collection on a Siemens P4 automated diffractometer (Mo$_{K\alpha}$, $\lambda = 0.71073$ Å, $T = 295$ K); space group $P\bar{1}$; $a = 12.660(3)$, $b = 15.359(3)$, $c = 16.963(3)$ Å, $\alpha = 78.72(3)$, $\beta = 74.37(3)$, $\gamma = 83.33(3)^\circ$, $V = 3108.0(11)$ Å^3, $Z = 2$, $\rho_{calcd} = 2.145$ g cm^{-3}. Cell parameters from 25 reflections ($20 < 2\theta < 28^\circ$), 8459 reflections collected by ω-scan method ($\Delta\omega = 1.2^\circ$): $4 < 2\theta < 46^\circ$, $0 \leq h \leq 13$, $-16 \leq k \leq 16$, $-17 \leq l \leq 18$; 4627 reflections observed [$F \geq 4\sigma(F)$]. After data reduction (Lorentzian and polarization corrections; absorption correction by face-indexed analytical method; min./max. equivalent transmission factors: 0.6994, 0.9129) and merging ($R_{int} = 0.0235$), the structure was solved by direct methods with SHELXTL PLUS, and refined by full-matrix least-squares methods. Anisotropic thermal factors were refined for V and O atoms only. $\Delta\rho = -0.59, +1.11$ e Å^{-3} associated with disorder on V11/V11′ (see legend to Figure 1). Final residuals: $R(F) = 0.0487$, $wR_2(F) = 0.0492$. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-410088.

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Combinatorial Methods for the Synthesis of Aluminophosphate Molecular Sieves**

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The optimization of existing hydrothermal procedures for the synthesis of microporous materials and the discovery of new phases depends on effective processing and structural screening methodologies. In view of the tremendous impact of combinatorial techniques in the areas of organic,[1] biochemical,[2] and inorganic[3] chemistry, it appears attractive to develop a combinatorial approach for the hydrothermal synthesis of microporous materials. Akporiaye and co-workers demonstrated the application of combinatorial methods for the hydrothermal synthesis of zeolites with a multiple autoclave;[4] the recovery and identification of the obtained phases required individual sample manipulation. Recently, Maier and co-workers reported the microgram-scale hydrothermal synthesis of microporous materials in an array format on a Si wafer which allowed for automated X-ray diffractometry.[5]

We have developed a new methodology based on automatic dispensing of reagents into autoclave blocks, followed by synthesis, isolation, and automated structure analysis without any manipulation of individual samples. Our reaction chambers ("multiclaves") are Teflon blocks (36 mm diameter, with 8 holes (6 mm diameter) or 19 holes (4.5 mm diameter), 25 mm in hole depth) that provide an inert reaction environment. This allows us to use reactant volumes of 150–300 μL per hole. A thin sheet and a lid of Teflon covers the reaction vessel, which is then sealed inside a specially designed stainless steel autoclave. The reagents are dosed directly into the multiclaves using a commercially available pipette robot, or a custom-built robot[6] which can inject multiple liquid reagents. After hydrothermal synthesis, the washing of the sample array by filtration and preparation of libraries is done with a custom-designed centrifuge apparatus,[7] which allows almost quantitative product recovery. The resulting products are identified in transmission using either a standard X-ray powder diffractometer or a rotating anode diffractometer with CCD detector. In both cases, an automated xy stage is used for sample translation. The advantages of our methodology include reduced reagent consumption by direct dosing at the microliter scale, production of multi-milligram sample

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quantities, and almost complete sample recovery, which enables determination of yields.

Here we present the synthesis of aluminophosphate phases applying combinatorial strategies. Of particular interest is the influence of combined organometallic ([Co(Cp)$_2$]OH, Cp = cyclopentadienyl) and organic structure-directing agents (here Pr$_2$NH) on the resulting aluminophosphate phases, based on the different size and flexibility of the organometallic component. Aluminophosphates of the types AFI (AlPO$_4$-5[8]) and AST (AlPO$_4$-16[9]) were synthesized previously using cobalticinium salts as templates. In a typical synthesis, the aluminophosphate gels were prepared by mixing an Al source with H$_3$PO$_4$ and water followed by addition of different templating molecules, including cobalticinium salts.

In this study, we examined the effect of the molar fraction of the two templates, at a fixed total concentration of 1.0 mol per mole of Al$_2$O$_3$. Furthermore, the influence of increasing amounts of each single template was studied. Table 1 lists the molar compositions of the various starting gels in each hole of a reactor block. In all samples, the molar ratio of framework precursors and water, Al$_2$O$_3$:P$_2$O$_5$:H$_2$O, was fixed to 1:1:190, and the reaction was carried out at 160 °C for 24 h.

Table 1. Chemical composition of the representative sample library shown in Figure 3.

Hole	Composition[a]		Hole	Composition[a]	
	x	*y*		*x*	*y*
1	1.0	0	11	0.4	0
2	0.8	0.2	12	0.3	0
3	0.6	0.4	13	0.2	0
4	0.4	0.6	14	0.1	0
5	0.3	0.7	15	0	0.9
6	0.2	0.8	16	0	0.8
7	0.1	0.9	17	0	0.7
8	0	1.0	18	0	0.6
9	0.8	0	19	0	0.4
10	0.6	0			

[a] $1\,Al_2O_3:1\,P_2O_5:x\,[Co(Cp)_2]OH:y\,Pr_2NH:190\,H_2O$.

Figure 1 displays a CCD camera image of the transmission powder diffractogram of the AFI-type phase as well as the corresponding circularly integrated presentation. The data collection time is 10 min or less per spot by using a rotating anode diffractometer with a CCD detector (Nonius). Increased resolution of the library diffractograms can be obtained with a commercial powder diffractometer (Scintag; standard Cu tube, 0.3 × 4 mm emission profile, equipped with a liquid N$_2$ cooled germanium solid-state detector, data taken in transmission). Figure 2 shows selected diffractograms of some of the observed phases which were obtained with a step size of 0.01°.

As seen in Table 1, holes 2–7 were used for the mixed template system ($x\,[Co(Cp)_2]OH + y\,Pr_2NH$). Holes 1 and 9–14 cover only the effect of [Co(Cp)$_2$]OH concentration, while holes 8 and 15–19 cover the effect of Pr$_2$NH concentration. The resulting phases associated with the various template concentrations are displayed in Figure 3. The different levels of template inclusion in the case of [Co(Cp)$_2$]OH are indicated by the gradients in the resulting physical library.

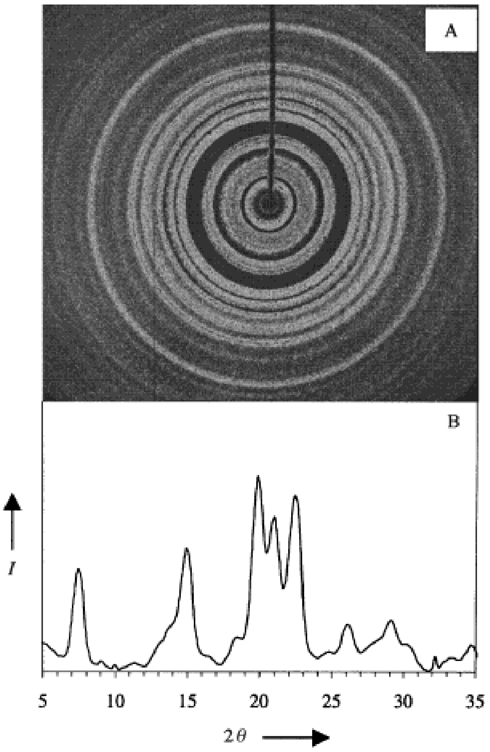

Figure 1. A) CCD camera image of the X-ray diffractogram of as-synthesized AFI-type product (Table 1, hole 4); the data collection time is 10 min per diffractogram. B) The corresponding circularly integrated diffractogram.

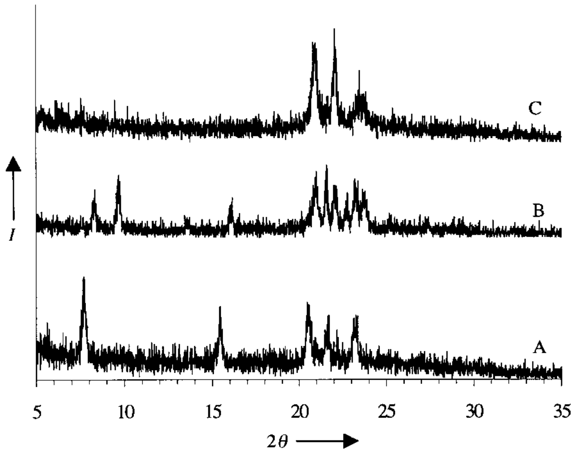

Figure 2. Selected diffractograms of the resulting phases recorded with a germanium solid-state detector. The data collection time is 60 min per diffractogram. A) The AFI structure (Table 1, hole 7), B) the AEL structure (hole 8), C) the tridymite structure (hole 16).

In the mixed template synthesis, starting with 100 mol% cobalticinium ion, no crystalline phase was observed after 24 h. Both AFI and AST types were observed at 20 mol% Pr$_2$NH. The AFI and AST structures have 12-membered channels and cages that are large enough to accommodate the larger [Co(Cp)$_2$]$^+$ ion (Figures 4 A and B). The formation of the pure AFI structure requires at least 40 mol% Pr$_2$NH under the conditions employed. A drastic switch to another phase is only observed on changing to 100 mol% Pr$_2$NH, when the AEL structure type emerges (Figure 3). The AEL

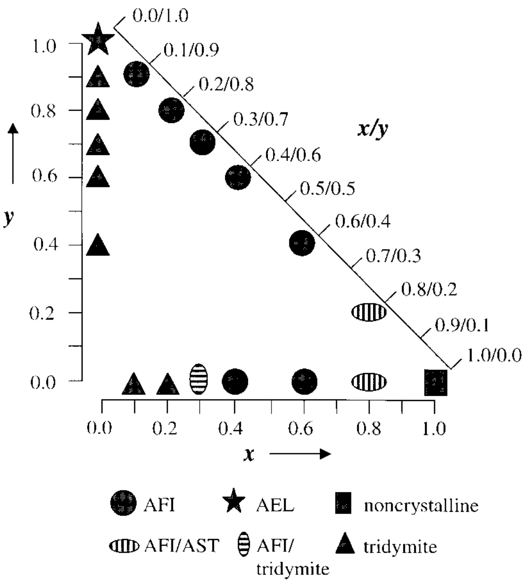

Figure 3. The effect of single and mixed templates on the resulting aluminophosphate phases. The chemical composition of starting gel was $1\,Al_2O_3$:$1\,P_2O_5$:x[Co(Cp)$_2$]OH:yPr$_2$NH:$190\,H_2O$; the molar compositions with hole numbers are listed in Table 1.

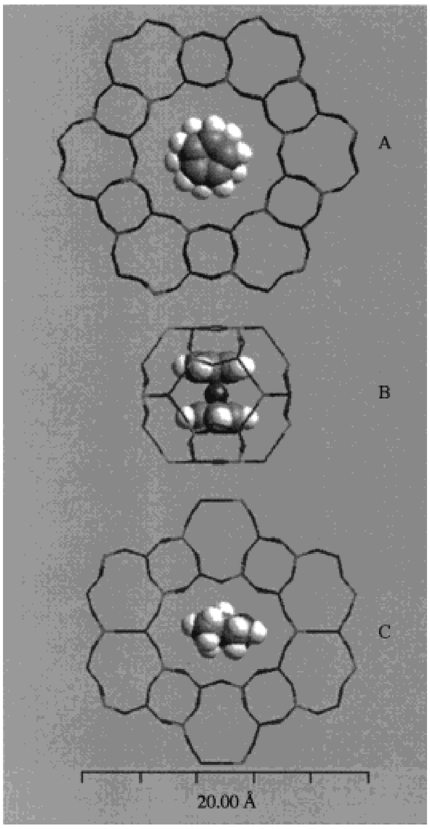

Figure 4. Structures of the different aluminophosphate phases with template molecules, modeled with Cerius2 software. A) AFI structure with [Co(Cp)$_2$]OH, B) AST structure with [Co(Cp)$_2$]OH, C) AEL structure with Pr$_2$NH.

structure offers a one-dimensional 10-ring channel system which is large enough to contain the Pr$_2$NH molecule but too small for the accommodation of cobalticinium (Figure 4C). These observations clearly demonstrate the important effect of template size (when the other synthesis parameters are kept constant) on the structure of the resulting aluminophosphate phase.

In addition, the influence of the concentration of single templates ([Co(Cp)$_2$]OH or Pr$_2$NH) on the resulting products was studied. The amount of [Co(Cp)$_2$]OH was varied from 0.1 to 1.0 mol per mole of Al_2O_3. As shown in Figure 3, a minimum amount of 30 mol% of cobalticinium ion is required to form a microporous framework in this system (at lower concentrations, tridymite is formed). The AFI structure was observed at template concentrations between 0.4–0.6 mol per mole of Al_2O_3; however, the use of more than 0.8 mol of [Co(Cp)$_2$]OH per mole of Al_2O_3 resulted in noncrystalline material. With Pr$_2$NH as template under these conditions, concentrations up to 0.9 mol per mole of Al_2O_3 result in a dense phase (tridymite). However, a sudden structural change occurs when the template concentration is increased to 1.0 mol per mole of Al_2O_3, resulting in the AEL phase as mentioned above.

An interesting feature in the mixed template system is the observation of a pure AFI-type structure when the molar ratios of [Co(Cp)$_2$]OH:Pr$_2$NH were either 0.2:0.8 or 0.1:0.9. In comparison, only dense phase (tridymite) was observed when either [Co(Cp)$_2$]OH or Pr$_2$NH was used alone at these template concentrations. This indicates that there is some synergy or interaction between the two template molecules to crystallize the AFI-type structure, although the molecular origin of this effect is not yet clearly understood.

Our methodology demonstrates a powerful, realistic combinatorial approach for the hydrothermal synthesis of microporous materials. Using inert reactor materials and a direct dosing system for reagents at the micromole scale, this approach permits the preparation and characterization of libraries of solids without any manipulation of individual samples. Low reagent consumption and efficient sample recovery make it feasible to explore many reaction conditions and templating agents for the discovery of new phases, and to perform additional characterization by, for example, thermogravimetric analysis or electron microscopy with material from the same library.

Experimental Section

Synthesis of [Co(Cp)$_2$]OH: [Co(Cp)$_2$]PF$_6$ was synthesized using a procedure similar to that previously reported by Sheats et al.[10] Cyclopentadiene, CpH, was prepared from the dimer.[11] The solutions of [Co(Cp)$_2$]OH were prepared by a modified ion-exchange method.[8] [Co(Cp)$_2$]PF$_6$ (3.24 g, 10 mmol) was dissolved in water (1.5 L). This solution was passed through a column containing Dowex-50W cation exchange resin. The resin containing the cobalticinium cation was washed with water and a 1M HCl solution until all the yellow cobalticinium chloride, [Co(Cp)$_2$]Cl, was eluted from the column. The [Co(Cp)$_2$]Cl was dried under vacuum and then dissolved in water (4 L). The yellow solution was passed through a column containing Dowex-SBR-OH anion exchange resin. The concentration of the [Co(Cp)$_2$]OH solution was determined by titration with 0.00990M sulfuric acid. A 0.5M [Co(Cp)$_2$]OH solution was used in the synthesis of the molecular sieve.

Aluminophosphate synthesis: In a typical synthesis the aluminophosphate gel was prepared by mixing alumina sol (45 µL, Condea vista, 10.6 wt% of Al_2O_3) and 29.2% H_3PO_4 (29.5 µL, $d = 1.128$). After vigorous shaking for 2 h, aliquots (10–100 µL) of 0.5M aqueous template solutions ([Co(Cp)$_2$]OH and Pr$_2$NH) were injected into the $AlPO_4$ mixture. The water contents were corrected for by adding distilled water in some cases. The gel was shaken at room temperature for 12 h for homogenization and aging. The multiclave was placed in an oven for 24 h at 160°C. The products were washed and isolated as an array by a custom-designed centrifuge apparatus. The sample array collected on filter paper was transferred to an X-ray sample holder for X-ray analysis. Automated X-ray diffraction analysis was carried out with a computer-controlled xy stage on either a Scintag XDS 2000 diffractometer equipped with a liquid N_2 cooled germanium solid-state detector using $Cu_{K\alpha}$ radiation, or on a rotating anode diffractometer with a Nonius CCD detector using $Mo_{K\alpha}$ radiation. In both cases, the diffractograms were obtained in the transmission mode. Data collection time varied from 10 to 60 min per spot depending on the detector. The data collection time for the standard powder diffractometer can be significantly reduced by using a more powerful X-ray source within the same setup. Powderize, a program from Nonius, was employed to integrate the CCD images.

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[6] The custom-built robot is a modified xy chart recorder which has a nozzle head that can hold four to six reagent lines. Each reagent line is made up of a unique reagent reservoir, an independently operable micropump, and a nozzle that has a sapphire tip with an orifice of 0.12 mm in diameter. The entire apparatus is controlled by a personal computer and was programmed using LabView.
[7] The custom-designed centrifuge apparatus consists of two different filter papers (glass microfibre and normal filter paper), a PVC block with a matching hole pattern, a filtrate reservoir, and a PVC cylinder. Two pieces of filter paper were placed between the multiclave and the PVC block that was connected to the filtrate reservoir. For washing, the multiclave and the PVC block were turned upside down, and water was added into the holes of the PVC block and then forced into the multiclave by centrifugation. These steps were repeated several times before isolation of the final library.
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“Scaffold-Hopping” by Topological Pharmacophore Search: A Contribution to Virtual Screening[**]

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In the process of drug discovery the crucial step to initiate a medicinal chemistry program is to identify molecular entities that interact with a specific target, namely an enzyme, a receptor, or an ion channel. The usual experiment one carries out to identify these lead structures is the so-called “blind screening”. Although today automation has made this process fast for large target families, there are still particular cases for which the set-up of the screen is expensive and time-consuming. This is especially true when a very complex device is used for measuring the interaction of chemical compounds with a protein, as for instance in functional receptor assays. In these latter cases as soon as a few lead structures have been identified a very appealing complementary approach is to derive a pharmacophore model from the known active structure (the “seed” or “query” structure) and perform a computer-based similarity search to speed up the process of lead identification.[1]

Several such “virtual screening” techniques have been invented on the basis of two- or three-dimensional representations of molecular structures and various definitions of biophores/pharmacophores.[2] The underlying idea is to define a measure of molecular similarity and collect the most similar compounds to a given seed from a large collection of prospective candidates. Despite recent advances in predicting three-dimensional molecular structures,[3] current high-throughput similarity searches are primarily based on two-dimensional (2D) topology.[4] Herein we present the successful application of a novel straightforward technique to “scaffold-hopping”, that is, identification of isofunctional molecular structures with significantly different molecular backbones.

Topological cross-correlation of generalized atom types is a simple molecular descriptor that leads to a compact, molecular size independent description of potential pharmacophores.[5] The general idea of this representation scheme is to count the distances between atom pairs and then to regard the histogram of counts as a simplifying but exhaustive pharmacophore fingerprint of the molecule. Distances are expressed as the number of bonds along the shortest path connecting two nodes (non-hydrogen atoms) in the molecular graph (Figure 1). Each node is checked as to whether it can be assigned one of the following generalized atom types: hydrogen-bond donor (D), hydrogen-bond acceptor (A), positively

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