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Ligand electronic effects on rates of copper mediated atom transfer radical cyclisation and polymerisation

Andrew J. Clark,[a,*] Gary M. Battle,[a] Alex M. Heming,[a] David M. Haddleton[a] and Andrew Bridge[b]

[a]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*
[b]*Aventis Pharma Ltd, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

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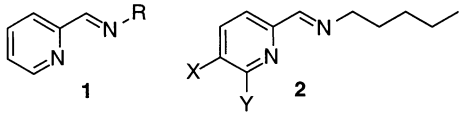
Abstract—The effect of different *N*-pentyl-2-pyridylmethanimine derivatives **2a**–**f** upon the rate of copper(I) mediated atom transfer radical cyclisation (ATRC) of **5** and living atom transfer radical polymerisation (ATRP) of methylmethacrylate were investigated.

The use of copper(1) complexes to mediate atom transfer radical cyclisation (ATRC)[1] and atom transfer radical polymerisation (ATRP)[2] has attracted considerable interest in recent years. By far the most successful catalysts have been those based upon bipyridine (bipy),[3] *N*-alkyl-2-pyridylmethanimines (NPMI) **1**[4] and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA).[5] The most widespread catalysts, particularly in ATRP have been based upon bipyridine and NMPI ligands.[3,4] In order to optimise both ATRC and ATRP processes it is necessary to make derivatives of these ligands to obtain structure–activity relationships. We have recently reported how varying the steric nature of the *N*-alkyl group in NPMI groups **1** changes the rate of ATRC[4a] and ATRP[4g] reactions, as well as publishing the X-ray structure details for such catalysts.[6] In this work we reported that primary alkyl groups (e.g. **1a**) were optimum in both ATRC and ATRP reactions. In this communication we detail how the rates of both ATRC and ATRP processes are affected by varying the substituents at the 5- and 6-positions of the pyridine nucleus **2**.[7]

Initial reactions were carried out using **3** (0.12 M) in CH_2Cl_2 with 30 mol% CuBr and 30 mol% ligand **2a**–**c** in CH_2Cl_2 at room temperature. However, attempted cyclisation reactions using **3** and ligands **2b**–**c** failed with only starting material being recovered after 24 h, indicating poor activity. Under the same conditions, the control ligand **2a** mediated the cyclisation of **3** completely to give **4** in 96% yield in 24 h. Repeating the screening with the more activated substrate, trichloroacetamide **5**, was more successful. Reactions were carried out as above but using CuCl instead of CuBr.

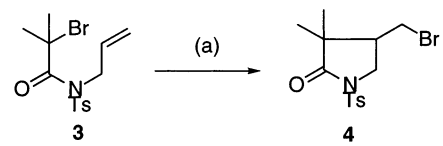


1

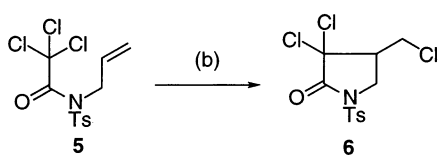
1a R = *n*-Bu,
1b R = *i*-Bu,
1c R = *s*-Bu,
1d R = *t*-Bu,

2

2a X = H, Y = H
2b X = H, Y = Me
2c X = H, Y = OMe
2d X = NO_2, Y = H
2e X = Me, Y = H
2f X = OMe, Y = H



3 **4**



5 **6**

(a) 30 mol% CuBr, 30 mol% ligand **2**, CH_2Cl_2
(b) 30 mol% CuCl, 30 mol% ligand **2**, CH_2Cl_2

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* Corresponding author.

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After 100 minutes the reactions were worked up by passing through a small silica plug and the conversions of the reactions were measured by ^{1}H NMR of the crude mixture. Analysis indicated that while the reaction with the ligand **2c** had proceeded to completion, reaction with **2b** had proceeded to give only a 2:1 mixture of **6**:**5**. As a comparison cyclisation of **5** with the control ligand **2a** was over in less than five minutes under these conditions. These results indicated that substitution at the 6-position significantly retarded the cyclisation reaction. The reason for this is likely to be steric in origin and parallels the loss of reactivity observed when the imine nitrogen was substituted with bulky alkyl groups.[4a,g] Due to the relative inactivity of these analogues we next investigated the affect of ligands substituted at the 5-position **2d**–**f**, where steric interactions would be less important and contributions from inductive electronic effects onto the pyridine nitrogen could be determined. Groups in these positions are also mesomerically linked to the imine nitrogen and hence any complete analysis of the effect of substituents is likely to be complicated by a combination of both these phenomena. Reactions were carried out using **3** with 30 mol% CuBr and 30 mol% ligand **2a** and **2d**–**f** in CH_2Cl_2 at room temperature for 2 h. The reactions were worked up as before and the conversion determined (Table 1). The strongly electron withdrawing NO_2 group had a substantial effect on the conversion of **3** with no cyclisation product **4** detected by ^{1}H NMR after 2 h. After 45 h 10 min the reaction had proceeded to give a 77:23 ratio of **3**:**4**. The use of the less inductively withdrawing methoxy ligand **2f** also retarded the rate but to a lesser extent. The conversions for the control **2a** and the methyl substituted ligand **2e** were of similar magnitude with the inductively donating **2e** being the most efficient.

Next we examined the trends with the three ligands **2a**, **2d**–**e** in the polymerisation of MMA[8] initiated with ethyl 2-bromo-2-methylpropionate under standard living radical conditions (100:1:1:2 = [MMA]:[initiator]:[CuBr]:[**2**] at 50% v/v in toluene at 90°C). All three polymerisations were fully homogenous at 90°C in toluene. The catalyst with ligand **2d** was differently coloured to the other experiments and appeared in solution to be a deep indigo compared with the dark brown of the catalysts in the control reaction. This was not the case in the ATRC reactions in CH_2Cl_2 where the solutions were dark brown in all cases. Each reaction run exhibited a linear first-order rate plot, indicating that the concentration of propagating species remained constant throughout the reaction (Fig. 1). The rates of polymerisation of MMA were found to parallel with that in the cyclisation of **3** with the electron withdrawing ligand **2d** being the slowest, while the methyl substituted complex **2e** was faster than the control **2a**.

Table 1. Cyclisation of **4**: effect of ligand on conversion

Ligand	Mass balance (%)	Ratio **3**:**4**[a]
2a	95	41:59
2d	96	>98:2[b]
2d	95	77:23[c]
2e	96	34:66
2f	95	73:27

[a] Determined by 300 MHz ^{1}H NMR.
[b] No **4** could be detected in the crude NMR.
[c] Ration after 2710 min.

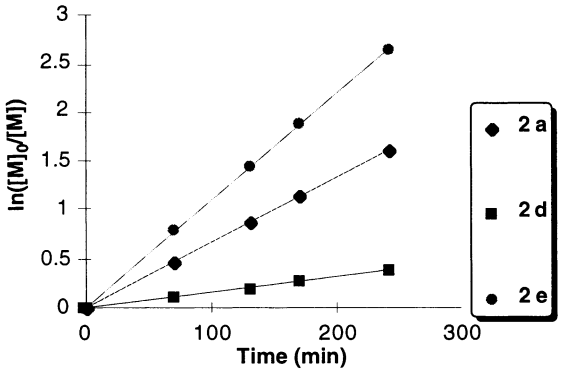

Figure 1. Rates of polymerisation of MMA with ligands.

The average molecular weights of polymers increase linearly with conversion in each case. Control is evidently greater when using ligands **2a** and **2e**, where M_n's fit well with those predicted, this was not the case for ligand **2d** which resembles a normal free radical polymerisation (Fig. 2). Polydispersities (PDIs) remain relatively low when ligands **2a** and **2e**[9] were utilised, indicating that initiation is fast compared to propagation and that all polymer chains grow at similar rates. However, the control in polydispersity with **2d** was significantly poorer.

In conclusion, we have demonstrated that substitution at the 6- and 5-positions of the pyridine nucleus in *N*-pentyl-2-pyridylmethanimine ligands can effect the rate of both ATRC and ATRP reactions significantly. This may be for electronic reasons, steric reasons, solubility reasons or a combination of all three. Substitution at the 6-position (mesomerically linked to the pyridine nitrogen) caused the ATRC reaction of **3** to fail presumably due to steric effects, while reaction with **5** indicated that the mesomerically electron donating

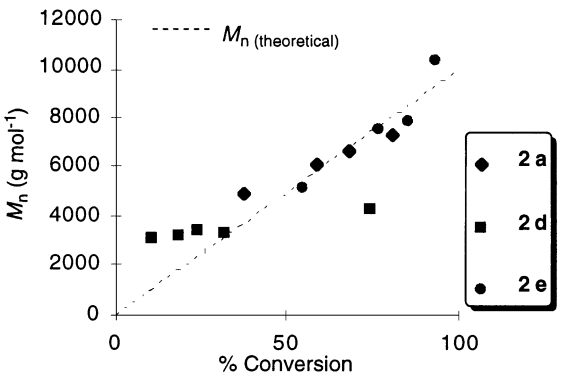

Figure 2. Dependence of M_n on conversion for the polymerisation of MMA with ligands.

OMe group **2c** was more efficient than **2b**. Groups at the 5-position can inductively alter the electron density of the pyridine nitrogen and mesomerically that of the imine nitrogen. For each substituent a balance of both these effects will determine the overall rate of the reaction. If the inductive effect on the pyridine nitrogen is the dominant feature then the order of activity/rate of reaction would be expected to follow **2e**>**2a**>**2f**>**2d** (paralleling σ_m). On the other hand, if the electronic mesomeric effect of substituents onto the imine nitrogen was dominant then the order would be expected to be **2f**>**2e**>**2a**>**2d** (paralleling σ_p). Our results show that in the ATRC of **3** the rate of reaction was found to follow the order **2e**>**2a**>**2f**>**2d**, suggesting that inductive effects onto the pyridine nitrogen are the dominant features for this class of ligands in cyclisation reactions. Thus, the rates of ATRC and ATRP reactions may well parallel the basicity of the ligands themselves. This fits in with the observation that more basic sp^3 hybridised amine ligands (TMEDA, *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine and tris(*N*,*N*-dimethylaminoethylene)-amine) are more active catalysts for both ATRC[10] of **3** and ATRP of MMA.[5d–e] Reaction with the most inductively electron withdrawing group, ligand **2d**, caused a significant decrease in the rate of both the ATRC reaction of **3** and the ATRP reaction of MMA. Although this may be due to the electronic effects mentioned above, the possibility of the NO_2 group competitively complexing the metal and changing the nature of the catalyst cannot be ruled out at this time. The observation that with ligand **2d** polymerisation of MMA proceeded with all the characteristics of a 'normal' free radical polymerisation confirms that initiation is relatively slow compared to propagation.

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7. Details of the preparation of the ligands **2a**–**2f** will be published separately.
8. Due to the poor yield in the synthesis of **2f** it was not examined as a catalyst in the polymerisation reactions.
9. **2a** (70 min, 1.18; 130 min, 1.16; 170 min, 1.17; 240 min, 1.18): **2d** (70 min, 1.16; 130 min, 1.17; 170 min, 1.19; 240 min, 1.15): **2e** (70 min, 1.23; 130 min, 1.25; 170 min, 1.24; 240 min, 1.31; 1260 min, 1.47).
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