Coding the Assembly of Polyoxometalates with a Programmable Reaction System

Andreu Ruiz de la Oliva, Victor Sans, Haralamos N. Miras, De-Liang Long, and Leroy Cronin

WestCHEM, School of Chemistry, The University of Glasgow, Glasgow G12 8QQ, Scotland, U.K.

ABSTRACT: Chemical transformations are normally conducted in batch or flow mode, thereby allowing the chemistry to be temporally or spatially controlled, but these approaches are not normally combined dynamically. However, the investigation of the underlying chemistry masked by the self-assembly processes that often occur in one-pot reactions and exploitation of the potential of complex chemical systems requires control in both time and space. Additionally, maintaining the intermediate constituents of a self-assembled system “off equilibrium” and utilizing them dynamically at specific time intervals provide access to building blocks that cannot coexist under one-pot conditions and ultimately to the formation of new clusters. Herein, we implement the concept of a programmable networked reaction system, allowing us to connect discrete “one-pot” reactions that produce the building block \( \{W_{11}O_{36}\} \equiv \{W_{11}\} \) under different conditions and control, in real time, the assembly of a series of polyoxometalate clusters \( \{W_{12}O_{42}\} \equiv \{W_{12}\} \), \( \{W_{22}O_{74}\} \equiv \{W_{22}\} \), \( \{W_{11}O_{38}\} \equiv \{W_{34}\} \), and \( \{W_{20}O_{50}\} \equiv \{W_{20}\} \) using pH and ultraviolet−visible monitoring. The programmable networked reaction system reveals that it is possible to assemble a range of different clusters using \( \{W_{11}\} \)-based building blocks, demonstrating the relationship between different conditions and control, in real time, the assembly of some common building blocks in solution in an automated fashion. However, with the previous focus being on discovery, there is now a pressing need to develop, and validate, a well-defined platform that incorporates programming and feedback control. Such a setup would allow us to explore different kinetic regimes, reagent combinations, and the control of variables like pH, ionic strength, and redox potential. Further, sequential, batch one-by-one conventional one-pot reactions for systematically exploring the POM systems and screening the parameter space are very time-consuming and limited in scope, allowing the reactions to be probed only in a comparatively narrow time domain. Most importantly, it is practically impossible to keep a self-assembled system “off equilibrium” or to trap and utilize transient building blocks in batch synthesis.

However, networking reaction systems applied in this case to the assembly of polyoxometalate clusters allow us to test the hypothesis that it is possible to “program” one-pot reactions in both the time and space domains simultaneously (see Figure 1). In this way, the one-pot reaction compositions \( r \) can be integrated across several different reaction vessels \( R_N \), simultaneously allowing the convolution of reaction variables \( r \rightarrow R_N \) as a function of fundamental programmable assembly of complex one-pot reaction syntheses in a more general way, increasing the yield and reproducibility and potentially giving access to non-specialists.

INTRODUCTION

The chemistry of molecular metal oxide polyoxometalate (POM) clusters is a rapidly expanding field because of the vast number of structures, the diversity of their properties, and a wide range of potential applications. However, the use of one-pot reaction methods for the synthesis of POM clusters presents an important problem because it is very hard to understand the steps taking place in solution giving rise to the building blocks, both transient and isolatable, for the assembly of such clusters. In fact, there is currently no general route for exploring one-pot reactions, especially for molecular metal oxides in which real-time kinetics are hard to obtain by nuclear magnetic resonance (NMR) and mass spectrometry. All of these issues mean that it is virtually impossible to devise testable hypotheses regarding the assembly of giant clusters, especially because many of the assembly processes are controlled by complex nonequilibrium kinetics. Indeed, it could be said that this problem is even more daunting because the one-pot system effectively masks a vast and interconnected range of intricate discrete reactions that underpin the self-assembly process. Furthermore, these issues are also relevant in the solution assembly of other complex molecules such as coordination frameworks and discrete giant metallo-supramolecular architectures.

In this respect, we have recently described the potential for new discoveries by the programmed manipulation of the
operations (Op) combining fully automated configurable reactors and externally attached in situ analytical techniques [pH, ultraviolet (UV), etc.). Following these principles, the addtion of reactants is denoted by $S_{m,n}$ transferring reaction solutions between reactors by $P_{N,m}$ and output of reaction solutions by $O_N$ according to the operation sequence (see eq 1).

$$\text{Op}(t): \{P_{N-m}, S_{m-n}, O_N\}$$

This means that, by controlling the reaction variables, we should be able to devise new ways to explore and probe one-pot reactions within networked reactor systems, ultimately leading to the discovery and programmable synthesis of molecules using algorithmic control. Indeed, continuous-flow systems have already been used to regulate reaction conditions under pressure, and we have also shown how flow-based methods led us to trap a reactive intermediate responsible for the assembly of a gigantic molecular inorganic $\{\text{Mo}_{154}\}$ wheel cluster. Because these flow reactor designs were first employed, we have expanded the concept to a new generation of automated digital programmable linear and networked reactor systems; these have led to the discovery and synthesis of gigantic macrocyclic POM architectures such as $\{\text{Mo}_{96}\}$ and $\{\text{W}_{36}\}$.

Figure 1. Schematic of our three-connected networked reactor system ($R_{N}$ where $N = 1, \ldots, 4$) with reagent inlets ($I_m$, where $m = 1, \ldots, 6$) and product outlets ($O_N$ where $j = 1, \ldots$) allowing the generation of time-dependent reaction compositions, $r(t)$ and performance of programmable operations as a function of time, $\text{Op}(t)$, such as network pumping ($P_{N,m}$), inputs ($S_{m-n}$ or $S_m$), or outputs ($O_N$ or $O_{N-j}$) (see the Supporting Information for further details).

Figure 2. (a) Scheme of the synthetic approach for the synthesis of compounds 1–3. The process starts from a virtual library of the simplest building blocks to form $\{W_{11}\}$ and $\{W_{12}\}$ subunits during the acidification process by means of programmable reaction conditions. Three configurations of the reactor system (b and c) correspond to the reaction connectivity of the filling and recycling steps in our approach, respectively. Also, the fundamental programmable operations ($P_{N-m}$, $S_{m-n}$ and $O_N$) are specifically assigned to each of the syringe pumps.

We investigated and integrated the synthesis of a set of iso-polypolyoxometalates (iso-POTs) in a single automated system giving $\text{Na}_{10}\{[\text{H}_2\text{W}_{22}\text{O}_{74}]\cdot50\text{H}_2\text{O}\}$, $\text{Na}_{16}\{[\text{H}_2\text{W}_{34}\text{O}_{116}]\cdot75\text{H}_2\text{O}\}$, and $\{\text{TEAH}\}^n\text{KNa}_{3}\{[\text{H}_3\text{W}_{36}\text{O}_{120}]\cdot21\text{H}_2\text{O}\}$ As such, the NRS allowed us to converge several distinct one-pot reactions using a programmable reaction sequence using one set of common reagents for the in situ isolation of $\{W_{11}\} \equiv \{W_{11}\}^1$, $\{W_{12}\} \equiv \{W_{12}\}^2$, $\{W_{34}\} \equiv \{W_{34}\}^1$, $\{W_{34}\} \equiv \{W_{34}\}^2$, $\{W_{36}\} \equiv \{W_{36}\}^3$, $\{W_{36}\} \equiv \{W_{36}\}^4$, $\{W_{36}\} \equiv \{W_{36}\}^5$, $\{W_{36}\} \equiv \{W_{36}\}^6$, $\{W_{36}\} \equiv \{W_{36}\}^7$ are very well-known iso-POT clusters, and compounds 1–3 constitute a family of structurally related clusters, namely, the $\{W_{11}\}$-based iso-POTs. Compounds 1–3 are formed by condensation of building blocks ($\{W_{11}\}$ and $\{W_{12}\}$) (see Figure 2a), synthesized by a programmable pumping sequence, whose reaction conditions were transiently formed, and linked to yield the final cluster...
compounds as outlined above. As described in the literature, sodium tungstate dihydrate (Na₉WO₄·2H₂O) and sodium sulfate (Na₂SO₄) solutions are required to synthesize these clusters using five distinct one-pot reactions. Using the NRS, we aimed to simplify syntheses of these compounds under (R₁ → R₂ → R₃)ₙ operation or R₁→₃ (Figure 2b).

The experiments were performed in the NRS using three aqueous solutions (I₁ is 6 M HCl, I₂ is 2.4 M Na₂SO₄, and I₃ is 2.8 M Na₂WO₄·2H₂O) as the main reagents. Moreover, two other stock solutions of amine-based hydrochloride salts [I₄ is 1 M triethanolamine (TEA)-HCl or 1 M dimethylamine (DMA)-HCl] and potassium chloride salt (I₅ is 4.5 M KCl) were also prepared to extend the family to {W₃₆O₁₂0}²⁻ and {W₁₁O₃₈}²⁻ clusters, using the same networked system (see Table 1), and finally, a H₂O reservoir (I₆) was attached to control the total volume of the final solution.

### Table 1. Initial Reaction Conditions Employed in the NRS for the Synthesis of Compounds 1–3

| pH³ | (W₁₁) | (W₁₂) | (W₁₃) | (W₁₄) | (W₁₅) |
|-----|-------|-------|-------|-------|-------|
| pH³ | 4.0   | 3.4   | 2.4   | 2.2   |       |
| C₀HCl (M) | 0.17  | 0.17  | 0.17  | 0 |       |
| C₀KCl (M) | 1.50  | 1.50  | 1.50  | 0.12 |       |
| C₀TEA (M) | -     | -     | -     | 0.008|       |
| t (min) | 60    | 60    | 60    | 30   |       |
| yield (%⁴) | 22    | 23    | 17    | 39   |       |

³pH value for the final solution. ⁴Time heating in R₄ at 80 °C. Yield based on tungsten composition.

We wondered whether it is possible to take three separate one-pot reactions, which use same initial reagent composition but produce different cluster building blocks as they are being acidified at different rates. Indeed, we were able to exploit the fact that the {W₁₁} cluster has a stability higher than that of the {W₁₄} cluster in the presence of sodium cations, and these polynuclear clusters are formed at different pH values as the {W₁₁} cluster forms at pH > 4 and the {W₁₄} cluster forms at lower pH values. Thus, by monitoring the pH and controlling the addition of acid, via simultaneous programmable transfer of reagents and acidification, we could observe a gradient of “local” pH changes according to the equation pH(R₁) < pH(R₂) < pH(R₃), which has been previously simulated for three interconnected continuously stirred tanks (see Figure S2). This approach allows us to alternate between near and far-from equilibrium thermodynamic states to determine populations of the building blocks (BBs) in each reactor, and the hypothesis can be defined by the applied pumping pathways such as BB(R₁) → BB(R₂) → BB(R₃), according to the pumping regime between the reactors.

The key point in the synthesis of compounds 1–3 is controlled by the BB distribution, which is time-dependent, in each R₁→₃, which is related to the space-dependent (only in R₃) acidification operation (see Figure 3). Such compounds 1–3 were obtained only after a second transfer stage, named the linkage step in R₄, where the pH successively decreases for each compound [1 at pH(R₄) 3.4, 2 at pH(R₄) 2.4, and 3 at pH(R₄) 2.2]. The isolation of 3 additionally requires the use of organic cations, in this case TEA-HCl. Alternatively, the NRS has the ability to integrate more chemical components because multiple inputs can be attached to the sequentially connected one-pot approach (Figure 4a).

Then, the hypothesis is specifically formulated by following the BB populations: 1 and 2 by R₁ {W₁₄} → {W₁₃} → {W₁₄} → R₂ {W₁₁} and 3 by R₃ {W₁₁} → {W₁₃} → {W₁₁}. Note that {W₁₁} is always isolated when the pH(R₃) is < 2.4. Compounds 1 and 2 are actually isolated within a working pH range of 3.4–2.4.

![Figure 3. Representation of the NRS of the final cluster, which results from the transfer of cluster building blocks. (a) {W₁₄} (paratungstate) appears when pH(R₃) is higher than 3.4. (b) Compound 3 was isolated when pH(R₃) was < 2.4. (c) Compounds 1 and 2 are actually isolated within a working pH range of 3.4–2.4.](image-url)
time scale, for instance comparing R2 to R3 (Figure 5c,d). The mechanistic studies are an interesting aspect to consider because reactor R2 may be affected and gradually populated by the \{W_{11}\} clusters, allowing the synthesis of \(\text{Co}^{2+}\) by reaction of \{W_{12}\} and \(\text{W}_{1}\) (see Figure 4d). Indeed, the study of the self-assembly processes has allowed us to reconsider the role of the \{W_{11}\} as a key building block. As described previously, subunit \{W_{11}\} is commonly found within these structures despite it is being difficult to isolate. Lehmann and Fuchs described this cluster in 1988, but the procedure is very hard to reproduce.39 However, using mechanistic observations explained above, we found that the \{W_{11}\} building block can be obtained very efficiently by adding a large excess of KCl during the synthesis of \{W_{22}\} [this is a modification of the previously reported “batch” synthesis (see the Supporting Information)]. This new methodology also gives a rational explanation of the formation of \(\text{Co}^{2+}\) that takes place by the condensation of two \{W_{11}\} clusters.

Other aspects of this particular reaction system are efficiency and reliability, which we can change with the counterions; this is very interesting because it is often very difficult, if not impossible, to change the counterions in the normal one-pot synthesis of a polyoxometalate without affecting the synthesis or structure formed. For instance, by using the same programmable reaction protocol that was applied while the TEA was replaced by a stock solution of DMA, we isolated \((\text{DMAH})_{9}\text{KNa}_{2}3\cdot22\text{H}_{2}\text{O}\) (anions 3a are isostructural, although they crystallize in distinct unit cells).34 These results suggest that the compounds presented in this work are related by a network of underlying reactions between the \{W_{11}\} and methodological studies.

Figure 4. (a) Picture of the NRS in which the local pH is controlled and monitored as a function of time in each reactor for the synthesis of compounds 1–5. (b) Diagram of the NRS method for the synthesis of compound 2, in terms of the sequence of operation (input, S; networking, P; outputs, O). (c) Monitoring of the pH allows us to observe a stepped profile (red) that corresponds to equal building cluster populations, as well as nonequal states (blue and green) in the different reactors during the process. (d) In the synthesis of compound 2, the increase in the \{W_{11}\} population allowed the entrapment of a single \{W_{12}\} (paratungstate) cluster between two \{W_{11}\} clusters.

Figure 5. UV monitoring during the synthesis of compound 2. (a) The profile plot (smoothed) for R2 compares three different peaks appearing at different time scales. (b) UV profiles (smoothed) of the band at 330 nm in R2 (red) and R3 (deep blue). Two three-dimensional plots of UV spectra vs time are shown for (c) R2 and (d) R3, allowing us to observe the evolution of the UV spectra in relation to the pumping sequence.
The assembly of labile coordination or organic clusters to achieve and potentially very useful in mechanistic studies and self-exploration of not only multiconnectivity and con-sense, the future potential of the NRS is focused on the di-space synthesis of compounds with the same operations P1. This feature makes the NRS unique in future work, we will extend the NRS approach to generate “sequence codes” for the synthesis of new compounds and reactive species from a given NRS connectivity with a predefined reagent set. We will also devise a standard reactor format suitable for cost-effective open-source duplication. This raises the real potential of vastly expanding the exploration of one-pot synthesis, across a variety of chemistries, for the isolation of industrially useful and functional materials that can be reliably synthesized on a large scale without highly specialized know-how from sequence codes and an open-source reactor format.

EXPERIMENTAL SECTION

Synthesis. All experiments are based on the operation of the networked reactor system, followed by regular analytics to fully characterize compounds 1–5. Crystal data and structure refinements are available for the following compounds: K3Na2{H2W11O39}·31H2O (4): H2K2Na2{H17W36O120}·M5 = 6195.99 g mol−1; colorless long crystal; monoclinic; space group C2/c; a = 40.2229(16) Å; b = 12.7409(5) Å; c = 19.5968(8) Å; β = 112.8562(7); V = 9254.3(6) Å3; Z = 4; ρ = 4.447 g cm−3; λ(Mo Ka) = 0.71073 Å; 50632 reflections measured; 8492 unique reflections (Rint = 0.0632) that were used in all calculations; 441 refined parameters; final R1 = 0.0574 and wR2 = 0.1736 (all data). (DMAH)KNa2{H13W16O52}·22H2O (5): C17H32K3Na2O14W66·22H2O (5): 

CONCLUSIONS

In conclusion, the NRS is used to integrate distinct syntheses of structurally related clusters, by multiple one-pot connected reactions. The common reaction variables were explored because of the NRS, which facilitates the automation of the syntheses of compounds 1–5. The NRS allowed us to modulate chemical compositions and an efficient pH adjustment during the application of a reaction protocol, thus producing different experimental conditions in each reactor within the system. As such, we propose a rational synthetic explanation (Figure 6) for the isolation of such isopolyoxometalates based on the NRS building blocks (BBs) formed in separate reactors. The hypothesis has been probed by using pH and UV real-time control to identify and monitor populations of transient species or building clusters, validating in a very basic sense the idea of a POM-based dynamic library.

UV-Integrated Networked Reactor System. The NRS presented here is assembled from 13 pumps; six of these are used to introduce the initial stock solutions of each reagent, and the other six are used for transferring the reaction mixtures and interconnecting the four stirred reactors. Finally, one pump is used to extract the final reaction mixture for collection. The current setup uses programmable syringe pumps (C3000 model, Tritontinent Ltd.) and a LabVIEW-based PC interface for the real-time monitoring and control of the setup.

In Situ Monitoring. The pH control was performed in the three primary reactors simultaneously using SevenMulti Mettler Toledo double-instant pH-meters. UV monitoring was performed simultaneously in R1 and R2 using a second LabVIEW PC interface connected to the Avantes AvaSpec-2048 spectrometer equipped with a DH-2000
halogen light source (Oceanoptics) that was connected further through a fiber-optic cable to a TP300 fiber probe.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.7b00206.

Experimental procedures, including full details of the NRS system, including pumps, controls, and configuration (PDF)

Crystallographic data (CIF)

CheckCIF/PLATON report (PDF)

Crystallographic data (CIF)

**AUTHOR INFORMATION**

**Corresponding Author**

E-mail: Lee.Cronin@glasgow.ac.uk.

**ORCID**

Victor Sans: 0000-0001-7105-5244

Haralampos N. Miras: 0000-0002-0086-5173

Leroy Cronin: 0000-0001-8035-5757

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**Notes**

The authors declare no competing financial interest.

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