Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1029–1034

TETRAHEDRON: *ASYMMETRY*

Polymer-supported bis-cinchona alkaloid ligands for asymmetric dihydroxylation of alkenes — a cautionary tale

Laetitia Canali,[a] Choong Eui Song[b] and David C. Sherrington[a,*]

[a]*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, UK*

[b]*Korea Institute of Science and Technology, Division of Applied Science, PO Box 131, Cheongryang, Seoul 130-650, South Korea*

Received 26 January 1998; accepted 9 February 1998

Abstract

Careful work-up and purification of purported copolymers formed by free radical copolymerisation of a bis-cinchona alkaloid with methyl methacrylate shows that the level of incorporation of the bis-alkaloid into the polymer skeleton is below the detection limit of a routine nitrogen microanalytical protocol. This reluctance of the C=C bonds in the bis-alkaloid to undergo copolymerisation with a methacrylate monomer is totally consistent with the well-known and extensively documented poor copolymerizability of allylic monomers. Direct free radical copolymerisation of allyl groups containing alkaloids and other allyl substituted optically active ligands is not therefore a general and simple option for the production of polymer-supported asymmetric catalysts. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently attention has been focused on the immobilisation of homogeneous asymmetric transition metal complexes onto polymers to allow these to be exploited as heterogeneous species.[1] We have an active interest in this area[2] and as polymer chemists have become concerned about some of the results being reported in the literature[3,4] which run quite contrary to well-known and well-demonstrated basic polymer chemistry.

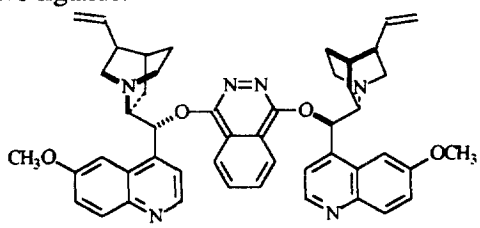
Generally, simple allylic C=C bonds do not participate in free radical vinyl polymerisations to any great extent. Indeed, the favoured reaction is the abstraction of an allylic hydrogen by a radical with the formation of a relatively stable allyl radical. Furthermore, allyl species can actually retard or inhibit free radical polymerisations. Examination of copolymerisation data and specifically monomer reactivity ratios (r_A, r_B) where one comonomer is allylic[5] confirms that copolymerisation of these monomers is highly

* Corresponding author. E-mail: M.P.A.Smith@Strath.ac.uk

PII: S0957-4166(98)00062-7

unfavoured. For example, for allyl acetate (r_A) and methyl methacrylate (r_B) $r_A = \sim 0$, $r_B \sim 25$; and for allyl acetate (r_A) and styrene (r_B) $r_A \sim 0$, $r_B \sim 90$. Where the comonomer forms a highly electron deficient free radical during polymerisation, e.g. acrylonitrile, then copolymerisation of allylic species can occur to a limited extent e.g. for allyl acetate (r_A) and acrylonitrile (r_B) $r_A \sim 0$, $r_B \sim 6.6$. An additional fundamental phenomenon in free radical vinyl-type addition polymerization is that monomers with two or more vinyl-type functionalities generate crosslinked polymer networks or gels which are not molecularly soluble. Typically, if more than ~1 mol% of a comonomer mixture consists of a reactive crosslinking monomer, gelation will be observed, with the product phase separating from any solvent employed. Depending on the nature of the solvent, the polymer network may remain highly swollen on the one hand, or become extensively desolvated on the other.

Bearing this basic polymer chemistry in mind, it came as a surprise to us to read claims of apparent facile copolymerisation of the allyl substituents in bis-cinchona alkaloids, such as $(QHN)_2$–PHAL, with monomers such as methyl methacrylate and ethylene glycol dimethacrylate[3,4] with, in the case of methyl methacrylate, the product remaining soluble in the reaction solvent. Were these observations to be so, the procedure would indeed provide a very convenient synthetic strategy for producing polymer-supported analogues of such optically active ligands.



$(QHN)_2$-PHAL

2. Results and discussion

Accordingly we have repeated the published work[3] involving the purported copolymerisation of $(QHN)_2$–PHAL with methyl methacrylate (MMA) (mole ratio $(QHN)_2$–PHAL:MMA, 5:95) using a sample of bis-alkaloid kindly supplied by Song et al.[3] and have also carried out a purification of a sample of purported copolymer also kindly supplied by the same group.

A key feature of the copolymerization is that no gelation effect is reported and the (co)polymer work-up procedure involves precipitation of the benzene-soluble product formed by pouring into *n*-hexane in which polymethacrylates are generally insoluble. Unfortunately, however, we quickly demonstrated that $(QHN)_2$–PHAL monomer itself is also highly insoluble in *n*-hexane, and any non-polymerised residue may well therefore be co-precipitated with any copolymer. In contrast, the (QHN_2)–PHAL monomer is very soluble in ethanol whereas poly(methyl methacrylate) is essentially insoluble in this solvent. Hence we argued that a more satisfactory work-up procedure to ensure removal of any unreacted $(QHN)_2$–PHAL from the (co)polymer would be precipitation of the benzene reaction solution into ethanol, and washing or extraction of any (co)polymer formed with ethanol.

We have now carried out a number of polymerisations with different work-up procedures and the microanalytical data for the nitrogen content of the (co)polymer products, and other components, are reported in Table 1. From the data (column 5) it is quite clear that undetectably low levels of the $(QHN)_2$–PHAL monomer are incorporated into methyl methacrylate (MMA) polymers. Using the published procedure it seems that precipitation of polymerised mixtures into *n*-hexane yields solid

poly(methyl methacrylate) (PMMA) with some physically trapped unreacted $(QHN)_2$–PHAL. If the isolation of this precipitate is carried out expeditiously, a second precipitation occurs more slowly in the filtrate and this is very rich in $(QHN)_2$–PHAL. Thus, our sample 1 has both precipitates combined, whereas in samples 2 and 3 the second precipitate has been retained within the filtrate fraction. The nitrogen analytical data is totally consistent with this picture. In addition, the $(QHN)_2$–PHAL that is physically trapped within the PMMA can be essentially quantitatively removed by prolonged extraction with ethanol in a Soxhlet (sample 3). Likewise, a sample of ethyleneglycol dimethacrylate crosslinked polymer obtained from Song et al.[3] showed zero nitrogen content following similar extraction.

In what we regard as a definitive procedure we have attempted to copolymerise $(QHN)_2$–PHAL with MMA in benzene under vacuum, and have reprecipitated the product three times by pouring benzene or toluene solution into ethanol using methodology routine to polymer chemists. The precipitated and dried polymer, sample 4, analyses as ~0% nitrogen, and the glassy white product has a ^{1}H NMR spectrum consistent with that expected for PMMA. The residue obtained from evaporation of the above filtrates and washings yielded a ^{1}H NMR spectrum identical to that of $(QHN)_2$–PHAL and with an elemental composition (%) C, 69.4; H, 6.8; N, 8.7, compared to C, 74.4; H, 6.5; N, 10.8% for pure $(QHN)_2$–PHAL.

Interestingly Salvadori et al. noted over two years ago[6] that (QHN_2)–PHAL had been unsuccessfully copolymerised with ethyleneglycol dimethacrylate but that even after repeated extraction of the crude white solid product with acetone, the material was still contaminated with unbound bis-alkaloid. They concluded that due to the high level of crosslinking, this monomer was strongly absorbed within the swollen polymer and the catalytic activity observed in the dihydroxylation of *trans*-stilbene was due to physically trapped bis-alkaloid: we have independently confirmed the effectiveness of $(QHN)_2$)–PHAL as an asymmetric catalyst in the dihydroxylation reaction. This is undoubtedly the explanation for significant nitrogen content of the purported crosslinked methacrylate copolymer with $(QHN)_2$–PHAL reported by Nandanan et al.[4] and it seems remarkable that work subsequent to the report of Salvadori et al.[6] has not taken due cognisance of their cautionary experience. In addition, a parallel issue arose some years ago in the case of the apparent copolymerisation of monomeric cinchona alkaloids with various vinyl monomers, where in due course it again emerged that significant copolymer formation occurs only with a highly electron deficient monomer such as acrylonitrile.[7–9]

This whole area of catalysis is an exciting and rapidly moving one but it is vital that proper checks and controls are made if the area is to maintain high credibility. A simple procedure is to filter off heterogeneous polymer catalysts and recharge the filtrate with substrate and reagents as appropriate. Catalytic reactions which continue must be due to leached species either originally weakly bound to the support, or simply physically trapped. Ultimately of course polymer-supported, catalysts should be re-cycled through a number of batch reactions, or preferably used in a fixed or fluidised bed in a continuous process. Leaching of catalyst, e.g. metal ions, should be assessed by direct analysis of filtrates or eluates. Only when satisfactory quantitative data with regard to recycling (or continuous use) and leaching becomes available can reports of highly effective polymer-supported metal complex catalysts be taken as truly significant.

3. Experimental

3.1. Materials

$(QHN)_2$–PHAL and polymer sample 1 were supplied by Song et al.[3] Other materials were from Aldrich and were used as supplied if not specified otherwise in the preparations.

Table 1
Elemental nitrogen microanalytical data for polymer products and residues isolated from (co)polymerizations of $(QHN)_2$–PHAL with methyl methacrylate

(Co)polymer Sample	Precipitation Solvent	%N Detected by Elemental Microanalysis			
		(Co)polymer precipitation	Residue from evaporated filtrate	(Co)polymer following ethanol wash/extraction	Residue from evaporated ethanol washings
published data[3]	*n*-hexane	3.7	N/A	N/A	N/A
1	*n*-hexane	3.2[a)]	5.3	0.7 (1 h)	N/A
2	*n*-hexane	1.6	8.5[b)]	0.9 (1 h)	6.5
3	*n*-hexane	1.1	9.5[b)]	~0 (24 h)	5.9
4	ethanol[c)]	~0	8.7	--	--

a) second precipitate forming in filtrate of first was combined with first.
b) second precipitate formed in filtrate of first was retained with filtrate.
c) reprecipitated three times into ethanol.

3.2. Instrumentation

^{1}H NMR spectra were recorded on a 250 MHz Bruker WM250 spectrometer with Me_4Si as standard. FTIR spectra were recorded on Matson or Nicolet 400^D spectrometers running 10 scans at a resolution of 4 cm^{-1}. Elemental microanalyses were performed on a Perkin–Elmer Series II Analyser by the Microanalytical Service at the University of Strathclyde with an error of ±0.3%.

3.3. Preparation of polymer sample 1

A solution of 1,4-bis(9-O-quininyl)phthalazine $(QHN)_2$–PHAL (0.5 g, 0.65 mmol), methyl methacrylate (1.23 g, 12.29 mmol) and azobisisobutyronitrile (AIBN) (8 mg) in calcium chloride dried benzene (20 ml) was heated to reflux under an N_2 atmosphere for 48 hours. The yellow solution was poured into cold *n*-hexane (50 ml) to yield two precipitate fractions; the second crystallising in the filtrate from the first precipitate. The combined precipitates were washed with *n*-hexane (25 ml) and dried under vacuum (55°C/10 mmHg) for 24 h to yield a white solid (0.96 g, 55%). Anal. found (calc.) %: C, 64.8 (64.10); H, 7.6 (7.67); N, 3.2 (3.14); FTIR 1729 cm^{-1}. The remaining supernatant solution was concentrated *in vacuo* and dried. Anal. found %: C, 80.8; H, 11.6; N, 5.3. The original combined precipitates were stirred for 1 h at room temperature in ethanol (50 ml) filtered and dried under vacuum (0.57 g). Anal. found %: C, 59.3; H, 8.4: N, 0.7.

3.4. Preparation of polymer sample 2

The polymerization procedure was the same as that for sample 1 and after the reaction was complete, the mixture was poured into cold *n*-hexane (50 ml). As before two precipitate fractions formed. The rapidly formed first white precipitate was collected and washed with *n*-hexane (25 ml). This material was dried under vacuum (55°C/10 mmHg) for 24 h to yield a white solid polymer (0.44 g, 26%). Anal. found (calc.) %: C, 60.3 (64.10); H, 5.9 (7.67); N, 1.6 (3.14). This solid was then stirred for 1 h at room temperature in ethanol (50 ml) filtered and dried under vacuum. Anal. found %: C, 61.1; H, 8.0; N, 0.9. The remaining washings were concentrated *in vacuo* and dried under vacuum. Anal. found %: C, 66.0; H, 7.5; N, 6.5. The second white precipitate appearing in the initial filtrate was left in the filtrate. This mixture was then concentrated *in vacuo* and dried. Anal. found %: C, 74.4; H, 7.0; N, 8.5.

3.5. Preparation of polymer sample 3

This preparation and work-up were essentially the same as used with sample 2 except that the extraction of the polymer product was more rigorous. The first white precipitate was collected, washed with *n*-hexane (25 ml) and dried under vacuum (55°C/10 mmHg) for 24 h to yield a white solid (0.46 g, 27%). Anal. found %: C, 61.5; H, 7.8; N, 1.1. This material was then extracted with ethanol in a Soxhlet for 24 h and dried under vacuum (55°C/10 mmHg) for 24 h to yield a white solid polymer. Anal. found %: C, 58.5; H, 8.3; N, 0. The washings were concentrated and dried under vacuum. Anal. found %: C, 65.1; H, 7.4; N, 5.9. The filtrate containing the second precipitate was concentrated and dried under vacuum for 24 h. Anal. found %: C, 73.6; H, 6.6; N, 9.5.

3.6. Preparation of polymer sample 4

A solution of $(QHN)_2$–PHAL (0.5 g, 0.65 mmol), methyl methacrylate (1.23 g, 12.29 mmol), AIBN (8 mg) in $CaCl_2$-dried benzene (4 ml) was degassed by four freeze–pump–thaw cycles using a high vacuum pump (6×10^{-4} mmHg). The reaction mixture was heated to 70°C for 48 hours. The slightly viscous yellow solution was poured into cold ethanol (40 ml) to yield a solid product. The latter was purified twice by re-dissolving in toluene and re-precipitating into cold ethanol, dropwise with vigorous stirring. The recovered material was dried in a vacuum oven (55°C/10 mmHg) for 24 h to form a glassy white solid polymer (0.8 g, 46%). ^{1}H NMR (250 MHz; $CDCl_3$) δ 0.8–1.03 (CCH_3), 1.46–1.90 (CCH_2), 3.61 ($(CO)OCH_3$). Anal. found (calc.) %: C, 60.1 (64.10); H, 7.8 (7.55); N, 0 (3.14). The filtrate and all washings were combined, concentrated *in vacuo* and dried. ^{1}H NMR (250 MHz; $CDCl_3$), same spectrum as $(QHN)_2$–PHAL. Anal. found %: C, 69.4; H, 6.8; N, 8.7. Calc. for (QHN_2)–PHAL (%): C, 74.4; H, 6.5; N, 10.8.

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