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^{13}C Kinetic isotope effects in the copper(I)-mediated living radical polymerization of methyl methacrylate†

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Carbon-13 kinetic isotope effects (KIEs) have been determined for free-radical and copper-mediated living radical polymerizations of methyl methacrylate at 60 °C. While free-radical polymerization shows only one primary ^{13}C KIE, on the least-substituted double bond carbon (k_{12}/k_{13} = 1.045), two significant KIEs are observed, one on each double bond carbon, for copper-mediated polymerization ($k_{12}/k_{13}(H_2C{=})$ = 1.050, $k_{12}/k_{13}({=}C<)$ = 1.010), showing that copper-mediated living radical polymerization does not propagate *via* a simple free radical process.

Transition metal mediated living radical polymerization has emerged as an excellent technique for the synthesis of low polydispersity polymers with controlled molecular architecture.[1,2] The method is applicable to a wide range of vinyl and acrylic monomers under diverse reaction conditions. For these reasons it has attracted substantial interest since its introduction in 1995.[3] The generally-accepted mechanism for these reactions involves chain propagation *via* a free radical, involving an equilibrium between a dormant halide-capped polymer and an active radical species, where the free radical is not associated with the abstracted halide atom in any way. This is supported by the reaction and reaction products showing many similarities to conventional free radical polymerization. The similarities include the stereochemistry of the polymers, many reactivity ratios, lack of sensitivity to certain functional groups and impurities, and other attributes.[4]

There are a number of observations, however, that are not wholly consistent with a free radical mechanism. For example, changes in the polarity of the reaction medium have dramatic effects on the rate of reaction, *e.g.* in the presence of oxyethylene groups,[5] substituted phenolic radical inhibitors[6] and in aqueous solution.[7] Significant differences compared to conventional polymerization are observed in the reactivity ratios of monomers that co-ordinate to the metal when they are at similar concentrations to the catalyst (*e.g.* MMA and poly(lactic acid) methacrylate).[8] In addition it is apparent that certain monomers containing donor atoms such as N or O will co-ordinate to all catalysts and with many catalysts π-bonding *via* the vinyl bond will be significant.[9] These results suggest that the propagating species may be constrained within the coordination sphere of the catalyst. Such 'caged' radicals have been implicated in the mechanisms of a number of similar transition-metal mediated addition reactions and polymerizations.[10–12] Thus the true nature of the active species in metal-mediated living radical polymerization remains unproven.

Deuterium kinetic isotope effects (KIEs) have been used to probe the mechanisms of propagation and chain transfer in various polymerization reactions.[13–15] However, in free-radical propagation, hydrogen atoms are not directly involved in the rate-limiting step and therefore only secondary deuterium KIEs exist. Less ambiguous mechanistic information requires the measurement of carbon KIEs. Measurement of these effects is often difficult and time-consuming due to the necessity of synthesizing ^{13}C- or ^{14}C-substituted test molecules. While isotope-ratio mass spectrometry can be used to measure heavy atom KIEs at natural abundance, this technique requires that each site of interest be selectively degradable into an analyzable small molecule.

A recently-introduced technique allows the measurement of multiple ^{13}C kinetic isotope effects (KIEs) at natural abundance using ^{13}C NMR.[16] This technique has been used to determine the mechanism of a large number of Diels–Alder, ene and other reactions involving addition to a double bond.[17] The method allows the simultaneous determination of KIEs on all but one of the atoms in the target molecule by making use of the enrichment in less reactive isotopomers that occurs during the course of a reaction. The KIE (= k_{12}/k_{13}) at a particular carbon is related to the fractional conversion of reactants (F) and the isotopic composition at that carbon relative to starting material (R/R_0) by eqn. (1).[16]

$$\mathrm{KIE} = \ln(1 - F)/\ln[(1 - F)R/R_0] \qquad (1)$$

In this work, free radical and copper(I)-mediated polymerizations of methyl methacrylate (MMA) were carried out at 60 °C. Unreacted MMA was extracted and its isotopic composition was analyzed by quantitative ^{13}C NMR.‡

The change in isotopic composition was calculated by dividing the integrals of the extracted MMA by the corresponding integrals of a sample of the starting material taken from the same batch. The methoxy carbon was assumed to take no part in the rate-determining step, and was used as an internal standard. The isotopic enrichments calculated by this method for each sample are shown in Table 1. This data was substituted into eqn. (1) and the results were combined to produce the ^{13}C kinetic isotope effects shown in Fig. 1.

The free radical reaction shows only one significant ^{13}C KIE, on the unsubstituted double bond carbon (C_1). This is consistent with the accepted mechanism of free radical polymerization, in which the only interaction between the radical and the double bond occurs at the less substituted carbon. There is a change in hybridization from sp^2 to sp^3 in the transition-state at the CH_2 group whilst the substituted carbon retains much of its sp^2 character with the radical largely residing in the p orbital.

Table 1 Isotopic enrichments and conversions for MMA polymerized by copper(I)-mediated (CMP) and free radical (FRP) methods

		^{13}C Isotopic Enrichment (relative to C_5)[b]			
Method	F[a]	C_1	C_2	C_3	C_4
CMP	0.861(10)	1.099(7)	1.025(3)	0.998(3)	1.009(2)
CMP	0.906(10)	1.127(9)	1.018(6)	0.999(5)	1.011(7)
CMP	0.961(5)	1.157(23)	1.031(6)	1.004(9)	1.004(2)
CMP	0.963(8)	1.169(2)	1.029(3)	0.991(4)	0.998(6)
FRP	0.850(5)	1.087(3)	1.001(2)	0.998(5)	1.003(2)
FRP	0.955(1)	1.139(9)	1.013(5)	0.998(8)	0.996(7)
FRP	0.978(1)	1.181(4)	1.000(5)	0.997(3)	0.998(3)

[a] Fractional conversion (measured by ^1H NMR at 400 MHz, $CDCl_3$). Standard errors in parentheses. [b] Standard errors in parentheses. Carbons numbered $C_1{=}C_2(C_3)$—$C_4({=}O)$—OC_5.

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† Electronic supplementary information (ESI) available: Sample spectra, procedures for reactions, NMR measurements and calculations. See http://www.rsc.org/suppdata/cc/b2/b203675d/

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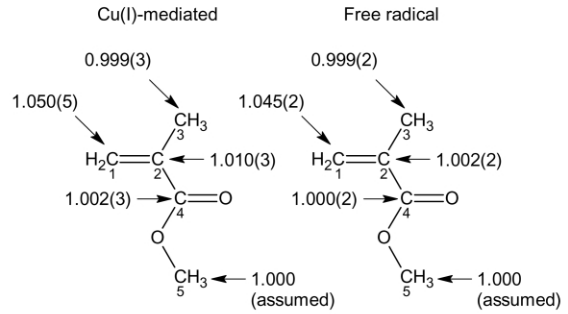

Fig. 1 ^{13}C kinetic isotope effects calculated for copper(I)-mediated (left) and free radical (right) polymerizations of MMA at 60 °C with standard errors in parentheses.

Copper(I) mediated polymerization shows a smaller but still significant isotope effect at position C_2 in addition to a large KIE at position C_1. This indicates that the carbon at position 2 is also involved in the rate-determining step of the reaction. The difference in KIEs at this position between free radical and living radical polymerizations is significant at the level of 98.7%.§

The results show that the mechanism of the propagation step in copper(I) mediated polymerization is *different* to that of a free-radical polymerization. If, as is often assumed, the propagating species in living radical polymerization is a free radical, the kinetic isotope effects for the two reactions should be identical. It is not possible that the effect on C_2 in copper(I)-mediated polymerization is due to another, non-propagating reaction, such as the capping reaction, as only the propagation step involves consumption of monomer. Thus it is only this step that can have an effect on the isotopic composition of the unreacted monomer.

The presence of KIEs on both carbons of the MMA double bond in copper-mediated living radical polymerization indicates a lowering of the zero-point energy of the double bond due to bonding or hybridization changes at C-2 compared to the free radical mechanism. There are a number of mechanisms that might cause this effect, including coordination of the monomer to copper prior to insertion, and concerted insertion of the monomer into the C–Br bond of the activated polymer. While it is not possible to differentiate between these mechanisms on the basis of the KIE data presented here, all possibilities require the radical species and the catalyst to be in close proximity. This strongly suggests that a significant proportion of the active species are ‘caged’ radicals, held within the coordination sphere of the metal, rather than the ‘free’ radicals that are usually assumed to be present. This is consistent with the caged radical mechanism of ruthenium- and nickel-catalyzed haloalkane additions to alkenes.[11]

These results have major implications for the many kinetic studies of metal-catalyzed living radical polymerizations that use rate constants determined from conventional radical polymerizations,[18] as these constants are unlikely to be valid for caged radicals. In particular, propagation rate constants derived from free radical pulsed-laser polymerization studies should not be used to estimate the concentration of active species in copper-mediated living radical polymerizations.

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Notes and references

‡ All polymerizations were carried out using 200 mL of MMA dissolved in 400 mL of xylenes at 60 °C. The reactions were taken to > 85% conversion, measured by ^1H NMR spectroscopy. Unreacted MMA was recovered by an initial, rapid vacuum distillation followed by repeated distillations to reduce the level of xylene impurities. These samples were then analyzed by quantitative carbon NMR at 125.7 MHz (Bruker DRX 500) with 2 × 5 integrations carried out for each sample (see ESI for further details), using 10% v/v C_6D_6 as a spectrometer lock and reference. Integrals were picked manually so as to include carbon satellites on signals and were evaluated relative to the OMe peak, which was set to 1. Representative signal to noise ratios were 5383 for unreacted MMA, 2772 for MMA recovered from a free radical polymerization, and 3033 for MMA recovered from a copper-mediated polymerization. Sample spectra are included in the ESI.

§ The significance level was calculated using a heteroscedastic t-test using the estimated values and standard errors shown in Fig. 1.

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