Coding the Assembly of Polyoxotungstates with a Programmable Reaction System


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 \( \{W_{11}O_{33}\} \equiv \{W_{11}\} \) under different conditions and control, in real time, the assembly of a series of polyoxometalate clusters \( \{W_{12}O_{42}\} \equiv \{W_{12}\} \), \( \{W_{22}O_{74}\} \equiv \{W_{22}\} \), 1a, \( \{W_{34}O_{116}\} \equiv \{W_{34}\} \), 2a, and \( \{W_{56}O_{230}\} \equiv \{W_{56}\} \), 3a, 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 the clusters within the family of iso-polyoxotungstates, with the final structural motif being entirely dependent on the building block libraries generated in each separate reaction space within the network. In total, this approach led to the isolation of five distinct inorganic clusters using a “fixed” set of reagents and using a fully automated sequence code, rather than five entirely different reaction protocols. As such, this approach allows us to discover, record, and implement complex one-pot reaction syntheses in a more general way, increasing the yield and reproducibility and potentially giving access to nonspecialists.

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,1–5 and a wide range of potential applications.6,7 However, the use of one-pot reaction methods8 for the synthesis of POM clusters6–11 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.12–14 Indeed, it could be that this problem is even more daunting because the one-pot system effectually 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 frameworks15 and discrete giant metallo-supramolecular16 architectures.

In this respect, we have recently described the potential for new discoveries by the programmed manipulation of the assembly of some common building blocks in solution17–19 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.20–22 Further, sequential, batch one-by-one conventional one-pot reactions for systematically exploring the POM systems23,24 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 systems25 applied in this case to the assembly of polyoxometalate clusters allow us to test the hypothesis that it is possible to “program” one-pot reactions26 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\(_v\)), simultaneously allowing the convolution of reaction variables (r \(\rightarrow\) R\(_v\)) as a function of fundamental programmable...
We investigated and integrated the synthesis of a set of iso-
polyoxotungstates (iso-POTs)\(^{35}\) in a single automated system
giving Na\(_{19}\)\([H\_11W\_12O\_34\]·50H\(_2\)O 1, Na\(_{19}\)\([H\_11W\_11O\_38\]·75H\(_2\)O 2,\(^{35}\) and \([TEAH]_4KNa_3\([H\_13W\_36O\_120\]·21H\(_2\)O 3.\(^{33,36−38}\) 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\(_{11}\)O\(_{38}\}\} ≡ \{W\(_{11}\)\}, \{W\(_{12}\)O\(_{42}\}\} ≡ \{W\(_{12}\)\}, \{W\(_{22}\)O\(_{74}\}\} ≡ \{W\(_{22}\)\} 1a,
\{W\(_{34}\)O\(_{116}\}\} ≡ \{W\(_{34}\)\} 2a, and \{W\(_{36}\)O\(_{120}\}\} ≡ \{W\(_{36}\)\} 3a.
\[H\_2W\_11O\_38\]\(_{\text{fl}}\) and \[H\_2W\_12O\_42\]\(_{\text{fl}}\) are very well-known iso-
POT clusters,\(^{39,40}\) 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.

![Figure 1](image_url)

**Figure 1.** Schematic of our three-connected networked reactor system (R\(_{10}\) where \(N = 1, ..., 4\)) with reagent inlets (I\(_m\) where \(m = 1, ..., 6\)) and product outlets (O\(_j\) where \(j = 1, ..., 6\)) allowing the generation of time-
dependent reaction compositions, \(r(t)\) and performance of program-
nable operations as a function of time, Op(t), such as network
pumping (P\(_{N,N'}\)) inputs (S\(_{m,N'}\) or S\(_{m'}\)) or outputs (O\(_N\) or O\(_{N',j}\)) (see the Supporting
Information for further details).

![Figure 2](image_url)

**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.
Two 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\(_{N,N'}\),
S\(_{m'}\) and O\(_j\)) are specifically assigned to each of the syringe pumps.
compounds as outlined above. As described in the literature, sodium tungstate dihydrate (Na₅W₁₀O₄·2H₂O) and sodium sulfite (Na₂SO₃) solutions are required to synthesize these clusters using five distinct one-pot reactions. Using the NRS, we aimed to synthesize these compounds under (R₁ → R₃), a 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 Na₂SO₃, and I₃ is 2.8 M Na₅W₁₀O₄·2H₂O) 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 {W₅XO₁₀} and {W₃O₃} 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

<table>
<thead>
<tr>
<th>pH</th>
<th>[W₁₂]</th>
<th>[W₂₂] (I)</th>
<th>[W₃₄] (2)</th>
<th>[W₃₆] (3)</th>
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<tr>
<td>4.0</td>
<td>3.4</td>
<td>2.4</td>
<td>2.2</td>
<td></td>
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<tr>
<td>C₆H₅NO₃ (M)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>−</td>
</tr>
<tr>
<td>C₆H₄NO₃ (M)</td>
<td>1.50</td>
<td>1.50</td>
<td>1.50</td>
<td>0.12</td>
</tr>
<tr>
<td>CCl₃ (M)</td>
<td>− −</td>
<td>− −</td>
<td>− −</td>
<td>0.008</td>
</tr>
<tr>
<td>C₆H₅NO₃ (M)</td>
<td>− −</td>
<td>− −</td>
<td>− −</td>
<td>0.27</td>
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<tr>
<td>t (min)</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>yield (%)</td>
<td>22</td>
<td>23</td>
<td>17</td>
<td>39</td>
</tr>
</tbody>
</table>

*pH value for the final solution. †Time 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 {W₁₂} cluster has a stability higher than that of the {W₁₁} cluster in the presence of sodium cations, and these polyoxometalate clusters are formed at different pH values as the {W₁₂} cluster forms at pH >4 and the {W₁₁} 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 determinate 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 R₄) 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 R₃ {W₁₁} → {W₁₁} + {W₁₂} → R₄ {W₁₁} and 3 by R₃ {W₁₁} → {W₁₁} → {W₁₁}. Note that {W₁₁} is always produced because the acid is being added uniquely into R₁ as giving {W₁₁} as the kinetically controlled cluster product. On the other hand, {W₁₂} is always produced when the pH is >3.4 because of its high thermodynamic stability under these reaction conditions. To investigate the validity of our hypothesis, we performed a real-time monitoring in situ analysis (pH and UV) (Figure 4c) by sequentially ordered operations (see the diagram in Figure 4b). The pH in the three reactors (R₁→₃) was monitored in parallel by three pH sensors over the 40 min reaction mixture transfer process. Figure 4c shows that pH measurements indicate different local pH values in each reactor, with the same stepped profiles, but shifted in time only because of different acidification rates. The values of pH (R₄) and pH (R₃) can be monitored from the beginning of the process, while pH (R₄) can be measured only ~30 min after initiation of the experimental procedure, because of the formation of the white precipitate that redissolves after further acidification. In sequence, the addition of acid stops and each of the R₁→₃ reactors have different “local” pH values leading to different re-equilibrated BB population distributions. By converging the R₁→₃ “one-pot” reactors in the central one (linkage step), we adjusted a suitable “global” pH or pH (R₄) for compounds 1–3 when all the components were homogeneously mixed in R₄, heated, and, finally, collected in an open flask.

UV–vis spectrometry was also used to monitor the reaction during the pumping sequence between reactors, showing how the UV bands evolve with the acidification process (Figure 5a). The band at 330 nm, assigned to {W₁₁} cluster formation (see Figure S6), was monitored in R₁ and R₃ simultaneously (Figure 5b), and the UV profiles are shifted in a time-dependent fashion. Hence, by dipping UV probes into every single “one-pot” reactor, we observed the formation of {W₁₁} on a different
mechanistic studies are an interesting aspect to consider because reactor R2 may be affected and gradually populated by the \{W11\} clusters, allowing the synthesis of 2 by reaction of \{W12\} and 1 (see Figure 4d). Indeed, the study of the self-assembly processes has allowed us to reconsider the role of the \{W11\} as a key building block. As described previously, subunit \{W11\} 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 \{W11\} building block can be obtained very efficiently by adding a large excess of KCl during the synthesis of \{W22\} [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 1 that takes place by the condensation of two \{W11\} clusters. The configurability of the NRS allowed sequential addition of the \{W11\} building block can be obtained very efficiently by adding a large excess of KCl during the synthesis of \{W22\} [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 1 that takes place by the condensation of two \{W11\} clusters. The configurability of the NRS allowed sequential addition of the \{W11\} building block can be obtained very efficiently by adding a large excess of KCl during the synthesis of \{W22\} [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 1 that takes place by the condensation of two \{W11\} clusters. The configurability of the NRS allowed sequential addition of the \{W11\} building block can be obtained very efficiently by adding a large excess of KCl during the synthesis of \{W22\} [this is a modification of the previously reported “batch” synthesis (see the Supporting Information)]. This new
The use of automated control of networked “one-pot” reactor systems allows us to test this idea of far-from equilibrium reaction conditions operating in volume transfer, flow rates, and pumping frequency basis (Figure 6). In this sense, the future potential of the NRS is focused on the exploration of not only multiconnectivity and configurability between the formation of transient $N \geq 5$ “one-pot” reactors but also different pumping regimes and reaction conditions in a programmed and sequential way (giving access to new compounds with the same “space synthesis” but with a different “time synthesis”). This feature makes the NRS unique and potentially very useful in mechanistic studies and self-assembly of labile coordination or organic clusters to achieve only-NRS accessible exotic products (kinetically unstable units 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.

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 possibility 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.

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 synthesis 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 $\{W_{12}\}$ and $\{W_{12}\}$ 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.

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: $\text{K}_{2}\text{W}_{12}\text{O}_{40}\cdot\text{H}_{2}\text{O}$ (4); $\text{H}_{2}\text{K}_{2}\text{W}_{20}\text{O}_{60}$; $M_r = 6195.99$ 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; $\beta = 112.8562(7)^\circ$; $V = 9254.3(6)$ Å$^3$; $Z = 4$; $\rho = 4.447$ g cm$^{-3}$; $\lambda (\text{Mo K}\alpha) = 0.7073$ Å; 50632 reflections measured; 8492 unique reflections ($R_{int} = 0.0632$) that were used in all calculations; 441 refined parameters; final $R_1 = 0.0574$ and $wR_2 = 0.1736$ (all data). (DMAH)$_2\text{K}_{2}\text{W}_{12}\text{O}_{40}\cdot\text{H}_{2}\text{O}$ (5); $C_{22}H_{32}K_{2}\text{W}_{20}O_{60} \cdot 2\text{H}_{2}O$; $M_r = 9446.97$ g mol$^{-1}$; colorless long crystal; monoclinic; space group $C2/c$; $a = 37.3679(17)$ Å; $b = 26.2614(17)$ Å; $c = 35.8129(4)$ Å; $\beta = 118.486(3)^\circ$; $V = 30890(3)$ Å$^3$; $Z = 8$; $\rho = 4.063$ g cm$^{-3}$; $\lambda (\text{Mo K}z) = 0.71073$ Å; 131486 reflections measured; 30320 unique reflections ($R_{int} = 0.1252$) that were used in all calculations; 1682 refined parameters; final $R_1 = 0.0540$ and $wR_2 = 0.1241$ (all data). Data collection and reduction were performed using the Crysalis software package, and structure solution and refinement were performed using the SHELXL-97 and SHELXLX-97 software program package of WINGX. Corrections for incident and diffracted beam absorption effects were applied using empirical absorption correction. CCDC 982262 (4) and 982261 (5) contain the supplementary crystallographic data for this paper. These data can be obtained from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/.

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, TritonTrent 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 $R_1$ and $R_2$ using a second LabVIEW PC interface connected to the Avantes AvaSpec-2048 spectrometer equipped with a DH-2000

$\{W_{12}\}$ BBs. The formation of these compounds has previously been justified entirely by the existence of a “virtual combinatorial library” of tungstate aggregates based on crystallographic observations. It is has long been suggested that large clusters must be assembled in solution from a series of smaller so-called building blocks accessible from a virtual combinatorial library of common building blocks.43

Figure 6. Evaluation of the volume effect during UV monitoring. (a) A decreasing volume leads a shift of the main peaks in the UV spectra. (b) Scheme of the NRS during the pumping pathway, employing operations $P_1\rightarrow P_2$, $P_1\rightarrow P_2$, and $P_1\rightarrow P_1$. (c) Plot of the plunger position vs time, showing how the volume oscillates along input–output alternating sequences and the flow rate becomes the operation rate when using syringe pumps in sequence.
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, control, 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: 0000-0001-7045-5244

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

Leroy Cronin: 0000-0001-8035-5757

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**Notes**

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