# Effects of Initiator Structure on Activation Rate Constants in ATRP

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ABSTRACT: Activation rate constants ($k_{act}$) for a variety of initiators for Cu-mediated ATRP have been determined under the same conditions. The ratio of the activation rate constants for the studied alkyl (pseudo)halides exceeds 1 million times. The activation rate constants increase with initiator substitution (e.g., for primary, secondary, and tertiary α-bromoesters the ratios are ∼1:10:80), with the radical stabilizing α-substituent (e.g., alkyl bromides with −C(O)NEt$_2$, −Ph, −C(O)OMe, and −CN groups the ratios are ∼1:4:8:600 but with both α-Ph and α-C(O)-OEt ∼ 140 000), and with the leaving atom/group (e.g., for methyl 2-halopropionates: chloro:bromo:iodo ∼1: 20:35, but benzyl bromide is ∼10 000 more reactive than the corresponding isothiocyanate/thiocyanate).

## Introduction

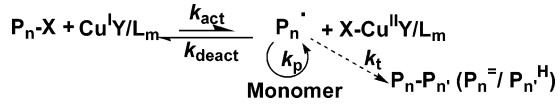
During the past decade, atom transfer radical polymerization (ATRP) has emerged as a powerful and robust technique for the synthesis of polymeric materials with well-defined compositions, architectures, and functionalities.[1−12] The success of ATRP depends largely on an appropriate equilibrium between the activation process (generation of radicals, $k_{act}$) and the deactivation process (formation of alkyl halides, $k_{deact}$). The equilibrium constants between the two rate constants ($K_{ATRP} = k_{act}/k_{deact}$) determines the concentration of radicals and subsequently the rates of polymerization and termination, as shown in eqs 1 and 2.[6,13] Usually $K_{ATRP}$ is small ($10^{-4}$−$10^{-9}$),[14] which ensures a low radical concentration and minimizes termination reactions. At the same time, each rate constant ($k_{act}$ and $k_{deact}$), especially $k_{deact}$ (eq 2), affects the level of control in the polymerization. A good control in the polymerization enables linear correlation between the molecular weight and the monomer conversion and a narrow molecular weight distribution. Ideally, both $k_{act}$ and $k_{deact}$ should be large enough (though $k_{act} \ll k_{deact}$) to provide good control over the polymerization while maintaining a reasonable polymerization rate.

$$\ln\left(\frac{M_0}{M}\right) = \frac{k_p k_{act}[P_n{-}X][Cu^I]}{k_{deact}[Cu^{II}]} \quad (1)$$

$$\frac{M_w}{M_n} = 1 + \frac{k_p[R{-}X]_0}{k_{deact}[Cu^{II}]}\left(\frac{2}{p} - 1\right) \quad (2)$$

It is crucial to evaluate both rate constants $k_{act}$ and $k_{deact}$ for better understanding and optimization of various catalytic/initiating systems. Studies have thus far concentrated on measuring $k_{act}$ for polymeric and monomeric systems using spectroscopy and chromatography.[15−33] However, most of the values were obtained under various reaction conditions (different temperatures, solvents, etc.) using a variety of techniques (high-performance liquid chromatography (HPLC), gas chromatography (GC), nuclear magnetic resonance (NMR), size exclusion chromatography (SEC), etc.) and methods (second-order, pseudo-first-order, etc.). It is difficult to obtain reliable structure−activity relationship by analyzing $k_{act}$ values determined under different conditions. To better compare and understand the kinetic processes in ATRP, we present here a systematic investigation of the effect of initiator structure on the activation process by determining the $k_{act}$ under the same reaction conditions (35 °C in acetonitrile) and using the same technique (GC) and method (pseudo-first-order process). Several initiators are the model compounds mimicking the dormant polymeric chain ends in ATRP; e.g., ethyl 2-bromoisobutyrate (EtBriB) is a model for poly(methyl methacrylate), methyl 2-bromopropionate (MBrP) a model for poly(methyl acrylate), and 1-phenylethyl bromide (PEBr) a model for polystyrene. Knowledge of such $k_{act}$ values is also useful in the kinetic simulations of ATRP processes.[34−36] Together with the values of $k_{act}$ for various ligands,[37] they will provide a clearer picture of the parameters affecting activation process in ATRP.

**Scheme 1. Proposed Mechanism for ATRP**




## Experimental Section

**Materials.** Cu$^I$Br (99.999%, Aldrich) and Cu$^I$Cl (99.995+%, Aldrich) were used as received. Ethyl 2-bromoisobutyrate (99%, Aldrich), 1,2,4-trichlorobenzene (TCB, 99%, Aldrich), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), 1,1,4,7,-10,10-hexamethyltriethylenetetramine (HMTETA, 97%, Aldrich), and 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) (99%, Aldrich) were used as received. Diethyl 2-bromopropionamide (DEBrPA)[38] and methyl 2-iodopropionate (MIP)[39] were synthesized according to the literature. *N*-(*n*-Propyl)pyridylmethanimine (NPPMI) was synthesized by condensation of *n*-propylamine with pyridine-2-carboxaldehyde.[40] All other reagents were used as received.

**Typical Activation Rate Constant Measurements (Cu$^I$Br/PMDETA with EtBriB).** Stock solutions of EtBriB ($4 \times 10^{-3}$ M) were prepared by adding 7.8 mg (0.04 mmol) of the corresponding reactant along with 14.5 mg (0.08 mmol) of internal standard, TCB, and 62.5 mg (0.4 mmol) of TEMPO in acetonitrile (MeCN) in a 10 mL volumetric flask. Similarly, a 0.08 M stock solution of PMDETA was prepared in MeCN. In a Schlenk flask, 11.5 mg (0.08 mmol) of Cu$^I$Br was taken, and the flask was degassed and backfilled with $N_2$ three times. 1 mL stock solution of PMDETA along with 2 mL of acetontrile was subjected to a freeze−pump−

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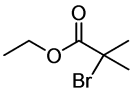
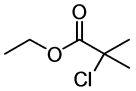
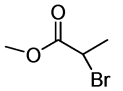
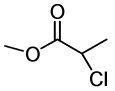
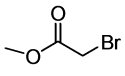
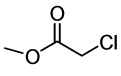
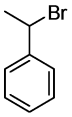
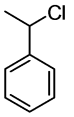
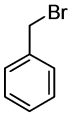
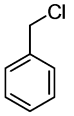
**Table 1. Activation Rate Constants for Alkyl Bromides and Chlorides (Values Were Measured Using [Initiator]$_0$ = 1 mM, [Cu$^I$Br/PMDETA]$_0$ = 20 mM, at 35 °C in MeCN)**

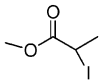
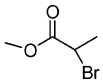
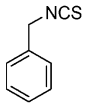
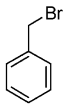
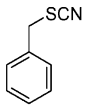
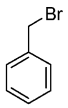
| Alkyl Bromide | $k_{act}$ ($M^{-1}s^{-1}$) | Alkyl Chloride | $k_{act}$ ($M^{-1}s^{-1}$) |
|---|---|---|---|
|  EtBriB | 2.7 |  EtCliB | 0.022 |
|  MBrP | 0.33 |  MClP | 0.015 |
|  MBrAc | 0.030 |  MClAc | $1.6\times10^{-3}$ |
|  PEBr | 0.17 |  PECl | 0.010 |
|  BzBr | 0.10 |  BzCl | $5.5\times10^{-3}$ |
|  BrPN | *23 |  ClPN | 0.46 |
|  BrAN | *7.1 |  ClAN | 0.14 |

*Value was extrapolated from the $k_{act}$ for Cu$^I$Br/HMTETA with BrPN or BrAN, i.e., $k_{act}$(Cu$^I$Br/PMDETA with BrPN) = $k_{act}$(Cu$^I$Br/HMTETA with BrPN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 1.2 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 23 $M^{-1}$ $s^{-1}$; $k_{act}$(Cu$^I$Br/PMDETA with BrAN) = $k_{act}$(Cu$^I$Br/HMTETA with BrAN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 0.37 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 7.1 $M^{-1}$ $s^{-1}$.

thaw cycle three times and then transferred to the Schlenk flask through a $N_2$-purged syringe. The flask was stirred, and a sample was taken immediately for GC analysis, generating the data for time zero. Then, 1 mL of the stock solution of EtBriB, TCB, and TEMPO was degassed by a freeze−pump−thaw cycle three times and transferred to the Schlenk flask through a degassed syringe. The reaction was carried out at 35 °C under constant stirring. Samples were taken at timed intervals, and the consumption of EtBriB with time was monitored by GC. GC was performed using a Schimadzu GC-17A, AOC-20i autosampler, and J & W Scientific DB 608 column (30 m × 0.53 mm) with an electron capture detector (ECD) detector. The ECD detector is very sensitive to alkyl halides and governed by radiation ($\beta$-ray) from a $^{63}$Ni source sealed in the ECD cell ionized by an inert gas ($N_2$).

The method used to determine the $k_{act}$ is the same as the those reported elsewhere.[31,32,37]

**Table 2. Activation Rate Constants for Initiators with Different Leaving Atom/Group (Values Were Measured Using [Initiator]$_0$ = 1 mM, [Cu$^I$Br/PMDETA]$_0$ = 20 mM, at 35 °C in MeCN)**

| Initiator | $k_{act}$ ($M^{-1}s^{-1}$) | Initiator | $k_{act}$ ($M^{-1}s^{-1}$) |
|---|---|---|---|
|  MIP | 0.53 |  MBrP | 0.33 |
|  BzNCS | *$8.9\times10^{-6}$ |  BzBr | 0.10 |
|  BzSCN | *$1.2\times10^{-5}$ |  BzBr | 0.10 |

*Value was extrapolated from the $k_{act}$ for Cu$^I$Br/Me$_6$TREN with BzNCS or BzSCN, i.e., $k_{act}$(Cu$^I$Br/PMDETA with BzNCS) = $k_{act}$(Cu$^I$Br/Me$_6$TREN with BzNCS) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/Me$_6$TREN with EtBriB) = 1.5 × $10^{-3}$ × 2.7/4.5 × $10^2$ $M^{-1}$ $s^{-1}$ = 8.9 × $10^{-6}$ $M^{-1}$ $s^{-1}$; or $k_{act}$(Cu$^I$Br/PMDETA with BzSCN) = $k_{act}$(Cu$^I$Br/Me$_6$TREN with BzSCN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/Me$_6$TREN with EtBriB) = 2.0 × $10^{-3}$ × 2.7/4.5 × $10^2$ $M^{-1}$ $s^{-1}$ = 1.2 × $10^{-5}$ $M^{-1}$ $s^{-1}$.

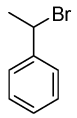
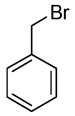
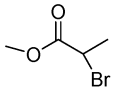
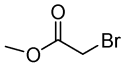
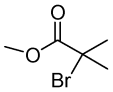
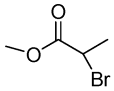
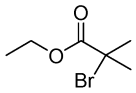
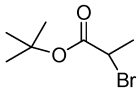
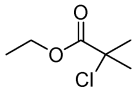
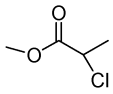
## Results and Discussion

Most of the ATRP initiators are alkyl bromides and chlorides. However, also alkyl iodides and pseudo-halides have been evaluated in this study. Most of the experiments have been carried out under similar conditions with one of the most commonly used ligands, PMDETA. For very active initiators such as BrPN and BrAN, a less active ligand (HMTETA) was employed to determine the $k_{act}$ values more precisely. The extrapolated values were thus calculated, assuming that PMDETA and HMTETA have the same selectivity toward active initiators and less active initiators (e.g., $k_{act}$(Cu$^I$Br/PMDETA with BrPN) = $k_{act}$(Cu$^I$Br/HMTETA with BrPN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 1.2 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 23 $M^{-1}$ $s^{-1}$). More extensive results of selectivity studies will be reported separately (cf. also Table 5). The ratio of activation rate constants extrapolated for the same catalyst (Cu$^I$Br/PMDETA) is as large as ~2 million times. The initiators studied include those with different leaving groups/atoms (i.e., iodo, bromo, chloro, and pseudo-halo), the substitution degree (i.e., tertiary, secondary, and primary initiators), and the α-substituents stabilizing radicals (i.e., cyanide, ester, benzyl, amide, and concurrent phenyl ester groups).

All the values of activation rate constants reported here are the average values of several measurements. For example, three measurements of Cu$^I$Br/PMDETA with EtBriB gave $k_{act}$ values of 2.1, 2.7, and 3.3 $M^{-1}$ $s^{-1}$, respectively. The activation rate constant for Cu$^I$Br/PMDETA with EtBriB was then determined as the average value, 2.7 $M^{-1}$ $s^{-1}$. Some potential problems affecting the reproducibility of measurements include sampling small amounts of the reagents, adventitious oxidation of Cu$^I$ catalyst due to leaking of air when experiment took a long time with very reducing catalysts, not instantaneous quenching of less active catalysts, and also reproducibility of GC. Nevertheless, typical errors of the kinetic measurements were within 30%.

**Leaving Atom/Group.** The leaving group or atom in the alkyl (pseudo)halide is reversibly transferred to the Cu complex

**Table 3. Activation Rate Constants for Tertiary, Secondary, and Primary Initiators (Values Were Measured Using [Initiator]$_0$ = 1 mM, [Cu$^I$Br/PMDETA]$_0$ = 20 mM, at 35 °C in MeCN)**

| Initiator | $k_{act}$ ($M^{-1}s^{-1}$) | Initiator | $k_{act}$ ($M^{-1}s^{-1}$) |
|---|---|---|---|
|  BrPN | *23 |  BrAN | *7.1 |
|  PEBr | 0.17 |  BzBr | 0.10 |
|  MBrP | 0.33 |  MBrAc | 0.030 |
|  MBriB | 2.6 |  MBrP | 0.33 |
|  EtBriB | 2.7 |  *t*BBrP | 0.085 |
|  EtCliB | 0.022 |  MClP | 0.015 |

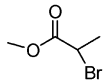
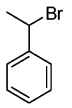
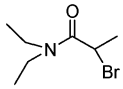
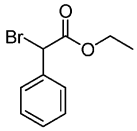
*Value was extrapolated from the $k_{act}$ for Cu$^I$Br/HMTETA with BrPN or BrAN, i.e., $k_{act}$(Cu$^I$Br/PMDETA with BrPN) = $k_{act}$(Cu$^I$Br/HMTETA with BrPN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 1.2 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 23 $M^{-1}$ $s^{-1}$; $k_{act}$(Cu$^I$Br/PMDETA with BrAN) = $k_{act}$(Cu$^I$Br/HMTETA with BrAN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 0.37 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 7.1 $M^{-1}$ $s^{-1}$.

in the activation process. The transferred group/atom consists of halogen (Cl, Br, I) or pseudo-halogen (SCN, NCS, etc.), as shown in Table 1. Alkyl bromides are usually more active than alkyl chlorides as ATRP initiators because the C−Br bond is much weaker than the C−Cl bond. However, the value of $K_{ATRP}$ depends not only on bond dissociation energy (BDE) in alkyl halide but also on bonding of the halide to a Cu species.[41,42] Moreover, the activation rate constants would depend not only on the overall change in the free energy of the atom transfer process but more precisely on the activation enthalpy and entropy for this process, as will be discussed later. It seems that alkyl bromides are ~20 times more active than alkyl chlorides. More precisely, MBrP is 22 times more active than MClP, MBrAc is 19 times more active than MClAc, PEBr is 17 times more active than PECl, and BzBr is ~18 times more active than BzCl. Similar values were found for polystyrene Br/Cl systems.[17] Larger differences reported earlier for a model system could be attributed to an adventitious catalyst oxidation and a loss of its activity for PECl/CuCl/2dNbpy.[22] Surprisingly, EtBriB is ~100 times more active than EtCliB.

Other types of initiators with different leaving groups are listed in Table 2. Methyl 2-iodopropionate (MIP) is slightly more active than its bromide counterpart (MBrP). One could anticipate much greater activity of alkyl iodide due to a significantly lower BDE for the C−I bond. However, this difference must be compensated by much weaker iodine affinity toward Cu. In fact, $Cu^{II}I_2$ species could not be isolated as a stable compound.

Benzyl thiocyanate (BzSCN) and benzyl isothiocyanate (BzNCS) are almost inactive, and no polymerization can proceed unless very active catalyst such as Cu$^I$Br/Me$_6$TREN is used. Regardless, the general activity of the transfer group for the initiators decreases in the order of I ≥ Br > Cl ≫ SCN ≈ NCS.

**Table 4. Activation Rate Constants for Secondary Bromides with Different α-Substituents (Values Were Measured Using [Cu$^I$Br/PMDETA]$_0$ = 20 mM, [Initiator]$_0$ = 1 mM, at 35 °C in MeCN)**

| Initiator | $k_{act}$ ($M^{-1}s^{-1}$) | Initiator | $k_{act}$ ($M^{-1}s^{-1}$) |
|---|---|---|---|
|  BrPN | [a]23 |  MBrP | 0.33 |
|  PEBr | 0.17 |  DEBrPA | 0.040 |
|  EBPA | [b]5.3×10$^3$ | | |

[a] Value was extrapolated from the $k_{act}$ for Cu$^I$Br/HMTETA with BrPN, i.e., $k_{act}$(Cu$^I$Br/PMDETA with BrPN) = $k_{act}$(Cu$^I$Br/HMTETA with BrPN) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Br/HMTETA with EtBriB) = 1.2 × 2.7/0.14 $M^{-1}$ $s^{-1}$ = 23 $M^{-1}$ $s^{-1}$. [b] Value was extrapolated from the $k_{act}$ for Cu$^I$Br/NPPMI with EBPA, i.e., $k_{act}$(Cu$^I$Br/PMDETA with EBPA) = $k_{act}$(Cu$^I$Br/NPPMI with EBPA) × $k_{act}$(Cu$^I$Br/PMDETA with EtBriB)/(Cu$^I$Cl/NPPMI with EtBriB) = 4.7 × 2.7/2.4 × $10^{-3}$ $M^{-1}$ $s^{-1}$ = 5.3 × $10^3$ $M^{-1}$ $s^{-1}$.[32]

**Primary, Secondary, and Tertiary Alkyl Halides.** The $k_{act}$ for primary, secondary, and tertiary alkyl halides follows the order of 1° < 2° < 3° (Table 3). Secondary 2-bromopropionitrile (BrPN) is ~3 times more active than primary bromoacetonitrile (BrAN). Secondary 1-phenylethyl bromide (PEBr) is 1.7 times more active than primary benzyl bromide (BzBr). However, secondary methyl 2-bromopropionate (MBrP) is 11 times more active than primary methyl bromoacetate (MBrAc). The tertiary methyl 2-bromoisobutyrate (MBriB) is 8 times more active than methyl 2-bromoprionate (MBrP). A similar reactivity trend is also found for the chlorides. The order of reactivity is consistent with the resulting radical stability and consistent with the inner-sphere electron-transfer (atom-transfer) process.

Substituents in the alkyl ester group have a smaller effect on rate constants. The activation rate constants are similar for methyl and ethyl bromoesters (e.g., MBriB and EtBriB) but 4 times slower for *tert*-butyl esters (MBrP vs *t*BBrP). This again is consistent with inner-sphere rather than outer-sphere electron-transfer process.

**Substituents Stabilizing Radicals.** Table 4 shows the activation rate constants for the secondary alkyl bromides with four different α-substituents. The reactivity increases progressively from amides through secondary benzyl and propionate to propionitrile derivatives in the relative order 1:4:8:600. This order is in general agreement with the BDE values calculated by DFT.[41]

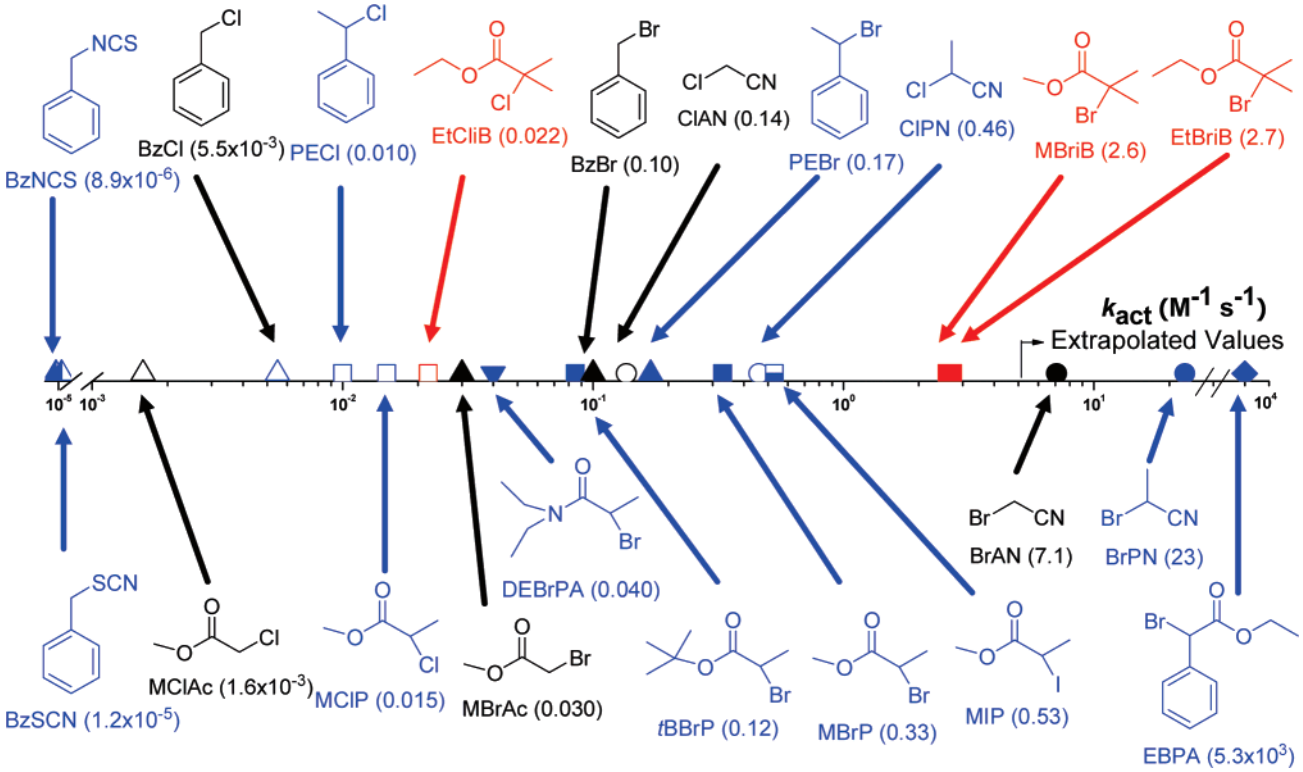



**Figure 1.** ATRP activation rate constants for various initiators with Cu$^{I}$X/PMDETA (X = Br or Cl) in MeCN at 35 °C: 3°, red; 2°, blue; 1°, black; isothiocyanate/thiocyanate, left half-filled; chloride, open; bromide, filled; iodide, bottom half-filled; amide, ▼; benzyl, ▲; ester, □; nitrile, ○; phenyl ester, ◇.

**Table 5. Comparison of Extrapolated Values with Measured Values**

| no. | ligand | initiator | $k_{act}$ ($M^{-1}$ $s^{-1}$ measured)[a] | $k_{act}$ ($M^{-1}$ $s^{-1}$ extrapolated)[b] |
|---|---|---|---|---|
| 1 | $Me_3TAN$ | BzBr | 0.014 | 0.012 |
| 2 | HMTETA | MBrP | 0.030 | 0.017 |
| 3 | N4[2,2,3] | MBrP | 0.050 | 0.028 |
| 4 | Me4Cyclam | MBrP | 0.10 | 0.082 |
| 5 | bpy | BrAN | 0.22 | 0.24 |
| 6 | $Me_6TREN$ | PECl | 1.5[22] | 1.7 |

[a] Values were measured using [Cu$^{I}$Br/Ligand]$_0$ = 20 mM, [initiator]$_0$ = 1 mM, at 35 °C in MeCN. [b] Value was extrapolated from following calculations: $k_{act}$(Cu$^{I}$Br/ligand with initiator) = $k_{act}$(Cu$^{I}$Br/ligand with EtBriB) × $k_{act}$(Cu$^{I}$Br/PMDETA with initiator)/(Cu$^{I}$Br/PMDETA with EtBriB).

It is interesting to compare this order with values presented for the latter three derivatives but also for the primary and chloro derivatives. Thus, secondary benzyl, ester, and nitrile bromo derivatives follow the relative order 1:2:150, and the secondary chlorides have a similar order, 1:1.5:50. The primary bromides follow the order 1:0.3:70 and primary chlorides 1:0.3:30. It appears that primary esters are slightly less active than benzyl derivatives, in contrast to the secondary species. Also, differences for alkyl chlorides are smaller than for the corresponding bromides.

The most active initiator found to date is the EBPA (mixed benzyl ester initiator), as shown in Table 4. This initiator is so active that we could not use a typical ATRP catalyst with a ligand such as PMDETA or bpy to measure its $k_{act}$. The model reaction for measurement of $k_{act}$ would be finished within seconds. Fortunately, the pseudo-first-order reaction could be slowed down by using one of the least active catalysts, Cu$^{I}$Br/$NPPMI_2$. However, the $k_{act}$ value for EBPA with Cu$^{I}$Br/$NPPMI_2$ was still as high as 7.1 $M^{-1}$ $s^{-1}$. By employing the same selectivity principle, a $k_{act}$ of ~5.3 × $10^3$ $M^{-1}$ $s^{-1}$ was extrapolated for EBPA with PMDETA, indicating that EBPA is ~2000 times more active than EtBriB. The high activity of EBPA can be attributed to the fact that both benzyl and carboxyethyl groups contribute to the stabilization of the generated radical. EBPA was successfully used the continuous activator regeneration (ICAR) ATRP of methyl methacrylate (MMA), giving a very good control over the molecular weight and polydispersities.[2,43,44]

EBPA is 20 000 more active than MBrP and also 30 000 more active than PEBr. If one could assume, at the first approximation, the additive contribution of both groups, it is tempting to estimate the reactivity of the dormant species in ATRP of α-olefin such as propylene or 1-hexene. The rate constant of activation should be ~$10^4$ times smaller than values for MBrP and PEBr, i.e., in the range of $k_{act}$ ~$10^{-5}$ $M^{-1}$ $s^{-1}$ (with Cu$^{I}$Br/PMDETA in MeCN at 35 °C). This is in a qualitative agreement with the extremely slow reactivation of model compounds and dormant species formed in copolymerization of acrylates with α-olefins.[33]

**Overview of Different Structural Parameters on the Activation Rate Constants.** As illustrated in Figure 1, the ratio of the activation rate constants for the studied alkyl (pseudo)-halides exceeds 1 million times. These values were mostly measured by using Cu$^{I}$Br/PMDETA catalyst in MeCN at 35 °C. The activation rate constants increase with initiator substitution, primary (black entries) < secondary (blue) < tertiary (red); with the radical stabilizing groups, −C(O)$NEt_2$ (inverted triangle) < −Ph (triangle) ~ −C(O)OR (square) ≪ −CN (circle), and both −Ph and α-C(O)OEt groups generate the most active initiator (diamond); and with the leaving atom/group (e.g., for methyl 2-halopropionates: chloro:bromo:iodo ~ 1:20:35, benzyl bromide is ~10 000 more reactive than the corresponding isothiocyanate/thiocyanate (left half-filled) ≪ chloride (open) < bromide (filled) ≤ iodide (bottom half-filled).

The structural variation of studied alkyl (pseudo)halides help to establish a structure−reactivity relationship for initiator

**Table 6. Summary of the Activation Rate Constants for Various Ligands[37] and Initiators (Measured and Extrapolated) (Values in Black Are Measured in MeCN at 35 °C and in Red Are Extrapolated (cf. Table 5))**

| $k_{act}$ | BzNCS | BzSCN | MClAc | BzCl | PECl | MClP | EtCliB | MBrAc | DEBrPA | tBBrP | BzBr | ClAN | PEBr | MBrP | ClPN | MIP | MBriB | EtBriB | BrAN | BrPN | EBPA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N4-[2,3,2] | 4.4E-9 | 5.3E-9 | 7.1E-7 | 2.4E-6 | 4.4E-6 | 6.7E-6 | 9.8E-6 | 1.3E-5 | 1.8E-5 | 3.8E-5 | 4.4E-5 | 6.0E-5 | 7.6E-5 | 1.5E-4 | 2.0E-4 | 2.4E-4 | 1.2E-3 | 1.2e-3 | 3.2E-3 | 1.0E-2 | 2.4E+0 |
| NPPMI | 8.9E-9 | 1.1E-8 | 1.4E-6 | 4.9E-6 | 8.9E-6 | 1.3E-5 | 2.0E-5 | 2.7E-5 | 3.6E-5 | 7.6E-5 | 8.9E-5 | 1.2E-4 | 1.5E-4 | 2.9E-4 | 4.1E-4 | 4.7E-4 | 2.3E-3 | 2.4e-3 | 6.3E-3 | 2.1E-2 | 4.7E+0 |
| NOPMI | 7.9E-9 | 1.1E-8 | 1.4E-6 | 4.9E-6 | 8.9E-6 | 1.3E-5 | 2.0E-5 | 2.7E-5 | 3.6E-5 | 7.6E-5 | 8.9E-5 | 1.2E-4 | 1.5E-4 | 2.9E-4 | 4.1E-4 | 4.7E-4 | 2.3E-3 | 2.4e-3 | 6.3E-3 | 2.1E-2 | 4.7E+0 |
| N4-[3,2,3] | 1.6E-8 | 2.2E-8 | 3.0E-6 | 1.0E-5 | 1.9E-5 | 2.8E-5 | 4.1E-5 | 5.6E-5 | 7.4E-5 | 1.6E-4 | 1.9E-4 | 2.5E-4 | 3.1E-4 | 6.1E-4 | 8.5E-4 | 9.8E-4 | 4.8E-3 | 5.0e-3 | 1.3E-2 | 4.3E-2 | 9.8E+0 |
| N3-[2,3] | 3.0E-8 | 4.0E-8 | 5.5E-6 | 1.9E-5 | 3.4E-5 | 5.1E-5 | 7.5E-5 | 1.0E-4 | 1.4E-4 | 2.9E-4 | 3.4E-4 | 4.6E-4 | 5.8E-4 | 1.1E-3 | 1.6E-3 | 1.8E-3 | 8.9E-3 | 9.2e-3 | 2.4E-2 | 7.9E-2 | 1.8E+1 |
| AN6TREN | 4.0E-8 | 5.3E-8 | 7.1E-6 | 2.4E-5 | 4.4E-5 | 6.7E-5 | 9.8E-5 | 1.3E-4 | 1.8E-4 | 3.8E-4 | 4.4E-4 | 6.0E-4 | 7.6E-4 | 1.5E-3 | 2.0E-3 | 2.4E-3 | 1.2E-2 | 0.012 | 3.2E-2 | 1.0E-1 | 2.4E+1 |
| TMEDA | 4.9E-8 | 6.6E-8 | 8.9E-6 | 3.1E-5 | 5.6E-5 | 8.3E-5 | 1.2E-4 | 1.7E-4 | 2.2E-4 | 4.7E-4 | 5.6E-4 | 7.6E-4 | 9.4E-4 | 1.8E-3 | 2.6E-3 | 2.9E-3 | 1.4E-2 | 0.015 | 3.9E-2 | 1.3E-1 | 2.9E+1 |
| Et6TREN | 1.5E-7 | 1.9E-7 | 2.6E-5 | 9.0E-5 | 1.6E-4 | 2.4E-4 | 3.6E-4 | 4.9E-4 | 6.5E-4 | 1.4E-3 | 1.6E-3 | 2.2E-3 | 2.8E-3 | 5.4E-3 | 7.5E-3 | 8.6E-3 | 4.2E-2 | 0.044 | 1.2E-1 | 3.8E-1 | 8.6E+1 |
| bpy | 3.0E-7 | 4.0E-7 | 5.5E-5 | 1.9E-4 | 3.4E-4 | 5.1E-4 | 7.5E-4 | 1.0E-3 | 1.4E-3 | 2.9E-3 | 3.4E-3 | 4.6E-3 | 5.8E-3 | 1.1E-2 | 1.6E-2 | 1.8E-2 | 8.9E-2 | 0.092 | 2.4E-1 | 7.9E-1 | 1.8E+2 |
| HMTETA | 4.6E-7 | 6.1E-7 | 8.3E-5 | 2.9E-4 | 5.2E-4 | 7.8E-4 | 1.1E-3 | 1.6E-3 | 2.1E-3 | 4.4E-3 | 5.2E-3 | 7.1E-3 | 8.8E-3 | 3.0E-2 | 2.4E-2 | 2.7E-2 | 1.3E-1 | 0.14 | 3.7E-1 | 1.2E+0 | 2.7E+2 |
| dHDbpy | 6.6E-7 | 8.8E-7 | 1.2E-4 | 4.1E-4 | 7.4E-4 | 1.1E-3 | 1.6E-3 | 2.2E-3 | 3.0E-3 | 6.3E-3 | 7.4E-3 | 1.0E-2 | 1.3E-2 | 2.4E-2 | 3.4E-2 | 3.9E-2 | 1.9E-1 | 0.20 | 5.3E-1 | 1.7E+0 | 3.9E+2 |
| N4-[2,2,3] | 7.6E-7 | 1.0E-6 | 1.4E-4 | 4.7E-4 | 8.5E-4 | 1.3E-3 | 1.9E-3 | 2.6E-3 | 3.4E-3 | 7.2E-3 | 8.5E-3 | 1.2E-2 | 1.4E-2 | 5.0E-2 | 3.9E-2 | 4.5E-2 | 2.2E-1 | 0.23 | 6.0E-1 | 2.0E+0 | 4.5E+2 |
| Me3TAN | 1.3E-6 | 1.7E-6 | 2.3E-4 | 7.7E-4 | 1.4E-3 | 2.1E-3 | 3.1E-3 | 4.2E-3 | 5.6E-3 | 1.2E-2 | 1.4E-2 | 1.9E-2 | 2.4E-2 | 4.6E-2 | 6.5E-2 | 7.5E-2 | 3.7E-1 | 0.38 | 1.0E+0 | 3.3E+0 | 7.5E+2 |
| dNbpy | 2.0E-6 | 2.6E-6 | 3.6E-4 | 1.2E-3 | 2.2E-3 | 3.3E-3 | 4.9E-3 | 6.7E-3 | 8.9E-3 | 1.9E-2 | 2.2E-2 | 3.0E-2 | 3.8E-2 | 7.3E-2 | 1.0E-1 | 1.2E-1 | 5.8E-1 | 0.60 | 1.6E+0 | 5.1E+0 | 1.2E+3 |
| Me4Cyclam | 2.2E-6 | 2.9E-6 | 4.0E-4 | 1.4E-3 | 2.5E-3 | 3.7E-3 | 5.5E-3 | 7.4E-3 | 9.9E-3 | 2.1E-2 | 2.5E-2 | 3.4E-2 | 4.2E-2 | 1.0E-1 | 1.1E-1 | 1.3E-1 | 6.5E-1 | 0.67 | 1.8E+0 | 5.7E+0 | 1.3E+3 |
| BPMODA | 3.6E-6 | 4.8E-6 | 6.5E-4 | 2.2E-3 | 4.1E-3 | 6.1E-3 | 9.0E-3 | 1.2E-2 | 1.6E-2 | 3.5E-2 | 4.1E-2 | 5.5E-2 | 6.9E-2 | 1.3E-1 | 1.9E-1 | 2.2E-1 | 1.1E+0 | 1.1 | 2.9E+0 | 9.4E+0 | 2.2E+3 |
| MA6TREN | 4.1E-6 | 5.4E-6 | 7.3E-4 | 2.5E-3 | 4.6E-3 | 6.8E-3 | 1.0E-2 | 1.4E-2 | 1.8E-2 | 3.9E-2 | 4.6E-2 | 6.2E-2 | 7.7E-2 | 1.5E-1 | 2.1E-1 | 2.4E-1 | 1.2E+0 | 1.23 | 3.2E+0 | 1.1E+1 | 2.4E+3 |
| PMDETA | 8.9E-6 | 1.2E-5 | 1.6E-3 | 5.5E-3 | 1.0E-2 | 1.5E-2 | 2.2E-2 | 3.0E-2 | 4.0E-2 | 8.5E-2 | 1.0E-1 | 1.4E-1 | 1.7E-1 | 3.3E-1 | 4.6E-1 | 5.3E-1 | 2.6E+0 | 2.7 | 7.1E+0 | 2.3E+1 | 5.3E+3 |
| BA6TREN | 1.3E-5 | 1.8E-5 | 2.4E-3 | 8.3E-3 | 1.5E-2 | 2.3E-2 | 3.3E-2 | 4.5E-2 | 6.1E-2 | 1.3E-1 | 1.5E-1 | 2.1E-1 | 2.6E-1 | 5.0E-1 | 7.0E-1 | 8.0E-1 | 3.9E+0 | 4.09 | 1.1E+1 | 3.5E+1 | 8.0E+3 |
| BPED | 1.5E-5 | 2.0E-5 | 2.7E-3 | 9.2E-3 | 1.7E-2 | 2.5E-2 | 3.7E-2 | 5.0E-2 | 6.7E-2 | 1.4E-1 | 1.7E-1 | 2.3E-1 | 2.8E-1 | 5.5E-1 | 7.7E-1 | 8.8E-1 | 4.3E+0 | 4.5 | 1.2E+1 | 3.9E+1 | 8.8E+3 |
| tNtpy | 2.7E-5 | 3.6E-5 | 4.9E-3 | 1.7E-2 | 3.0E-2 | 4.6E-2 | 6.7E-2 | 9.1E-2 | 1.2E-1 | 2.6E-1 | 3.0E-1 | 4.1E-1 | 5.2E-1 | 1.0E+0 | 1.4E+0 | 1.6E+0 | 7.9E+0 | 8.2 | 2.2E+1 | 7.0E+1 | 1.6E+4 |
| TPEDA | 3.5E-5 | 4.6E-5 | 6.2E-3 | 2.1E-2 | 3.9E-2 | 5.8E-2 | 8.6E-2 | 1.2E-1 | 1.6E-1 | 3.3E-1 | 3.9E-1 | 5.3E-1 | 6.6E-1 | 1.3E+0 | 1.8E+0 | 2.1E+0 | 1.0E+1 | 10.5 | 2.8E+1 | 9.0E+1 | 2.1E+4 |
| TPMA | 2.1E-4 | 2.7E-4 | 3.7E-2 | 1.3E-1 | 2.3E-1 | 3.5E-1 | 5.1E-1 | 6.9E-1 | 9.2E-1 | 2.0E+0 | ##### | 3.1E+0 | 3.9E+0 | 7.6E+0 | 1.1E+1 | 1.2E+1 | 6.0E+1 | 62.4 | 1.6E+2 | 5.3E+2 | 1.2E+5 |
| Me6TREN | 1.5E-3 | 2.0E-3 | 2.7E-1 | 9.3E-1 | 1.7E+0 | 2.5E+0 | 3.7E+0 | 5.1E+0 | 6.7E+0 | 1.4E+1 | ##### | 2.3E+1 | 2.9E+1 | 5.6E+1 | 7.8E+1 | 8.9E+1 | 4.4E+2 | 455.6 | 1.2E+3 | 3.9E+3 | 8.9E+5 |
| Cyclam-B | 2.3E-3 | 3.1E-3 | 4.2E-1 | 1.4E+0 | 2.6E+0 | 3.9E+0 | 5.8E+0 | 7.9E+0 | 1.0E+1 | 2.2E+1 | ##### | 3.6E+1 | 4.5E+1 | 8.7E+1 | 1.2E+2 | 1.4E+2 | 6.8E+2 | 708.7 | 1.9E+3 | 6.1E+3 | 1.4E+6 |

similar to that for ATRP catalysts.[14] Most results were obtained using EtBriB as a standard initiator and PMDETA as a standard ligand. Combining data from the previous report on the effect of ligand structures on the activation rate constants in ATRP,[37] it is possible to extrapolate the values of $k_{act}$ to other ligands with initiators other than EtBriB and initiators with ligands other than PMDETA. The extrapolation was carried out based on the same selectivity principle, i.e., that $Cu^{I}Br$/ligand have the same selectivity as $Cu^{I}Br$/PMDETA toward more active initiators and less active initiators. Also, initiators have the same selectivity as EtBriB toward more active $Cu^{I}Br$/ligand and less active $Cu^{I}$-Br/ligand. Comparisons of some of the extrapolated and measured values are listed in Table 5. Their close resemblance demonstrates that the extrapolation of $k_{act}$ values is justified, especially for less active catalyst/initiators.

It is possible that for systems special effects may affect the selectivity. For example, some steric effects may start contribute for tertiary species. Some additional functionalities (amine, amide, or unsaturation) may interact with catalyst. Eventually, alkyl halides with strong electron affinity may undergo outer-sphere electron transfer (OSET) instead of inner-sphere electron transfer (ISET).[20] An independent project is being carried out to investigate the selectivities of ligands and initiators.

Table 6 shows the actually measured values in black and the extrapolated values in red for a large number of alkyl (pseudo)-halides and complexes of $Cu^{I}Br$ with various ligands.[37] These extrapolated values of $k_{act}$ should be at least useful for a simple estimation of the activity of a particular catalyst/initiator system. It also could be useful for kinetic simulations when the $k_{act}$ values are not immediately available.

## Conclusions

Activation rate constants ($k_{act}$) for various alkyl (pseudo)-halides as ATRP initiators were determined under similar conditions using $Cu^{I}Br$/PMDETA as a standard ATRP catalyst in acetonitrile at 35 °C. The activity of alkyl group for initiators follow the order of 3° > 2° > 1° and phenyl ester > cyanide > ester > benzyl > amide. The activity of the leaving atom/group for the initiators decreases in the order of I ≥ Br > Cl ≫ SCN ≈ NCS. The values of $k_{act}$ for various $Cu^{I}Br$/ligands and initiators were either measured directly or extrapolated assuming similar selectivity principle. The extrapolated values for some catalytic systems are very close to those measured directly. Because activation rate constant is only one parameter affecting kinetics of ATRP, equilibrium constants ($K_{ATRP}$)[14] and deactivation rate constants ($k_{deact}$) either measured directly or calculated from $K_{ATRP}/k_{act}$ are needed in order to further reveal the structure−activity relationship for the ATRP systems. The effects of solvent, temperature, and other factors on the activation rate constants are also under investigation in our laboratories.

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