gave spectra which displayed a different behaviour. The initial reaction product from n-butylamine exhibited signals at 3.15δ and 8.70δ, assigned to the protonated ligand $-CH_2-\overset{+}{N}H_2-CH_2-$ since these were shifted to 2.90δ and 0.95δ respectively on treatment with alkali, and they could be regenerated by subsequent addition of trifluoroacetic acid. Again, D_2O additions demonstrated the lability of the amine protons. Directly analogous changes were observed in the spectra of the product derived from cyclohexylamine (*Table 3*).

It is therefore confirmed that the reactions of living polyTHF with the above primary amines go cleanly under the conditions employed to form secondary amine, either as the free base or its acid salt. ^1H n.m.r. spectroscopy supports the g.p.c. evidence by establishing that when aniline is used the product is essentially the free amine, whereas with n-butylamine and cyclohexylamine the acid salt is primarily formed.

This result implies that the ratio of the basicity of aniline to that of its secondary amine product is greater than the ratios for the other two amines. Surprisingly, however, this difference is not reflected in any substantial difference in the relative proportions of mono- and disubstituted product generated with these reagents at a given reagent molar ratio, *r* (*Table 1*). Since the nucleophilicities of the acid salt products of the aliphatic amines should be very low, they would not be expected to participate as such in any further coupling reactions with living polyTHF. Thus it was anticipated that more diadduct would result under given conditions with aniline than with the other two amines. This is evidently not so, and therefore an alternative explanation must be sought.

These experimental observations may be rationalized if the ratios of the basicities of the primary and secondary amines involved toward the generated acid (HPF_6) are similar to the ratios of their nucleophilicities with regard to attack by living polyTHF, a reasonable assumption considering the similarities of the processes involved. Under such circumstances the relative proportions of mono- and disubstituted products would be controlled by a function containing the equilibrium constant of equation (6) divided by the ratio of nucleophilicities to polyTHF attack, and, since these would then be of similar values, they should roughly cancel and so confirm the observed independence of products on relative basicities. Thus with aniline, the basicity equilibrium (equation (6)) lies very much to the RHS, and so the nucleophilicity to living polyTHF of the polymer secondary amine should be compensatingly very low relative to free aniline in order to yield the comparatively small proportions of disubstituted product found.

Although we have not tested this hypothesis experimentally with model compounds, it is known that secondary amines containing phenyl groups react only slowly with living polyTHF, only a small fraction of diphenylamine reacts in 3 hours at $-10°C$[3], and this gives some qualitative support to the explanation.

PolyTHF possessing a terminal secondary amine group may be reacted with further living polyTHF to yield a linear polyTHF with a tertiary amine grouping at a point along the chain predetermined by the relative molecular weights of the two living polymers involved (equation (2)). Further, this tertiary amine may subsequently be reacted with fresh living polyTHF to generate a quaternary ammonium salt in which the polymer chains constitute the three arms of a star (equation (1)). Such systems have been studied and the results will be reported in a separate communication.

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