High-Throughput Methods

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Implementation of a Temperature-Gradient Reactor System for High-Throughput Investigation of Phosphonate-Based Inorganic–Organic Hybrid Compounds**

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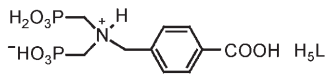
High-throughput (HT) methods applied to materials science are a powerful technique for the rapid investigation of large parameter spaces in a short time, and they give rise to the accelerated discovery of new materials and the optimization of synthesis parameters.[1] The resulting information density contributes to a better understanding of the role of compositional and process parameters. After the pioneering work of Schultz et al. based on thin-film methods[2] several approaches for the HT investigation of the hydrothermal synthesis of zeolitic microporous materials have been reported.[3]

In a recent HT study, the influence of pH, temperature, concentration, and time on the synthesis of hybrid inorganic–organic materials was investigated in detail.[4] It was shown that acid/base ratio, time, concentration, and, most importantly, temperature play a role in determining which structure forms. Due to the application of HT methods, these systematic investigations involving 383 individual reactions could be carried out in only three weeks. The method allows automated dispensing of reagents, identical treatment under hydrothermal conditions for up to 48 reaction mixtures, parallel workup, and automated characterization without manipulation of individual samples.[5] Although this setup is ideal for the isothermal study of compositional parameters, parallel screening of temperature in a single HT experiment was not possible. However, since temperature often has a profound impact on product formation, a HT method that allows parallel investigation of the influence of temperature on identical reaction mixtures in one HT experiment would be of great benefit for systematic investigations of solvothermal reactions.

Whenever a well-established HT methodology is expanded, new tools must be integrated in the workflow in order to avoid bottlenecks. We successfully integrated a thermocycler (also known as PCR machine) with a gradient function in our HT methodology and thus extended the HT investigation of parameter spaces from only composition to a further dimension, temperature. This allows us to efficiently screen the role of temperature in solvothermal synthesis, since all experiments are carried out in parallel. The thermal block with a maximum gradient of 40 K allows the investigation of six different compositions at eight different temperatures and therefore 48 individual reactions at a time.

Whereas in zeolite chemistry the influence of compositional (e.g., Si/Al ratio, pH, concentration) and process parameters (e.g., reaction time, temperature, homogenization) is well understood,[6] similar studies on inorganic–organic hybrid compounds are quite rare.[7] Apart from reticular chemistry, which allows the tailoring of functionalized carboxylate-based hybrid materials (metal–organic frameworks, MOFs), in phosphonate chemistry many parameters for directing the structure remain unexplored. Nevertheless, metal phosphonates are promising candidates for sorbents, ion-exchange materials, and catalysts.[8]

In our ongoing study on the use of polyfunctional phosphonic acids containing iminobis(methylphosphonic acid) units $(H_2O_3PCH_2)_2N-$ for the synthesis of metal phosphonates, the phosphonocarboxylic acid $(H_2O_3PCH_2)_2NCH_2C_6H_4COOH$ (H_5L) has proved to be a versatile ligand.[9–11]



Herein we present results on the systematic investigation of the role of temperature and pH value in product formation in the system $CdCl_2/H_5L/NaOH$.[12] Due to the specifications of the thermocycler ($T_{max} = 99.9\,°C$, $\Delta T_{max} = 40\,K$) two HT experiments were set up to cover the range from room temperature to $T_{max} = 99.9\,°C$. The used reaction parameters are listed in Table 1.

In a previous study employing H_5L and Co^{2+} it was shown that the metal/ligand molar ratio has a less profound impact on product formation than the pH value.[9] Thus, the molar $CdCl_2/H_5L$ ratio was kept constant at 1:1 and the $NaOH/H_5L$ ratio was varied in six steps from 0 to 2.5. The resulting

Table 1: Temperatures and acid/base ratios simultaneously explored in this work. The Cd^{2+}/H_5L ratio was kept constant at 1:1; the reaction time was 24 h.

T [°C]	17.0	20.8	26.9	33.6	40.3	47.1	53.2	57.0
T [°C]	59.9	63.7	69.8	76.5	83.3	90.0	96.1	99.9
$NaOH/H_5L$	0	0.5	0.75	1	1.5	2	2.5	

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crystallization diagram is shown in Figure 1. Unconsumed H_5L was omitted for clarity. Five cadmium phosphonates with varying molar ratios Cd^{2+}/H_5L and H_2O/Cd^{2+} were discovered (phases A to E in Table 2).

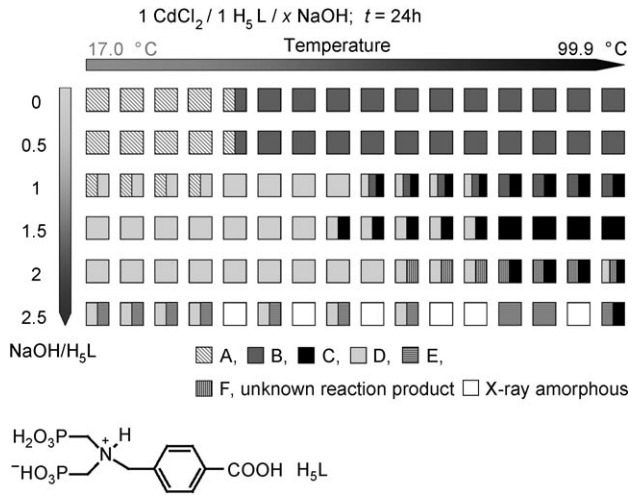

Figure 1. Crystallization diagram for the HT investigation of the influence of temperature and pH value on product formation in the system $CdCl_2/H_5L/NaOH$. The chemical formulae of A–E are given in Table 2.

Table 2: Observed cadmium phosphonate phases. Compounds A to F were discovered in the HT experiment in a thermocycler with temperature gradient.[13] G was obtained at 200 °C.

Code	Cd^{2+}/H_5L	H_2O/Cd^{2+}	Formula
A	0.5	4	$Cd[H_4L]_2 \cdot 4\,H_2O$[14]
B	0.5	0	$Cd[H_4L]_2$[15]
C	1	1	$Cd[H_3L] \cdot H_2O$[16]
D	1.5	4.25	$Cd_3[H_2L]_2 \cdot 14\,H_2O$[17]
E	2	1.5	$Cd_2[H_1L] \cdot 3\,H_2O$[18]
F			unknown reaction product
G	2	0.5	$Cd_2[H_1L] \cdot H_2O$[19]

To prove the reproducibility of the results, a second set of experiments was performed (see Figure S1). Within the investigated parameter space the same reaction trends are observed and no additional phases occur. Despite thorough calibration of the equipment, a small shift in phase formation was observed that reflects the sensitivity of the reaction system. Most importantly, the results of the second set of experiments are consistent with those of the first.

The high information density obtained by our HT method clearly shows the influence of reaction temperature on cadmium phosphonate formation. For a given molar $Cd^{2+}/H_5L/NaOH$ ratio, an increase in reaction temperature results in a higher Cd^{2+}/H_5L molar ratio, and fewer water molecules per Cd^{2+} ion are incorporated in the product (Figure 2). This is in accordance with the results of a series of experiments in which cobalt(II) hydroxide was treated with succinic acid in 1:1 molar ratio at five temperatures between 60 and 250 °C.[20] Five cobalt succinates were obtained, which became more dense and less hydrated with increasing temperature. To

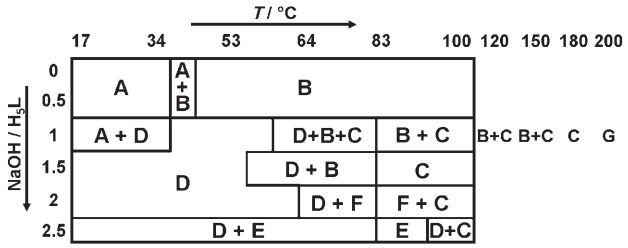

Figure 2. Schematic and extended crystallization diagram for the investigation of the influence of pH value and temperature on the system $CdCl_2/H_5L/NaOH$ (the reaction time was 24 h). The phases are indicated by their letter codes as assigned in Table 2. The left-hand part corresponds to the HT experiments, whereas in the right-hand part the results of single experiments in conventional autoclaves are given. Unconsumed H_5L has been omitted for clarity.

further support our results, four single experiments in conventional autoclaves were carried out for the molar ratio $Cd^{2+}/H_5L/NaOH = 1:1:1$. Indeed, whereas at 120 and 150 °C a mixture of phases B and C is still obtained, at higher temperature (180 °C) pure phase B is observed, and at 200 °C product G is formed with even a higher molar Cd^{2+}/H_5L ratio (Figure 2 and Table 2).

In agreement with observations in previous work on manganese(II) phosphonocarboxylates, the pH value has a profound impact on product formation due to successive deprotonation of the phosphonocarboxylic acid with increasing pH, which results in an increased dimensionality of the formed compounds.[21] Thus, the molar Cd^{2+}/H_5L ratio increases with increasing molar $NaOH/H_5L$ ratio in the synthesis mixture. This trend becomes even clearer when looking at structural features. Comparing the extended coordination spheres of the CdO_6 octahedra in the compounds A,[14] B,[15] and C[16] it is clear that higher temperature results in more condensed phases. All three phases can be obtained from identical reaction mixtures. Whereas in A isolated CdO_6 octahedra are connected by $(HO_3PCH_2)_2N$-groups forming chains, in B the octahedra are connected by hydrogenphosphonate groups in a layered structure. In C a cadmium phosphonate layer is again formed, but with edge-sharing CdO_6 octahedra instead of isolated octahedra (Figure 3).

The flexibility of the ligand H_5L itself in addition to the high coordinative flexibility of the phosphonic acid groups allows the formation of a large number of different structures. Although in this work we only explored water as solvent, and no coligands or amine templates were used, already five new compounds were discovered in a single HT investigation. Among the cadmium phosphonocarboxylates presented herein, $Cd_2[(O_3PCH_2)_2NHCH_2C_6H_4COOH] \cdot 14\,H_2O$ (D) shows reversible dehydration/hydration properties. Currently we are working on elucidating the structure of this interesting compound in order to fully explore its capacity for host/guest exchange and sorption properties.

Our work clearly demonstrates the power of HT methods in the systematic investigation of parameter spaces leading to the discovery of new materials. Furthermore, extension of our methodology towards parallel exploration of the influence of the reaction temperature leads to deeper insight into the

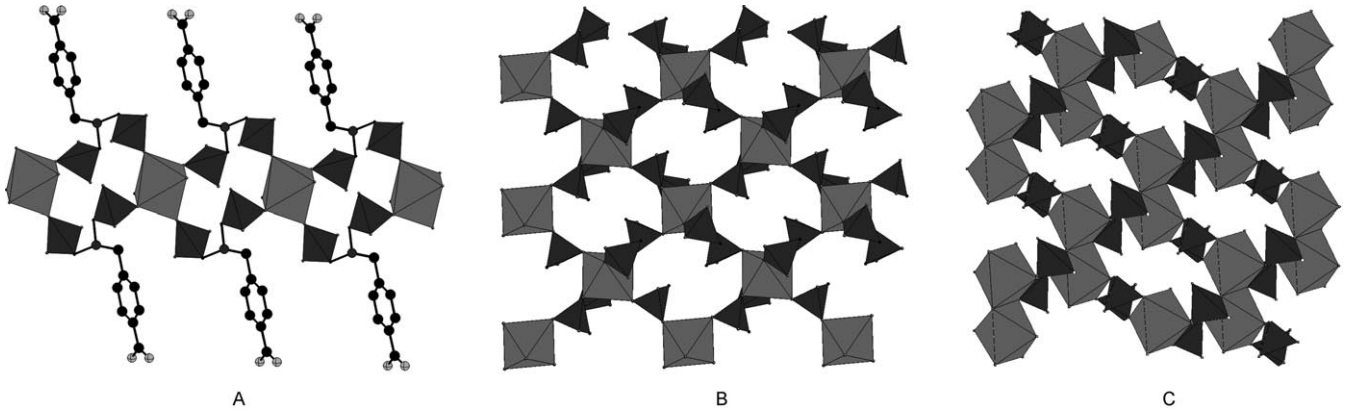

Figure 3. Evolution of the structure in $Cd[(HO_3PCH_2)_2NHCH_2C_6H_4COOH]_2{\cdot}4\,H_2O$ (A), $Cd[(HO_3PCH_2)_2NHCH_2C_6H_4COOH]_2$ (B), and $Cd[(HO_3PCH_2)_2NHCH_2C_6H_4COOH]{\cdot}H_2O$ (C) with increasing temperature. CdO_6 octahedra are presented in medium gray and PO_3C tetrahedra in dark gray.

synthesis of hybrid materials. The high information density obtained for a reaction system in a short period of time allows the identification of reaction trends and opens the door to an improved understanding of the formation of compounds and an accelerated discovery of new compounds. Increasing the feasible temperature range in the thermocycler will allow further investigations to gain a better understanding of the formation of crystalline inorganic–organic hybrid materials.

Experimental Section

A detailed description of the HT methodology is given in reference [5]. The HT experiments were carried out in a Whatman Biometra TGradient thermocycler using PP-PCR tubes with a capacity of 500 μL. A total volume of 200 μL of solution was used per tube. After dosing H_5L as a solid, a 0.4 M solution of NaOH, deionized water, and 0.3 M $CdCl_2$ were successively added. The reaction mixtures were allowed to react in the thermocycler without homogenization. At the end of the experiment the products were immediately collected by filtration and washed with water and acetone. Exact amounts of starting compounds and pH values are given in the Supporting Information. The synthesis of H_5L is described in detail in reference [9]. The sample arrays were characterized by X-ray powder diffraction on a STOE high-throughput powder diffractometer equipped with a linear position-sensitive detector. The data collection time was 15 min per sample in the 2θ range from 3 to 35°.

Individual reactions for exploring reaction temperatures above 100 °C were carried out in stainless-steel autoclaves with teflon liners. A mixture of 150 mg (442 μmol) H_5L, 829 μL (442 μmol) 0.4 M NaOH, 1474 μL (442 μmol) 0.3 M $CdCl_2$, and 2697 μL H_2O was heated for 24 h at 120, 150, 180, and 200 °C. The reaction products were collected by filtration and washed with water and acetone.

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[12] We are well aware of the high toxicity of cadmium-containing compounds. The use of cadmium in this system leads to well-crystallized compounds, which assist in deriving chemical trends. For potential applications, cadmium can often be replaced by other divalent cations, such as calcium.
[13] CCDC 641071 (A), 641072 (B), and 641073 (C) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Since compounds B and C were discovered previously in a HT experiment at higher temperature, detailed characterization will be published elsewhere.
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378, 118). The structure of the isotypic calcium compound[10] was used as starting model. Crystal data: $M = 824.53\ g\,mol^{-1}$, monoclinic $P2_1/c$, $a = 16.932(1)$, $b = 7.293(1)$, $c = 13.905(1)$ Å, $\beta = 113.99(1)°$, $V = 1568.6(3) \times 10^6\ pm^3$, $Z = 2$, $\rho_{calcd} = 3.491$, $R_p = 10.7$, $R_{wp} = 13.1$, $R_{exp} = 3.45$, $R_F = 4.92$, $R_{Bragg} = 6.11$; $\lambda(Cu_{K\alpha1}) = 154.06$ pm; 2θ range: 3.0–70.0°; number of reflections: 725; number of atoms: 24; number of structural parameters: 69; number of profile parameters: 14. The final Rietveld plot is given in the Supporting Information.

[15] The structure of B was solved from powder data using the FOX program (V. Favre-Nicolin, R. Cerny, *J. Appl. Crystallogr.* **2002**, *35*, 734) and refined with Fullprof2k using the Winplotr software package.[14] Crystal data: $M = 760.53\ g\,mol^{-1}$, monoclinic $P2_1/c$, $a = 14.913(1)$, $b = 8.702(1)$, $c = 10.477(1)$ Å, $\beta = 95.60(1)°$, $V = 1353.0(2) \times 10^6\ pm^3$, $Z = 2$, $\rho_{calcd} = 1.867$, $R_p = 19.3$, $R_{wp} = 18.4$, $R_{exp} = 14.75$, $R_F = 6.97$, $R_{Bragg} = 6.42$; $\lambda\ (Cu_{K\alpha1}) = 154.06$ pm; 2θ range: 4.0–80.0°; number of reflections: 1204; number of atoms: 22; number of structural parameters: 62; number of profile parameters: 14. The final Rietveld plot is given in the Supporting Information.

[16] The structure of C was refined with Fullprof2k using the Winplotr software package.[14] The structure of the isotypic calcium compound[10] was used as starting model. Crystal data: $M = 467.58\ g\,mol^{-1}$, monoclinic $P2_1/n$, $a = 5.654(1)$, $b = 7.874(1)$, $c = 31.532(1)$ Å, $\beta = 94.58(1)°$, $V = 1399.3(3) \times 10^6\ pm^3$, $Z = 4$, $\rho_{calcd} = 2.148$, $R_p = 14.1$, $R_{wp} = 15.0$, $R_{exp} = 4.83$, $R_F = 10.6$, $R_{Bragg} = 9.44$; $\lambda(Cu_{K\alpha1}) = 154.06$ pm; 2θ range: 4.0–80.0°; number of reflections: 950; number of atoms: 23; number of structural parameters: 69; number of profile parameters: 14. The final Rietveld plot is given in the Supporting Information.

[17] Due to the sensitivity of the position of the reflections in the powder pattern of D to the water content, all attempts to index the powder pattern failed. The composition is based on energy-dispersive X-ray (EDX), elemental, and thermogravimetric analyses.

[18] Since no structure could be determined so far, the composition was derived from EDX, elemental, and thermogravimetric analysis. The powder pattern could be indexed and refined: monoclinic, $P2_1/c$, $a = 14.548(6)$, $b = 11.946(4)$, $c = 9.842(4)$ Å, $\beta = 93.19(3)°$, $V = 1707.9(1) \times 10^6\ pm^3$; $F(30) = 44.8$ (0.009, 71).

[19] No structure could be determined so far. The composition was derived from EDX, elemental, and thermogravimetric analyses.

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