Rapid screening of atom transfer radical polymerization catalysts by electrospray ionization mass spectrometry†

Fabio di Lena and Krzysztof Matyjaszewski*

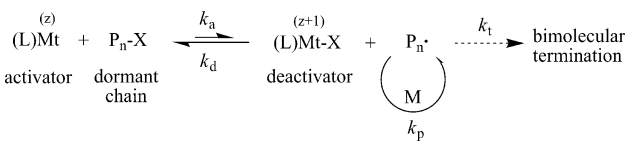
Received (in Cambridge, UK) 4th August 2008, Accepted 9th October 2008
First published as an Advance Article on the web 4th November 2008
DOI: 10.1039/b813466a

An ESI-MS-based methodology allows for a rapid assay of ATRP catalyst performance without prior polymerization experiments.

Atom transfer radical polymerization (ATRP) is a powerful technique that enables the facile synthesis of macromolecules with precisely controlled compositions, architectures and functionalities.[1] There is a continuous search for more efficient ATRP catalysts to reduce their concentration, increase selectivity and expand the range of polymerizable monomers. Thermodynamic and kinetic studies of the ATRP equilibrium (Scheme 1) provide fundamental understanding of catalyst structure–reactivity relationships[2] and, consequently, routes to more powerful metal/ligand combinations.[3] However, conventional procedures for catalyst evaluation are laborious and usually require relatively large amounts of materials, making the development of new metal complexes for ATRP a slow and inefficient process. In this work, we present a simple method for the rapid screening of ATRP catalysts.

Mechanistic studies have shown that, when using the same alkyl halide in the same solvent, the activity of an ATRP catalyst depends largely on the electron transfer equilibrium between the metals of the redox couple, K_{ET}, and the metal halide affinity equilibrium, K_X (Scheme 2). These are two of the four simpler reversible reactions formally representing the overall atom transfer process.[4] K_{ET} is related to the redox potential of the couple, which in turn depends on the ratio β^{II}/β^{I}, *i.e.* on the relative stability of the higher (β^{II}) and lower (β^{I}) oxidation states of the metal complex.[5] Consequently, ligands forming very stable metal complexes are likely to form active ATRP catalysts.

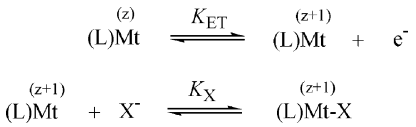
Recently, it was demonstrated that Cu(I) has a relatively small preference for specific donor atoms, and the stabilities of its complexes vary much less than those of Cu(II) complexes, as the ligands are altered.[6] Thus, the ligands forming very stable



Scheme 1

Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213, USA.
E-mail: km3b@andrew.cmu.edu; Fax: +1-412-268-6897;
Tel: +1-412-268-3209

† Electronic supplementary information (ESI) available: Experimental details, control experiments and catalysts' reactivity/stability relationships. See DOI: 10.1039/b813466a

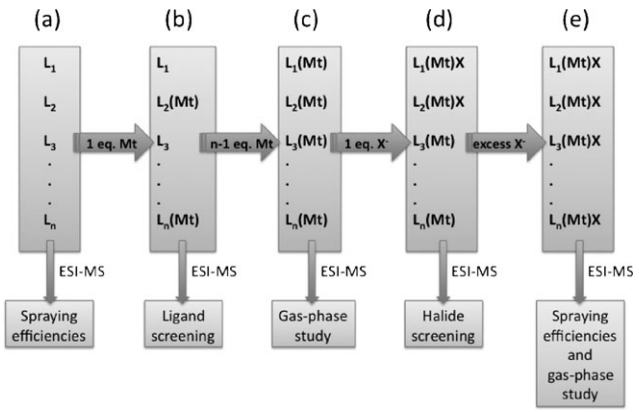


Scheme 2

Cu(II) complexes lead to high ratio β^{II}/β^{I}, high K_{ATRP} and a strongly reducing Cu(II)L/Cu(I)L couple. These mechanistic considerations infer that one can roughly predict the catalytic activity of a metal complex in ATRP by simply knowing its stability constants β^{II} and K_X.

The qualitative and quantitative evaluation of noncovalent binding interactions such as coordination bonds has been very successful since the advent of electrospray ionization mass spectrometry (ESI-MS) and other soft ionization techniques such as MALDI.[7] The gentleness by which ESI forms the ions and transfers them into the gas-phase leaves host–guest adducts practically intact,[8] and does not significantly perturb equilibria in solution.[9] Several recent examples demonstrated the feasibility of using ESI-MS to simultaneously measure either the relative[10] or the absolute[11] binding affinities and selectivity of different hosts (*e.g.* organic and bioorganic ligands, enzymes *etc.*) for various guests (metals, inhibitors *etc.*) by means of competitive experiments. This suggests that ESI-MS could be used for the rapid assay of ATRP catalysts. Through consecutive competitive experiments, both the relative binding affinities (β^{II}) of libraries of ligands and the relative halidophilicities of the resulting complexes (K_X) could be evaluated.

A typical screening procedure (Scheme 3) started with dissolving a library of equimolar amounts of *n* ligands in a given solvent and subjecting the resulting solution to ESI-MS analysis in order to determine the spraying efficiencies of the ligands and to calculate the relative correction factors



Scheme 3

(Scheme 3a). The intensity of a peak in an ESI-MS spectrum is a function of both the concentration of the corresponding species and its ionization efficiency, *i.e.* the efficiency with which the particular ion is desolvated and transferred into the gas-phase.[12] Therefore, if two ions have different response factors, the quantitative comparison of peak intensities requires determination of the correction factors.[13] The correction factors were obtained by normalizing the peak intensities with respect to the most intense one. The solution was subsequently used to dissolve 1 equivalent of a metal salt (*e.g.* $Cu(OTf)_2$), which distributed over the array of ligands on the basis of its specific affinities (Scheme 3b). The analysis of the mixture at the ESI-MS quickly showed which ligand had preferentially complexed the metal. Notably, by spraying a number of different catalyst solutions, it became apparent that metal complexes could be involved not only in metal–ligand equilibria but also in equilibria with the solvent, the counterion, various impurities *etc*.

This significantly complicated the ESI-MS spectra, as different peaks for the same metal–ligand couple were present, making the extraction of accurate quantitative information difficult. For this reason, metal–ligand affinities were determined by measuring not the amount of the formed complexes but the amount of ligands left free after the addition of metal. This is based on the assumption that the higher the amount of free ligand, the lower the stability of the corresponding complex. After the addition of $n - 1$ equivalents of metal salt, to quantitatively complex all the ligands (Scheme 3c), the solution was used to dissolve 1 equivalent of a halide salt, *e.g.* $N(Bu)_4Br$. As in the competitive experiment described above, Br^- distributed over the array of metal complexes on the basis of its specific affinities (Scheme 3d). This could be estimated by subjecting the mixture to ESI-MS analysis and measuring the relative abundances of halide-containing species. The subsequent addition of $N(Bu)_4Br$ in an excess sufficient to form equimolar amounts of halogenated complexes enabled the determination of correction factors for each peak intensity (Scheme 3e). Importantly, since the isolation is done by the instrument, no reaction workup was necessary in any of the steps above, and each metal complex could be easily picked out from the mixture and subjected individually to further reactions in the MS, including MS^n.

The part of the methodology concerning the ligand screening was validated by evaluating the relative binding affinities for Cu(II) of various ligands employed in ATRP. In a typical experiment, 3.3×10^{-5} mol of several ligands: tris[(2-pyridyl)-methyl]amine (TPMA, 9.4 mg), 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA, 9 μL), tris(2-aminoethyl)amine (TREN, 4.9 μL), diethylenetriamine (DETA, 3.6 μL) and pentamethyldiethylenetriamine (PMDETA, 6.9 μL) were dissolved in 10 mL of H_2O : MeOH 9 : 1 (v : v). 150 μL of the resulting solution was diluted in 20 mL of H_2O : MeOH 9 : 1 (v : v) and analyzed with ESI-MS to determine the spraying efficiencies of the ligands and to calculate the relative correction factors (Fig. 1). Tetra-amines spray better than tri-amines, alkylated amines better than hydrogenated ones, and aromatic amines much better than those with alkyl substituents. The rest of the solution was used to dissolve 3.2×10^{-5} mol (11.7 mg) of $Cu(OTf)_2$, from which 150 μL were taken, diluted

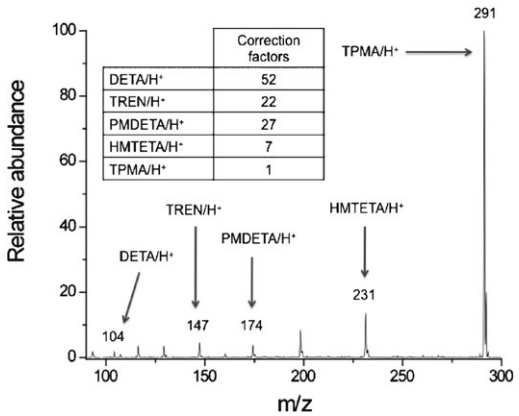


Fig. 1 ESI-MS spectrum of ligands before the addition of $Cu(OTf)_2$ together with the correction factors for the relative abundances.

in 20 mL of H_2O : MeOH 9 : 1 (v : v), and sprayed for the actual competition experiment. The peak intensities corresponding to each ligand were multiplied by the correction factors and normalized to 100 (Fig. 2), resulting in the following order of ligand affinities towards Cu(II): PMDETA < HMTETA < DETA < TPMA < TREN. This is the same order as reported in the literature on the basis of the stability constants determined by conventional potentiometric or calorimetric titrations in water.[14] Also, since high values of β^{II}/β^{I} correspond to high values of K_{ATRP}, this order corresponds also to the order of catalytic activities of the copper complexes (PMDETA < HMTETA < TPMA).[2] TREN is the most reducing complex and could be an even stronger ATRP catalyst, but its activity has not yet been quantified.

As a control experiment, tris(2-(dimethylamino)ethyl)amine (Me_6TREN), which could not be used in the previous competition, since it has the same m/z as HMTETA, was employed in a one-to-one competition experiment with TPMA for $Cu(OTf)_2$, employing the same procedure described above. A normalized relative intensity of 71 was found for free Me_6TREN. This value, with respect to the affinity for copper(II), places it between HMTETA and TPMA, in agreement with the β^{II} values from the literature. Additional series of control experiments proved that: (*i*) metal complexes are in thermodynamic equilibrium one with the other; and (*ii*) ligands can compete not only by reacting with uncomplexed

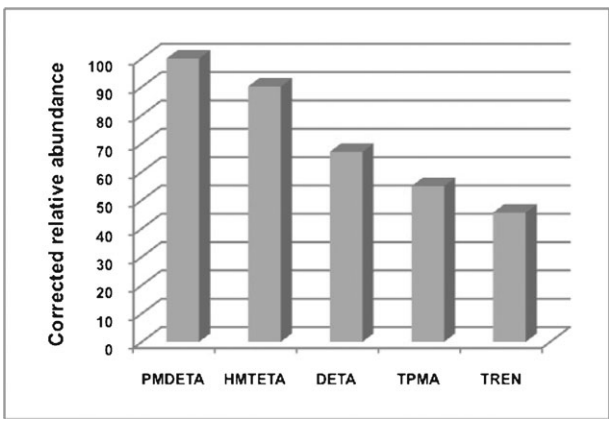


Fig. 2 Relative amounts of ligands remaining uncomplexed in the competition experiment.

copper, but also *via* direct ligand exchange. The affinity of the five above ligands for Cu(II) was determined also in methanol, acetone and acetonitrile, solvents in which conventional potentiometric or calorimetric titration methods were not reported. The results will be presented in a follow-up publication.

The part of the methodology concerning the halidophilicity screening was demonstrated by evaluating the relative bromidophilicity of $[PMDETA/Cu(II)]^{2+}$, $[HMTETA/Cu(II)]^{2+}$, $[DETA/Cu(II)]^{2+}$, $[TREN/Cu(II)]^{2+}$, and $[TPMA/Cu(II)]^{2+}$ in acetonitrile. This solvent was preferred to water because it is known that, in protic solvents, K_X is several orders of magnitude smaller.[15] In a typical procedure, 3.3×10^{-5} mol of PMDETA, HMTETA, DETA, TREN, and TPMA were dissolved in 10 mL of acetonitrile together with 16.5×10^{-5} mol (5 eq., 59.5 mg) of $Cu(OTf)_2$. The resulting solution was used to dissolve 3.3×10^{-5} mol (10.6 mg) of $N(Bu)_4Br$, from which 150 μL were taken, diluted in 20 mL of acetonitrile, and sprayed for the actual competition experiment. The mass spectrum clearly showed that only $[HMTETA/Cu(II)]^{2+}$ and $[TPMA/Cu(II)]^{2+}$ complexed the bromide, showing higher bromidophilicity than the other three complexes. The absence of the bromide anion in the negative mode suggested that most of Br^- was complexed to copper. Control experiments ruled out the possibility that doubly halogenated copper complexes were formed. It was not possible to measure the spraying efficiencies of the five bromo-containing complexes at once as the addition of four equivalents of $N(Bu)_4Br$ resulted in the precipitation of a white solid. The individual reaction of each ligand with $CuBr_2$ revealed the relatively poor solubility of $[DETA/Cu(II)Br]^+$ and $[TREN/Cu(II)Br]^+$ in acetonitrile. The spraying efficiencies of $[HMTETA/Cu(II)Br]^+$ and $[TPMA/Cu(II)Br]^+$ were then determined by dissolving 3.3×10^{-5} mol of HMTETA and TPMA together with 6.6×10^{-5} mol of $CuBr_2$ in 10 mL of acetonitrile, diluting 150 μL of the resulting solution in 20 mL of the same solvent and carrying out the ESI-MS analysis. As during the screening of ligands, the so calculated correction factors were used to quantify the relative amounts of $[HMTETA/Cu(II)Br]^+$ and $[TPMA/Cu(II)Br]^+$ in the competition zexperiment (Fig. 3). The lack of halidophilicity data in the literature does not allow the cross-validation of these results but, on the other hand, shows the importance and the utility of the present approach.

In conclusion, a general ESI-MS-based strategy allows for the rapid assay of ATRP catalyst performance without prior polymerization experiments, using only a few milligrams of compounds, and with no reaction workup necessary. This novel methodology could significantly contribute to the development of a new generation of ATRP catalysts of wide academic and industrial interest and applicable to a larger range of monomers. A similar impact on the synthesis of small organic molecules *via* the mechanistically analogous atom transfer radical addition (ATRA)[16] is also anticipated. The description of the gas-phase study of copper complexes will be published elsewhere.

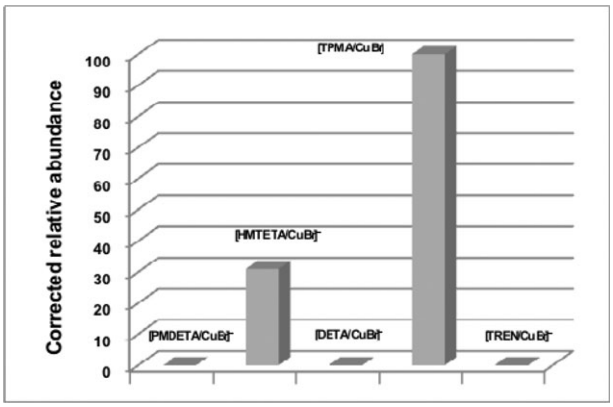


Fig. 3 Relative amounts of halogenated metal complexes formed in the competition experiment.

FdL acknowledges the Swiss National Science Foundation for a postdoctoral fellowship. Support from NSF (CHE-07-15494) is also acknowledged.

Notes and references

1 K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921.
2 R. Poli, *Angew. Chem., Int. Ed.*, 2006, **45**, 5058; W. Tang, Y. Kwak, W. A. Braunecker, N. V. Tsarevsky, M. L. Coote and K. Matyjaszewski, *J. Am. Chem. Soc.*, 2008, **130**, 10702.
3 N. V. Tsarevsky, W. A. Braunecker, W. Tang, S. J. Brooks, K. Matyjaszewski, G. R. Weisman and E. H. Wong, *J. Mol. Catal. A: Chem.*, 2006, **257**, 132.
4 N. V. Tsarevsky, W. A. Braunecker and K. Matyjaszewski, *J. Organomet. Chem.*, 2007, **692**, 3212.
5 R. Tamamushi and G. P. Sato, *Prog. Polarography*, 1972, **3**, 1.
6 D. B. Rorabacher, *Chem. Rev.*, 2004, **104**, 651.
7 J. M. Daniel, S. D. Friess, S. Rajagopalan, S. Wendt and R. Zenobi, *Int. J. Mass Spectrom.*, 2002, **216**, 1; M. A. R. Meier, B. G. G. Lohmeijer and U. S. Schubert, *J. Mass Spectrom.*, 2003, **38**, 510; B. Chiavarino, M. E. Crestoni, S. Fornarini and C. Rovira, *Inorg. Chem.*, 2008, **47**, 7792; S. Torker, D. Merki and P. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 4808.
8 C. A. Schalley, *Int. J. Mass Spectrom.*, 1999, **194**, 11.
9 A. Wortmanna, A. Kistler-Momotovaa, R. Zenobi, M. C. Heine, O. Wilhelm and S. E. Pratsinis, *J. Am. Soc. Mass Spectrom.*, 2007, **18**, 385.
10 X. Cheng, R. Chen, J. E. Bruce, B. L. Schwartz, G. A. Anderson, S. A. Hofstadler, D. C. Gale and R. D. Smith, *J. Am. Chem. Soc.*, 1995, **117**, 8859; M. L. Reyzer, J. S. Brodbelt, A. P. Marchand, Z. Chen, Z. Huang and I. N. N. Namboothiri, *Int. J. Mass Spectrom.*, 2001, **204**, 133.
11 T. J. D. Jorgensen, P. Roepstorff and A. J. R. Heck, *Anal. Chem.*, 1998, **70**, 4427; T. J. D. Jorgensen, T. Staroske, P. Roepstorff, D. H. Williams and A. J. R. Heck, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1859.
12 S. M. Clark and L. Konnerman, *Anal. Chem.*, 2004, **76**, 1257.
13 V. Gabelica, N. Galic, F. Rosu, C. Houssier and E. De Pauw, *J. Mass. Spectrom.*, 2003, **38**, 491.
14 F. J. C. Rossotti and H. Rossotti, in *The Determination of Stability Constants*, McGraw-Hill, New York, 1961.
15 N. V. Tsarevsky, T. Pintauer and K. Matyjaszewski, *Macromolecules*, 2004, **37**, 9768.
16 T. Pintauer and K. Matyjaszewski, *Chem. Soc. Rev.*, 2008, **37**, 1087.

