Comparison of the Structure-Directing Effect of Ephedrine and Pseudoephedrine during Crystallization of Nanoporous Aluminophosphates

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Abstract. We present here a systematic study about the behavior of two diastereomeric chiral organic molecules, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, for directing the crystallization of crystalline nanoporous aluminophosphates. We apply a combination of extensive synthetic experiments, characterization and molecular simulations in order to relate the different structure-directing effects of the two isomers experimentally observed with their particular molecular structure. Our results show a higher efficiency of pseudoephedrine to direct the crystallization of AFI materials: in contrast, ephedrine tends to give a layered-like phase with a strong supramolecular aggregation together with AFI materials. In addition, aggregation of ephedrine within the AFI channels is stronger than that of pseudoephedrine. Molecular simulations show a different conformational behavior for the two diastereoisomers, which is manifested in a different supramolecular behavior, and as a consequence a different structure-directing behavior. This multi-level study shows the intricacy between the absolute configuration of the structure-directing agents, and hence their molecular structure which results in the development of distinct intramolecular H-bonds, the molecular conformational space, the supramolecular chemistry associated, and the structure-directing mode of action during the crystallization of AFI-aluminophosphate materials, providing a molecular-level understanding of the structure-directing phenomena of these molecules.

Keywords: Aluminophosphate, zeolite, ephedrine, pseudoephedrine, supramolecular, self-assembly, chirality.

1 Introduction

Since life works in an asymmetric fashion, with only particular enantiomers of chiral building-blocks, L-aminoacids and D-sugars, making up the essential biological macromolecules, proteins and nucleic acids, chirality is fundamental for the correct functioning of living beings [1]. As a consequence, the metabolism of living beings differentiates between enantiomers of chiral compounds, very frequently having only one enantiomer the desired therapeutic effect [2]. In this context, the design of chiral solids able to discriminate between enantiomers of a chiral compound, either during separation or catalytic processes, represents one of the greatest challenges in contemporary chemical research [3,4]. In the quest for chiral functional solids, zeolites and crystalline nanoporous materials in general have been proposed as ideal candidates since they could potentially combine their high surface area and characteristic shape-selectivity with a potential enantioselectivity that might be enhanced by the confinement effect [5-8]. Several chiral zeolites do actually exist and have been recognized as such [9], like polymorph A of zeolite Beta [10], the chiral zincophosphate CZP [11], the mesoporous chiral ITQ-37 zeolite [12] and HPM-1 [13], the silica-form of the chiral SU-32 silicogermanate [14]. However, almost always these nanoporous materials crystallize as racemic crystals, and consequently these solids cannot be used for asymmetric operations.

The traditional strategy to induce chirality in zeolite frameworks has been the use of chiral molecules as organic structure-directing agents (SDAs). These organic SDAs organize the inorganic tetrahedral units in a particular geometry from which crystallization of a particular framework takes place [15]. Despite the successful use of several chiral organic molecules as SDAs for the synthesis of zeolite materials, even some of them leading to chiral frameworks [7], the occurrence of racemic crystals

evidences a lack of transfer of chirality from the organic molecule to the framework. In order to produce chiral solids, we have argued that self-assembling molecules that can develop supramolecular long-ranged chiral arrangements, more suitable to fit to the chiral dimension of zeolite frameworks which is manifested also at long-range, are more likely to promote such transfer of chirality. In this context, we have recently proposed the use of chiral (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine as organic SDAs (see Figure 1). The selection of these chiral precursors is four-folded, they have i) an aromatic ring which triggers the formation of supramolecular dimers through π - π type interactions, ii) two stereogenic centers that will impart a strong asymmetric molecular structure, iii) H-bond donor and acceptor groups that will promote the formation of strong interactions between consecutive dimers, potentially leading to long-range chiral orderings, and iv) $R-NH_2^+-R'$ positively-charged groups that will develop strong electrostatic interactions with the negative charge associated to the isomorphic substitution of Al^{3+} by divalent dopants (typical of nanoporous aluminophosphates). Such special features of these chiral molecules would potentially enable a transfer of chirality from the supramolecular long-range chiral ordering of the molecules not only to the overall framework itself, but also to the spatial distribution of dopants, leading potentially to solids with chirally-ordered distributions of dopants, representing a new concept of chirality in zeolite materials [16,17].

In recent works, we reported the structure-directing ability of (1R,2S)-ephedrine towards the crystallization of the AFI aluminophosphate framework in the presence of different dopants, showing a strong trend to self-assemble as π - π stacked dimers when confined within the AFI framework [18,19]. A complementary study based on molecular simulations [20] suggested that ephedrine dimers tend to pack within the AFI channels developing a helicoidal ordering within the AFI channels, which might be

transferred to the spatial distribution of dopants through H-bonds [21] and electrostatic interactions. On the other hand, we have recently reported a notably different supramolecular aggregation behavior of the two diastereoisomers, ephedrine and pseudoephedrine, during the crystallization of nanoporous aluminophosphates, which was explained with the aid of molecular simulations in terms of a different conformational behavior because of the occurrence of distinct intramolecular H-bonds in aqueous solution [22]. Due to the interest and novelty on the use of this type of chiral self-assembling molecules as SDAs, here we report an extensive and systematic study about the structure-directing phenomena of (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine during the crystallization of nanoporous aluminophosphates in the presence of different dopants and under very different synthesis conditions, paying special attention to their supramolecular aggregation behavior when confined within the porous materials. The experimental and characterization work is complemented with molecular simulations in order to understand from a molecular level the experimentally observed trends.

2 Methodology

2A Experimental Details

Mg, Zn, Co and Si-doped AFI aluminophosphate materials were synthesized by hydrothermal methods using (1R,2S)-Ephedrine (EPH) (Sigma Adrich, 98 %) or (1S,2S)-Pseudoephedrine (PsEPH) (Sigma Adrich, 98 %) as organic structure-directing agents. Four different gel molar compositions were studied, $1R:xMeO:(1-x/2)Al_2O_3:1P_2O_5:100H_2O$, $2R:xMeO:(1-x/2)Al_2O_3:1P_2O_5:100H_2O$, $1R:xMeO:(1-x/2)Al_2O_3:1P_2O_5:50H_2O$ and $2R:xMeO:(1-x/2)Al_2O_3:1P_2O_5:50H_2O$, where x was 0.11, 0.22, or 0.32; R stands for the organic SDA (EPH or PsEPH), and Me for the dopant

(Mg, Zn, Co or Si). Pseudoboehmite (Pural SB-1 77.5% Al_2O_3 , Sasol), phosphoric acid (Sigma-Aldrich, 85%), magnesium acetate $\text{Mg}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ (Sigma-Aldrich, 99%), zinc acetate $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (Sigma-Aldrich, 98%), cobalt acetate $\text{Co}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ (Sigma-Aldrich, 98%) and tetraethylorthosilicate TEOS ($\text{Si}(\text{CH}_3\text{CH}_2\text{O})_4$, Merck 99%) were used as sources of Al, P, Mg, Zn, Co and Si, respectively. The gels were transferred into Teflon-lined stainless steel autoclaves with a capacity of 14 mL, which were heated statically at temperatures between 140 and 180 °C under autogeneous pressure for 24 hours. The resulting solids were collected by filtration, washed thoroughly with ethanol and water and dried at room temperature.

2B Characterization

The obtained solids were characterized by powder X-Ray Diffraction (XRD), using a Philips X'PERT diffractometer with CuK_α radiation with a Ni filter. Thermogravimetric analyses (TGA) were registered using a Perkin-Elmer TGA7 instrument (heating rate = 20°C/min) under air flow. UV–Visible diffuse reflectance spectroscopy was recorded with a UV-Vis Cary 5000 Varian spectrophotometer equipped with an integrating sphere, using the synthetic polymer Spectralen as reference. MAS-NMR spectra were recorded with a Bruker AV 400 WB spectrometer, using a BL7 probe for ^{13}C and a BL4 probe for ^{31}P . ^1H to ^{13}C Cross-Polarization spectra were recorded using $\pi/2$ rad pulses of 4.5 μs for ^1H , a contact time of 5 ms and a recycle delay of 3 s. For the acquisition of the ^{13}C spectra, the samples were spun at the magic angle (MAS) at a rate of 5-5.5 kHz. For ^{31}P , $\pi/2$ rad pulses of 4.25 μs and recycle delays of 80 s were used; these spectra were recorded while spinning the samples at ca. 11 kHz. ^1H single pulse experiments were acquired using a 2.5 mm double-resonance MAS probe, $\pi/2$ rad pulses of 3.5 μs , and a recycle delay of 2s; in this case, the spinning speed was set at 25 kHz. Solution

^1H and ^{13}C NMR spectra were collected using a Bruker Avance III-HD Nanobay 300MHz (7.05T), using CDCl_3 and D_2O as solvents for the amines and the corresponding hydrochlorides, respectively.

The aggregation state of the molecules within the solid samples was studied by fluorescence spectroscopy. Solid state UV-Visible fluorescence emission spectra were recorded in a RF-5300 Shimadzu fluorimeter. The fluorescence spectra were registered in the front-face configuration by a solid sample holder in which the samples were oriented 30 and 60° with respect to the excitation and emission beams, respectively. Fluorescence spectra of the solid samples were recorded by means of thin films supported on glass slides elaborated by solvent evaporation from a CH_2Cl_2 suspension of the solid samples.

Potential racemization of the chiral organic molecules during the hydrothermal treatments was studied by polarimetry. An aqueous solution of ephedrine hydrochloride was prepared by adding equimolar amounts of the amine and HCl, and was subjected to similar hydrothermal treatments (in the autoclaves at 180 °C). Potential racemization during crystallization was determined by comparison of the rotation angle before and after the hydrothermal treatment; the optical rotation of the solutions was determined by using a manual optical polarimeter (P1000 LED, A. Krüss-Optronic).

2C Computational Details

Molecular-mechanics simulations were performed in order to analyze the structure-directing behavior and supramolecular aggregation of (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine molecules during the synthesis of AFI materials. Molecular structures of the organic molecules were described with the cvff forcefield [23]. Due to the strong basicity of ephedrine ($\text{pK}_a = 9.6$) [24] the low pH of the synthesis medium (3-5), and the

necessity for charge-balancing the negative charge imposed by the incorporation of dopants, protonated EPH and PsEPH molecules were studied. The atomic charge-distribution of the protonated cations was obtained from DFT+D calculations, using the B3LYP hybrid functional and the ESP charge calculation method, setting the total net charge to +1. The charges of the framework atoms were initially fixed to 3.4, 1.4 and -1.2 for P, Al and O, respectively. The positive charge of the EPH/PsEPH molecules was compensated by a uniform charge-background in which the charge of all the Al atoms was decreased from 1.4 until charge-neutrality.

The most stable location of the SDA molecules confined within the AFI framework was obtained by simulated annealing calculations (NVT ensemble) followed by geometry optimization. These calculations were performed using the Forcite module, as implemented in Material Studio 2016 [25]. 1x1x3 AFI supercells were constructed, and 4 molecules in the required orientation were loaded. Selected calculations were repeated at the DFT+D level, using plane-waves as basis set and PBE as functional, as implemented in CASTEP [26]. Interaction energies were calculated by subtracting the energy of the molecules in vacuum to the total energy of the systems, and were normalized per unit cell and per molecule; all energies are given in kcal/mol.

3 Results

The present work involves a combination of synthesis, characterization and computational studies applied to understand the structure-directing behavior of ephedrine and pseudoephedrine as a function of their stereochemical configuration. First, the product phase distribution of the solids obtained with the two SDA molecules under different synthesis conditions will be reported, followed by the characterization of the most interesting materials by a range of techniques, paying special attention to the

supramolecular aggregation monitored by fluorescence spectroscopy. A computational study will then be reported in an attempt to understand the experimental observations.

3A Crystallization of aluminophosphates as a function of the SDA

We have performed an extensive systematic study of the synthesis conditions in order to scan the structure-directing behavior of the two diastereoisomers in very different conditions, including different amounts of SDA (1 or 2 R) (and hence different pH of the gel) and of water (50 or 100 H₂O), different dopant nature (Mg, Zn, Co or Si) and concentration in the gel (0.11, 0.22 or 0.32), and different crystallization temperature (140, 160/165 or 180 °C).

Mg-containing AlPOs

The crystalline products obtained with the two SDAs in the presence of Mg in the synthesis gels are reported in Table 1, where the main crystalline phase observed is labelled as ‘major phase’; in cases, some additional crystalline phases (with low concentration with respect to the major phase) were identified together with the major phase, and these were labelled as ‘secondary phases’ (if they occurred) (the same scheme was used in Tables 2, 3 and S1). We can clearly observe that the dominant crystalline nanoporous phase when ephedrine and pseudoephedrine are used as SDAs is MgAPO-5 (AFI-type structure, with blue background) (see Figure S1 in the Supporting Information for an example of the XRD pattern); however, pure AFI materials (with no secondary phases) were obtained only under particular synthesis conditions (Table 1). This framework is composed of non-interconnected one-dimensional 12-R channels (with a diameter of 7.3 Å) where the organic molecules are hosted, surrounded by smaller 4-R and 6-R channels, with only the latter being able to host just water

molecules. It is interesting to note that despite their very similar molecular structure, the two diastereomeric molecules develop a different structure-directing behavior under particular synthesis conditions. When ephedrine is used as the SDA, another crystalline phase shows up (green background), especially when using a high amount of SDA (under 2R:100H₂O and 2R:50H₂O compositions). This phase shows a diffraction peak at very low 2θ (4.4) indicative of a large unit cell (Figure S2 in the Supporting Information, top-left), with an extremely large organic content of 39 %, as measured by TGA (Figure S2, top-right); both features points to a low-dimensional AlPO phase with a large organic content in the interlaminar space. Fluorescence spectroscopy (Figure S2, bottom-left) shows a band with a vibronic structure centered at 310 nm, and a broad feature-less band between 400 and 500 nm. The vibronic-structure of the former band led us to assign it to ephedrine monomers; however, this band is strongly red-shifted with respect to the usual monomer band of ephedrine which appears at 282 nm [22]. This suggests that these monomers are strongly interacting with other ephedrine species in the interlaminar space, possibly through coplanar interactions (not through π - π stacking since this would give a band at higher wavelengths without vibronic structure). The other feature-less band at 450 nm is instead clearly indicative of π - π stacking between ephedrine molecules in the interlayer space. These characterization results allow us to propose a schematic model for this layered phase (Figure S3 in the Supporting Information), which would be composed of AlPO layers (or even chains) with the interlaminar space formed by a bilayer of ephedrine molecules, where the polar charged ammonium groups of ephedrine interact through electrostatic and H-bond interactions with negatively-charged PO_x⁻ groups of AlPO, and the aromatic rings locate in the center of the interlaminar space stabilized by the development of hydrophobic interactions (Figure S3).

It is remarkable that this layered phase is exclusively produced by ephedrine, but never shows up with pseudophedrine, despite their very similar molecular structure, bearing the same functional groups that should drive the formation of the layered-like phase (the aromatic ring and the polar OH and NH_x^+ moieties). This ephedrine-layered phase predominates with high SDA concentrations (2R), and especially at low temperatures (140 and 165 °C). In contrast, pseudoephedrine displays a stronger ability to drive the crystallization of the AFI framework (Table 1), which could be ascribed either to a stronger structure-directing efficiency towards this framework or to the lack of a competition with a layered-like phase as in the case of ephedrine. In general, higher Mg concentrations in the gel (0.22) and high temperatures (180 °C) favors the crystallization of the AFI framework; in addition, lower SDA concentrations (1R) avoid the formation of the undesired layered phase with ephedrine.

Zn-containing AlPOs

The crystalline products obtained in the presence of Zn in the gels are reported in Table 2. Again the dominant microporous phase is the AFI framework (ZnAPO-5); however, the crystallization of this material is slightly less favored than in the presence of Mg at composition 1R:100H₂O, where trydimite constitutes the main crystalline product for both SDAs. As for Mg-containing gels, an increase in the concentration of the SDA (2R:100H₂O) drives the system towards a similar layered-phase (L) only when ephedrine is used as SDA, especially at low (140 and 160 °C) temperatures. As previously, the best synthesis conditions for the crystallization of ZnAPO-5 corresponded to 1R:50H₂O since this reduced the formation of ephedrine-layered materials, and in this case ZnAPO-5 materials with low (0.11) and high (0.22) Zn contents in the gels were obtained (with minor impurities of trydimite in some cases).

ZnAPO-43 (GIS framework type) showed up in certain cases as a minor phase at high temperature (180 °C), possibly as a consequence of a degradation of the SDA.

Co-containing AlPOs

We next tried the incorporation of Co in the synthesis gels (Table 3). In this case we observe that the crystallization of CoAPO-5 is much less favorable than with Mg or Zn: CoAPO-5 crystallized in very few cases, predominantly at high temperature (180 °C) and high SDA concentration (2R:100H₂O). In contrast, composition of 1R:50H₂O led preferentially to AlPO-trydimite, while composition of 2R:50H₂O led preferentially to amorphous materials (with pseudoephedrine) or the layered phase (with ephedrine), showing the low ability of these molecules to promote the structure-direction of the AFI framework in the presence of Co.

Si-containing AlPOs

Finally, the incorporation of Si in the synthesis gels completely prevented the crystallization of the AFI framework (Table S1 in the Supporting Information). In this case, all the synthesis conditions led to the formation of the layered phase in the presence of ephedrine, while amorphous materials and trydimite were the only products in the presence of pseudoephedrine, showing the inability of these molecules to direct the crystallization of the AFI framework doped with Si.

3B Characterization of AFI materials

Once known the product distribution for the different synthesis conditions as a function of the SDA employed in the synthesis, we characterized the most interesting AFI materials to analyze the structure-direction behavior of the two diastereoisomers.

Analysis of the incorporation of the SDAs by TGA, ^{13}C and ^1H MAS NMR

TGA of the AFI materials confirm the incorporation of organic species within the AFI frameworks (see Figure S4 in the Supporting Information for MgAPO-5 samples obtained with 1R:50H₂O composition as an example); a weight loss below 200 °C is associated to desorption of water molecules (strongly-retained by electrostatic interactions with Mg atoms), while weight losses above 200 °C are due to desorption and combustion of the organic molecules. A slightly higher organic content is found in samples obtained with higher Mg content (1.0-1.1 and 1.2-1.3 SDAs/u.c. for samples obtained with 0.11 and 0.22 Mg, respectively); nonetheless the slightly lower organic content of the former samples could also be related to the minor presence of the dense-tridymite phase. It should also be noted that samples obtained with a higher concentration of the SDA in the gel (2R) contains also a slightly higher SDA content in the AFI framework (1.3-1.4 SDAs/u.c.).

In order to confirm the integral incorporation of the ephedrine and pseudoephedrine molecules within the AFI framework, and their resistance to the hydrothermal treatment, selected AFI materials (MgAPO-5 and ZnAPO-5) obtained at the highest temperature (180 °C) were studied by ^{13}C CP MAS NMR (Figure 1). All the bands corresponding to the different C atoms of ephedrine (left) and pseudoephedrine (right) were observed, clearly demonstrating the integral incorporation of the molecules in the different materials. Nonetheless, additional bands (with a minor intensity) at ~115 and ~46 ppm were observed in certain samples obtained with pseudoephedrine (especially in the material obtained with 0.22Mg and 2R:100H₂O composition, right-black line), which suggest a minor presence of degradation products for this molecule. These results

thus suggest a slightly lower hydrothermal stability of pseudoephedrine compared to ephedrine.

^1H MAS NMR was also applied in order to confirm the intact incorporation of the molecules, as well as study their charge state when confined within the AFI materials. For the sake of comparison, liquid ^1H NMR of neutral ephedrine (in CDCl_3) (green dotted line) and ephedrine hydrochloride (in D_2O) (orange dotted line) were also recorded (Figure 2); the assignment of the observed bands to the different protons is included in the Figure. Comparison of the liquid ^1H NMR spectra of ephedrine (green dotted line) and ephedrinium (orange dotted line) indicates that protonation of ephedrine involves a slight shift of all the protons (except the aromatic ones) to higher chemical shifts. ^1H NMR of the MgAPO-5 materials (obtained with a composition of 1R:50H₂O with the two Mg contents) shows 5 bands (at 1.0, 2.2, 3.3, 5.0 and 7.5 ppm) associated to the different protons of ephedrine species (to H₂, H₁, H₃, H₄, and aromatic H₅-H₇, respectively, as indicated in the Figure), again demonstrating the resistance of the molecules to the hydrothermal treatment and their integral incorporation within the AFI framework; bands corresponding to protons bonded to N and O atoms should resonate between 2 and 4 ppm, and hence these signals would be overlapped, if they appear. Due to the large width of the signals caused by dipolar coupling in Solid State NMR, it is difficult to unambiguously assign the observed spectra to neutral or protonated ephedrine molecules; this is especially true in the central region corresponding to H₁ and H₃ protons (Figure 2-left). If we look at protons H₂ and H₄, their chemical shift is more similar to that of liquid protonated ephedrinium (orange dotted line), as is expected because of ephedrine basicity and of the necessity of charge-balancing the negative charge introduced by the isomorphic substitution of Al^{3+} by Mg^{2+} . Nevertheless, if we compare the EPH-AFI samples obtained with high (red line) and

low (blue line) Mg contents, we can observe the presence of particular features in the latter sample, with a small shoulder at ~0.8 ppm and at ~2.8 ppm, which roughly corresponds to the H2 and H3 protons of neutral ephedrine; additionally, another shoulder is observed only in the low-Mg sample at 4.2 ppm, which although shifted to lower shifts, could also be tentatively assigned to H4 of neutral ephedrine. These results suggest that all the ephedrine species in MgAPO-5 obtained with high Mg content are protonated, whilst ephedrine species are also mostly protonated in the material with low Mg content, although a minor amount of neutral species seems to be also incorporated, possibly due to the lower charge density of the framework.

^1H MAS NMR of the samples obtained with pseudoephedrine also showed similar bands at 1.2, 2.5, 3.3, 4.7 and 7.5 ppm, which are assigned to H2, H1, H3, H4 and aromatic H5-H7, respectively, again demonstrating the incorporation of pseudoephedrine molecules in these materials (Figure 2-right). As occurred for ephedrine, protonation of pseudoephedrine also involves a shift of the H resonances towards higher chemical shifts; this is especially noticeable for H4, which shifts from ~4.2 to ~4.7 ppm in solution. Hence, the resonance of H4 in the AFI samples at around 4.8 ppm suggests that pseudoephedrine molecules also incorporate as charged species to provide charge-balance.

It is important to note that while the ^{13}C NMR spectra of the two molecules confined within the AFI framework is very similar, the ^1H NMR spectra show some differences, which are especially noticeable for H4 (5.0 ppm for ephedrine and 4.7 ppm for pseudoephedrine). In this context, the diastereomeric nature of ephedrine and pseudoephedrine, only differing in the absolute configuration of the C with the hydroxyl group (C4, see Figure 2), involves that racemization of this C atom should transform one isomer in the other; similarly, racemization of the other stereogenic center (C3)

should also provoke a transformation of the diastereoisomer. Due to the harsh hydrothermal conditions, it would be possible that this process could occur during crystallization. However, the absence of a peak at 4.7 ppm in the AFI materials obtained with ephedrine (and analogously the absence of a peak at 5.0 ppm in the AFI materials obtained with pseudoephedrine, although in this case it is less evident) (see Figure S5 in the Supporting Information) suggests that no individual racemization of the stereogenic centers that transforms one diastereoisomer into the other occurs during crystallization (or at least they are not incorporated in the AFI materials). This observation is important since it suggests a retention of the absolute configuration of the molecules during the crystallization of these frameworks, an essential point for the development of chiral frameworks. However, we cannot discard at this point a simultaneous racemization of the two stereogenic centers, that would transform one enantiomer into the other ((1R,2S)-ephedrine into (1S,2R)-ephedrine, for instance), although the previous observation suggests this not to be the case.

Stability and potential racemization of the SDAs during hydrothermal treatment

At this point, we wanted to further confirm the absence of racemization processes during the hydrothermal crystallization process. The best way to study this would be to desorb the SDA molecules occluded within the AFI materials, and measure the optical activity. In an attempt to release the SDA molecules from the framework, we treated the samples with HF in order to dissolve the AFI network and release the SDA molecules; however such harsh conditions led also to a degradation of the SDA molecules. Therefore, in an attempt to study the potential racemization of these chiral molecules, ephedrine was transformed into the corresponding hydrochloride (by adding equimolar amounts of HCl), and a solution of this species (at an approximate concentration of 0.1

M, with a pH of 2) was introduced into autoclaves and subjected to the same hydrothermal treatment in the oven (180 °C for 24 hours). ^{13}C NMR of this solution (Figure S6 in the Supporting Information) showed that a large fraction of the ephedrinium species resisted the hydrothermal treatment, however some additional bands were also observed, evidencing that part of the molecule was degraded due to the low pH and high temperature.

The optical activity was measured before and after the treatment in order to analyze the enantiomeric purity, and so the occurrence of racemization of ephedrine during this treatment. Results showed a very similar optical rotation before and after the treatment ($\sim -40^\circ$), suggesting that no racemization occurred. However, due to the partial degradation of the ephedrine species observed by ^{13}C NMR, this observation should be treated with care.

These results suggest that during crystallization, the SDA species that remain in the solution are gradually degraded at the high temperature of 180 °C (in fact, the mother liquor of these syntheses had a yellowish/brown color, probably indicative of degradation of the molecules that remain dissolved in the aqueous phase), whilst those molecules that are occluded within the AFI framework resist the hydrothermal treatment since the framework act as a shield against attack by the medium. Hence, it is reasonable to expect that the SDA species occluded within the framework will keep their integrity and absolute configuration due to such shielding role provided by the surrounding AFI network, as indeed is suggested by our racemization studies.

^{31}P MAS NMR: Incorporation of Mg and Zn dopants

A selection of the most pure AFI samples was studied by ^{31}P MAS NMR in order to analyze the incorporation of Mg (and Zn) divalent dopants by isomorphic substitution

of Al in the network. P surrounded by 4 Al in the AFI network gives a signal at -30 ppm; the incorporation of Mg in the network by substitution of Al can be clearly established by the appearance of a P resonance band at around -24 ppm, characteristic of P surrounded by 3 Al and 1 Mg. Comparison of the ^{31}P NMR spectra of samples obtained with ephedrine and pseudoephedrine under the same synthesis conditions showed no notable differences in the amount of Mg incorporated (Figure 3), although in particular cases a slightly higher Mg substitution was found for materials obtained with pseudoephedrine.

We then analyzed the effect of the composition of the gel on the incorporation of Mg atoms (Figure 3). As expected, an increase of the Mg content in the gel results in a notable increase of the isomorphic substitution of Mg in the framework (compare Figure 3-left and right). Interestingly, there is a strong effect of the SDA and water contents in the gel composition ($x\text{R}:y\text{H}_2\text{O}$) on the Mg incorporation. Both for ephedrine and pseudoephedrine SDAs, a decrease of the water content from $100\text{H}_2\text{O}$ (blue lines) to $50\text{H}_2\text{O}$ (red lines) (for organic contents of 1R) (for 2R, see evolution from green, $100\text{H}_2\text{O}$, to black, $50\text{H}_2\text{O}$, lines) results in a notable increase of the Mg incorporation, as evidenced by the higher intensity of P(3Al,1Mg) environments at -24 ppm. In addition, an increase of the organic content from 1R to 2R also results in a notable increase of the Mg incorporation (compare blue and green lines, or red and black lines). In sum, the highest Mg incorporation is achieved for low H_2O and high SDA contents: these conditions should force a higher incorporation of protonated SDAs in the AFI framework (in detriment of the competing incorporation of H_2O) and as a consequence, a higher incorporation of Mg to provide charge-balance.

^{31}P NMR of selected samples of ZnAPO-5 materials also demonstrated the incorporation of Zn in the AFI framework (see Figure S7-left in the Supporting

Information). On the other hand, the incorporation of Co in the AFI framework (in samples obtained with 2R:100H₂O at 180 °C) was evidenced by UV–Visible diffuse reflectance spectroscopy (Figure S7-right in the Supporting Information), which showed the typical triplet between 450 and 700 nm characteristic of tetrahedral Co²⁺ embedded in the AFI framework [27].

The incorporation of Al in the AFI network in tetrahedral positions was evidenced by the resonance at 38 ppm, characteristic of tetrahedral Al (see Figure S8 in the Supporting Information); the presence of penta-coordinated (band at ~8 ppm) or octahedral Al (band at ~10 ppm) (coming from amorphous or unreacted material) is very minor, if at all.

Fluorescence Spectroscopy: Supramolecular aggregation of SDAs

Fluorescence spectroscopy was then applied in order to investigate the aggregation state of the molecules confined within the different AFI materials. Figure 4 shows the fluorescence spectra of AFI samples obtained with the two SDA molecules from gels with 1SDA:50H₂O composition at different crystallization temperatures. The occurrence of π - π stacked dimers is evidenced by the appearance of broad red-shifted fluorescence bands between 350 and 500 nm. As observed in our previous work [19], the increase of the crystallization temperatures provokes a remarkable effect on the aggregation state of the occluded SDA species: higher temperatures notably enhance the aggregation of the molecules. An increase from 140 (blue lines) to 165 °C (green lines) provokes a red-shift of the monomer band (with its characteristic vibronic structure) from ~280 to ~310 nm, suggesting an interaction between aromatic rings (possibly through coplanar interactions, but not through π - π stacking). Interestingly, if we compare the occurrence of dimers on the samples obtained at 165 °C (green lines) as a

function of the SDA used, a stronger aggregation trend of ephedrine (compared to pseudoephedrine) is clearly observed, as evidenced by the higher intensity of the broad band between 350 and 500 nm. A further increase of the crystallization temperature to 180 °C (red lines) drastically reduces the emission from monomers and results in the major incorporation of π - π stacked dimers, as evidenced by the featureless broad bands between 350 and 500 nm; the presence of monomers is even lower in the samples obtained with less Mg (0.11, see Figure 4-left, red lines). Two different bands corresponding to π - π stacked dimers can indeed be appreciated, centered at 375 and around 425-450 nm; these two bands might probably come from different configurations/orientations of the stacked dimers, with the latter developing a stronger π - π stacking interaction resulting in a stronger red-shift of the emission band. It is interesting to remark a notable difference found between the two diastereoisomers: ephedrine molecules tend to form the strongly-interacting stacked dimers, as shown by the higher intensity of the 450 nm band, whilst samples obtained with pseudoephedrine display a higher concentration of the weakly-interacting stacked dimers, with a higher intensity of the band at 375 nm (see Figure 4). Indeed, it seems that an increase of the Mg content brings a decrease of the weakly-interacting dimers and a consequent increase of the strongly-interacting dimers. These observations suggest a different stability of the possible configurations/orientations of the stacked dimers as a function of the stereochemical configuration of the SDA molecule.

We then analyzed the effect of the SDA:H₂O ratio (in relation to $x\text{Al}_2\text{O}_3:1\text{P}_2\text{O}_5$ molar composition) on the incorporation of the SDA molecules within the AFI framework; Figure 5 shows the fluorescence spectra of the MgAPO-5 materials obtained with pseudoephedrine at 165 (top) or 180 (bottom) °C, and with low (left) or high (right) Mg contents (the corresponding spectra for samples obtained with ephedrine are shown in

Figure S9 in the Supporting Information). We first look at the effect of varying the water content (from 1SDA:100H₂O, blue line, to 1SDA:50H₂O, red line): it can be clearly observed that a decrease of the water content involves a notable increase of the aggregation of the SDA molecules, as evidenced by the increase of the dimer fluorescence band. This is also observed when moving from 2SDA:100H₂O to 2SDA:50H₂O (see Figure 5-top-left for samples obtained at 165 °C). Similarly, an increase of the SDA concentration notably enhances the formation of stacked dimers: if we compare samples obtained with 1SDA:100H₂O (blue lines) and 2SDA:100H₂O (green lines), a much stronger occurrence of dimers is observed for the samples obtained with a higher concentration of SDAs in the gel. This is also observed when comparing samples obtained with 1SDA:50H₂O (red lines) and 2SDA:50H₂O (black lines) (see Figure 5-top-left and bottom-right). Indeed, even at the low crystallization temperature of 165 °C which favors the incorporation of monomers, an increase of the SDA concentration and decrease of water content (2SDA:50H₂O, black line) results in a major incorporation of dimers (Figure 5-top-left). In addition, it should be noted that an increase of the SDA concentration and/or decrease of the water content increases the incorporation of the strongly-interacting dimers (band at 450 nm) in detriment of the weakly-interacting dimers (band at 375 nm). Exactly the same trends are observed for the incorporation of ephedrine molecules within the AFI framework (see Figure S9 in the Supporting Information; note that in this case most of the samples obtained with 2SDA:50H₂O did not lead to pure AFI materials). As previously, in the samples obtained at 180 °C where dimer species predominate over monomers, again we observe a lower occurrence of weakly-interacting dimers for ephedrine than for pseudoephedrine.

These results clearly evidence that the incorporation of the SDA species as monomers or aggregates can be controlled by the SDA/H₂O contents in the synthesis gels: by increasing the SDA content and decreasing the water content, we can maximize the incorporation of dimers. Indeed, these synthesis conditions also results in a higher incorporation of Mg, as shown previously by ³¹P MAS NMR, and a higher organic content, as observed by TGA, indicating that the enhancement of the incorporation of dimers (which are more tightly packed than monomers) is accompanied by a higher incorporation of Mg in order to provide charge-balance.

Fluorescence spectroscopy of the samples obtained with Zn and Co as dopants showed the same trend as with MgAPO-5 materials: higher crystallization temperatures resulted in a major incorporation of dimers (see Figure S10 in the Supporting Information for ZnAPO-5 materials). Interestingly, the same trend as before with respect to the type of π - π stacked dimers as a function of the diastereoisomer is observed for ZnAPO-5 and CoAPO-5 materials (Figure S11 in the Supporting Information): samples obtained with pseudoephedrine showed a higher incorporation of the weakly-interacting dimers (band at 375 nm) than with ephedrine; this was more noticeable in CoAPO-5 samples.

3C Computational study of the structure-directing effect

Experimental results reported so far indicate that both molecules direct efficiently the crystallization of the AFI framework, being the structure-directing ability of pseudoephedrine higher due to the lack of a competing layered phase. On the other hand, fluorescence spectroscopy shows that both diastereoisomers display a strong trend to incorporate as π - π stacked dimers, but ephedrine mostly incorporate as strongly-interacting dimers, while pseudoephedrine prefers the incorporation as weakly-

interacting dimers. We then performed a computational study based on molecular mechanics of the incorporation of ephedrine and pseudoephedrine dimers within the AFI framework in an attempt to understand, from a molecular point of view, these experimental observations.

After an extensive search (by simulated annealing calculations), two different types of stable dimer configurations confined within the AFI channels were found, one where the aromatic rings are roughly parallel to the channel axis, which is stabilized by the development of intermolecular H-bonds between molecules in consecutive dimers (dimer A) (see Figure 6-top), and another one where the aromatic rings are bent $\sim 60^\circ$ with respect to the channel axis, in which the SDA molecules are stabilized by the development of intramolecular H-bonds (see Figure 6-bottom). Such different configuration and orientation of these two types of dimers might be associated to the two dimer emission bands found in the fluorescence spectra. Interestingly, a different stability of the two types of dimers was found for the two diastereoisomers: the confinement of ephedrine molecules as dimers is more stable in configuration A, with configuration B being notably less favorable (with an energy difference with respect to dimer A of +3.4 kcal/mol per u.c.). In contrast, the opposite was observed for the confinement of pseudoephedrine dimers: in this case, dimers in configuration B were even slightly more favorable than in configuration A (being the energy difference small, of 1.2 kcal/mol per u.c.). Repetition of the calculations but at the DFT+D (PBE) level [26] showed a similar trend, dimers in configuration B were much less stable for ephedrine than for pseudoephedrine. Nonetheless, we note here that the net interaction with Mg is not taken into account in these calculations (due to the huge number of possible spatial configurations that makes the calculations impractical) but is averaged between all possible positions.

If we compare these computational results with the fluorescence spectra reported previously, we can tentatively assign dimers in configuration B as those giving an emission signal at around 375 nm (referred to as weakly-interacting dimers), which are observed more frequently in AFI materials obtained with pseudoephedrine, whilst dimers in configuration A are assigned to those with an emission signal centered at 450 nm (referred to as strongly-interacting dimers), which are observed mostly in AFI materials crystallized with ephedrine. Interestingly, the energy difference calculated by our molecular simulations between the two different types of dimer configurations is small for pseudoephedrine, what explains that both types of dimers can be present depending on the synthesis conditions. In configuration A, both molecules composing the dimer are in a conformation with the alkyl chain in an extended configuration, which is stable for both isomers [22]. In contrast, in order to efficiently pack in the AFI channels, configuration B requires the simultaneous presence of one of the molecules in an extended configuration and the other one in a folded conformation (see Figure 6-bottom); we already observed in our previous work [22] that this folded conformation is stable for pseudoephedrine but not for ephedrine, explaining the low stability of ephedrine under this dimer configuration B, and consequently the minor presence of these dimers in materials obtained with ephedrine as the SDA.

As shown in our previous work [20], dimers in configuration A can develop a long-range helicoidal arrangement within the AFI channels: there is a particular more stable rotation (around the channel axis) between consecutive dimers, which corresponds to +30 deg. Since, depending on the synthesis conditions, we can also get AFI samples with pseudoephedrine where these arrange mostly as A-type dimers (when increasing the organic and Mg contents), we repeated the same type of calculations for this isomer, and observed a similar energy profile, with the +30 deg rotation being the most stable

one (see Figure S12 in the Supporting Information). This involves that pseudoephedrine dimers in configuration A can also develop a helicoidal (and hence chiral) long-range supramolecular arrangement, which could be eventually transferred to the spatial distribution of dopants. However, it should be noted that pseudoephedrine arrange mostly as dimers B which do not develop a long-range helicoidal arrangement.

4 Discussion

Our combined experimental and computational study has shown a notably different structure-directing behavior of the two isomers, ephedrine and pseudoephedrine, during crystallization of AFI-based nanoporous aluminophosphates. Our previous work [22] showed a higher supramolecular aggregation of ephedrine compared to that of pseudoephedrine in aqueous solution, which resulted in a higher incorporation of dimers in AFI samples obtained with ephedrine. A Molecular Dynamics study showed that this distinct supramolecular aggregation is due to the different conformational space depending on the stereochemical configuration: ephedrine molecules arrange in a conformation with an extended configuration of the alkyl chain, while pseudoephedrine displays a mixture of conformers, one with the alkyl chain in an extended configuration and another one in a folded configuration. Interestingly, only the extended configuration enables the formation of supramolecular dimers, explaining the lower aggregation observed for pseudoephedrine. In this work, we have observed very frequently the crystallization of a competitive phase, a layered-like material, only in the presence of ephedrine, but not for pseudoephedrine. This material must possess a bilayer-like organic structure as a result of a strong supramolecular aggregation in the interlaminar space, which might be the reason for being only crystallized in the presence of ephedrine. Due to the versatility in the Al coordination and P condensation degree,

crystallization of layered aluminophosphates with different compositions and dimensionalities is very common [28]; indeed, in occasions some of these materials can be transformed into 3D nanoporous aluminophosphates [29,30]; however, calcination of our layered material gives trydimite as a result, and hence has no major interest. Certain layered materials prepared with aromatic molecules have in fact an organic bilayer in the interlaminar space [31,32] similar to that proposed for our layered material. In contrast, pseudoephedrine displays a stronger structure-directing behavior towards the AFI framework, possibly due to the absence of this competitive phase.

Our results show that the incorporation of dopants is much more favorable for Mg, followed by Zn; Co, and especially Si, are much more difficult to incorporate in tetrahedral positions in the AFI framework using these chiral SDAs. The difficult incorporation of Si in the AFI framework with these aromatic SDA molecules may be associated to the trend of Si to incorporate as Si islands in the AlPO network which provokes a high distortion of the framework and leads to a low average negative charge per Si atom [33], while the difficult incorporation of Co must be associated to its particular electronic configuration and stability in tetrahedral coordination.

The incorporation of the SDA molecules as monomers or dimers is strongly affected by the crystallization conditions. Notably, high crystallization temperatures favor the incorporation of π - π stacked dimers; furthermore, high organic and low water contents also favor the occlusion of dimers. Interestingly, the higher formation of these dimers upon an increase of the organic concentration is generally accompanied by a higher incorporation of dopants to provide charge-balance. Furthermore, these conditions also favor the formation of A-type dimers in detriment of B-type dimers.

Figure 7 shows a schematic picture describing the main findings of this work related to the different structure-directing behavior of the two diastereoisomers. It is worth

remarking the different incorporation of dimers within the AFI framework, as suggested by the combination of fluorescence spectroscopy and computational simulations. Ephedrine dimers are more stable in configuration A, with the aromatic rings parallel to the channel axis, which can then develop long-range helicoidal arrangements; in these dimers, ephedrine species arrange as conformers with the alkyl chain in an extended configuration, corresponding to the most stable conformation in vacuo (Figure 7-top). In contrast, pseudoephedrine dimers confined within the AFI channels are more stable in configuration B, with the aromatic rings bent with respect to the channel axis; in this configuration, half of the molecules arrange in a conformation with an extended configuration, and half in a folded configuration, both of which are indeed present in aqueous solution (Figure 7-bottom). This different conformational behavior thus explains the distinct crystallization behavior of these systems: ephedrine in conformation A promotes a strong aggregation as dimers in configuration A that, depending on the synthesis conditions, can lead to layered-like phases (at low crystallization temperatures) or AFI frameworks with A-type dimers occluded (at high crystallization temperature) (Figure 7-top), while pseudoephedrine displays in solution a mixtures of conformers, in extended and folded configurations, resulting in a weaker supramolecular aggregation (since the folded conformer avoids the aggregation), hence preventing the formation of layered-like phases, and directing the crystallization of AFI materials with monomers occluded (at low crystallization temperature) or with dimers in configuration B which contains both types of conformations (at high crystallization temperature) (Figure 7-bottom). The two types of dimer configurations observed for ephedrine and pseudoephedrine should also result in a different spatial distribution of dopants, with only dimers in configuration A potentially leading to a long-range chiral ordering of these dopants.

Conclusions

In this work we have analyzed in depth the structure-directing behavior of two closely-related chiral diastereoisomers, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, during the crystallization of nanoporous aluminophosphates. A combination of extensive synthesis experiments, characterization (especially fluorescence) and computational studies have allowed us to establish clear relationships between the conformational behavior of the molecules, their supramolecular chemistry and the structure-directing mode of action during crystallization.

We have shown that ephedrine displays a stronger supramolecular aggregation trend due to the occurrence of only one type of conformer that favor such supramolecular chemistry, resulting in a major incorporation of dimers as well as the crystallization of a layered-like framework with a very strong supramolecular aggregation in the interlaminar space. In contrast, pseudoephedrine in aqueous solution occurs as two different conformations, one of them preventing the supramolecular aggregation, and therefore avoiding the formation of the competing layered-like framework (and favoring the crystallization of the AFI phase) and reducing the incorporation of dimers within the AFI framework. Interestingly, the combination of fluorescence and molecular simulations suggest a different configuration of the dimers confined within the AFI channels for ephedrine and pseudoephedrine, giving place to different fluorescence bands. On the other hand, our results also show that the occlusion of monomers/dimers within AFI materials can be controlled by the synthesis conditions: high crystallization temperatures, high organic contents and low water contents in the gel all favor the occlusion of dimer species, and consequently a higher incorporation of dopants to ensure neutrality.

Supporting Information

Additional thermogravimetric analyses (TGA), NMR spectra, UV–visible diffuse reflectance spectra, fluorescence spectra, and energy profiles are included as Supporting Information.

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Tables

Table 1. Crystalline products obtained from Mg-containing gels under different synthesis conditions, with a general molar composition of x R: y MgO : $(1-y/2)$ Al₂O₃ : 1.0 P₂O₅: z H₂O. ‘AFI’ stands for MgAPO-5 materials (blue background; when the material is pure MgAPO-5, the blue background is darker and with white letters); ‘L’ stands for the layered phase (green background), ‘Tr’ for AlPO-trydimite, ‘Am’ for amorphous material (red background), and ‘U’ for an unidentified dense phase; ↓ and ↓↓ accounts for low and very low amounts, respectively. Additional phases (if any) to the major identified phase in each material are given in the ‘secondary phase’ column.

Gel composition		Crystallization Temperature	Major phase		Secondary phase	
x R : z H ₂ O	y MgO		EPH	PsEPH	EPH	PsEPH
1R:100H ₂ O pH = 2.8-3.5	0.11	140	AFI	AFI	L(↓)+APC(↓)	APC(↓)
		165	AFI	AFI	Tr	Tr
		180	AFI	AFI	Tr	Tr
	0.22	140	AFI	AFI	L(↓)+APC(↓)	APC
		165	AFI	AFI		
		180	AFI	AFI		Tr
	0.32	140	AFI	AFI		U(↓)
		165	AFI	AFI		U(↓)
		180	AFI	AFI	U(↓)	U(↓)
2R:100H ₂ O pH = 5.4-5.8	0.11	140	L	Am		
		165	L	AFI	AFI(↓↓)	
		180	AFI	AFI	L(↓)	
	0.22	140	L	AFI(↓)		
		165	AFI	AFI	APC(↓)	
		180	AFI	AFI		
	0.32	140	L	AFI(↓↓)		
		165	AFI	AFI	L	
		180	AFI	AFI		
1R:50H ₂ O pH = 3.0-3.6	0.11	140	AFI	AFI		
		165	AFI	AFI	Tr(↓)+L(↓)	Tr(↓↓)
		180	AFI	AFI	Tr(↓)	Tr(↓↓)
	0.22	140	AFI	AFI	L(↓)+ATS(↓)	
		165	AFI	AFI		
		180	AFI	AFI		

2R:50H ₂ O pH = 5.3-5.6	0.11	140	L(↓)	AFI(↓)		
		165	L	AFI		L(↓↓)
		180	AFI(↓)	AFI	L	
	0.22	140	L	Am		
		165	L	AFI		
		180	AFI	AFI		

Table 2. Crystalline products obtained from Zn-containing gels under different synthesis conditions, with a general molar composition of x R: y ZnO : $(1-y/2)$ Al₂O₃ : 1.0 P₂O₅: z H₂O. The legend is the same as in Table 1.

Gel composition		Crystallization Temperature	Major phase		Secondary phase	
x R : z H ₂ O	y ZnO		EPH	PsEPH	EPH	PsEPH
1R:100H ₂ O pH = 2.8-3.0	0,11	140	Tr	Tr	L(↓)+AFI(↓)	AFI(↓)
		165	Tr	Tr		AFI(↓)
		180	Tr	AFI(↓)	AFI(↓)+GIS(↓)	Tr+GIS
2R:100H ₂ O pH = 5.4-5.8	0,11	140	L (↓)	Am		AFI(↓↓)
		160	L	AFI		
		180	AFI	AFI		
	0,22	140	L	AFI(↓)		
		160	L	AFI	AFI	
		180	AFI	AFI	GIS(↓)	GIS(↓)
1R:50H ₂ O pH = 3.1-3.7	0,11	140	AFI	AFI(↓)	L	Tr(↓↓)
		160	AFI	AFI	L	Tr(↓)
		180	AFI	AFI	Tr(↓)	Tr(↓)
	0,22	140	AFI	AFI	L(↓↓)	Tr(↓↓)
		160	AFI	AFI		Tr(↓)
		180	AFI	AFI		Tr
2R:50H ₂ O pH = 5.2-5.7	0,11	140	L (↓)	Am	Am	
		160	L	Am	Am	AFI(↓)
		180	L	AFI	AFI(↓)	
	0,22	140	L	L (↓)		Am
		160	L	AFI(↓)		L
		180	AFI	AFI	GIS+L(↓)	ATS+GIS

Table 3. Crystalline products obtained from Co-containing gels under different synthesis conditions, with a general molar composition of x R: y CoO : $(1-y/2)$ Al₂O₃ : 1.0 P₂O₅: z H₂O. The legend is the same as in Table 1.

Gel composition		Crystallization Temperature	Major phase		Secondary phase	
x R : z H ₂ O	y CoO		EPH	PsEPH	EPH	PsEPH
2R:100H ₂ O 5.5-5.9	0,11	140	L(↓)	Am		
		160	L	AFI(↓)		L(↓)
		180	AFI	AFI	L	
	0,22	140	Am	Am	L(↓↓)	
		160	L	AFI(↓)		
		180	AFI	AFI	L	
1R:50H ₂ O 3.5-3.7	0,11	140	L	AFI(↓)	Tr	Tr
		160	Tr	Tr		
		180	Tr	Tr	AFI(↓)	AFI(↓↓)
	0,22	140	Tr	AFI(↓)		Tr
		160	Tr	Tr		
		180	Tr	Tr	AFI(↓↓)	
2R:50H ₂ O 5.3-5.5	0,11	140	L	Am		
		165	L	Am		
		180	L	AFI		
	0,22	140	L	Am		
		165	L	Am		
		180	L	AFI		GIS(↓)

Figures

Figure 1. ^{13}C CP NMR spectra of several AFI samples obtained at 180 °C with ephedrine (left) and pseudoephedrine (right). Bands assigned to degradation products are indicated by asterisks.

Figure 2. ^1H MAS NMR spectra of AFI samples obtained at 180 $^\circ\text{C}$ (1R:50 H_2O composition) with ephedrine (left, solution ^1H NMR of neutral ephedrine in CDCl_3 , green dotted line, and ephedrine hydrochloride in D_2O , orange dotted line, are also included for comparison) and pseudoephedrine (right).

Figure 3. ^{31}P MAS NMR spectra of Mg-AFI samples obtained at 180 °C (under different compositions) with ephedrine (top) and pseudoephedrine (bottom), from gels with 0.11 (left) or 0.22 (right) Mg contents.

Figure 4. Fluorescence spectra (exc = 265 nm) of MgAPO-5 samples synthesized under 1R:50H₂O composition at different temperatures, using ephedrine (top) or pseudoephedrine (bottom) as SDA, with 0.11 (left) or 0.22 (right) Mg contents.

Figure 5. Fluorescence spectra (exc = 265 nm) of MgAPO-5 samples obtained with pseudoephedrine under different SDA:H₂O compositions at 165 (top) or 180 (bottom) °C, with 0.11 (left) or 0.22 (right) Mg contents. The corresponding spectra for AFI samples obtained with ephedrine are included in Figure S9 in the Supporting Information.

Figure 6. Most stable arrangement of the two types of π - π stacked dimers for ephedrine (left) and pseudoephedrine (right). All energies are normalized per unit cell.

Figure 7. Schematic picture of the relationship between molecular structure, conformational space, supramolecular chemistry and structure-directing behavior for ephedrine (top) and pseudoephedrine (bottom) during the synthesis of nanoporous aluminophosphates.

References

- (1) M. Gardner, *The Ambidextrus Universe. Symmetry and Asymmetry from Mirror Reflections to Superstrings*, 3rd Revised, Penguin Books, 1964.
- (2) M. Rouhi, Top Pharmaceuticals: Thalidomide, *Chem. Eng. News*. 883 (2005).
- (3) D. Dubbledam, S. Calero, T. J. H. Vlugt, Exploring New Methods and Materials for Enantioselective Separations and Catalysis, *Molec. Sim.* 40 (2014) 585-598.
- (4) K. D. M. Haris, S. J. M. Thomas, Selected Thoughts on Chiral Crystals, Chiral Surfaces, and Asymmetric Heterogeneous Catalysis, *ChemCatChem*. 1 (2009) 223-231.
- (5) T. S. Van Erp, T. P. Caremans, D. Dubbeldam, A. Martín-Calvo, S. Calero, J. A. Martens, Enantioselective Adsorption in Achiral Zeolites, *Angew. Chem. Int. Ed.* 49 (2010) 3010-3013.
- (6) J. M. Castillo, T. J. H. Vlugt, D. Dubbeldam, S. Hamad, S. Calero, Performance of Chiral Zeolites for Enantiomeric Separation Revealed by Molecular Simulation, *J. Phys. Chem. C* 114 (2010) 22207-22213.
- (7) M. E. Davis, Reflections on Routes to Enantioselective Solid Catalysts, *Top. Catal.* 25 (2003) 3-7.
- (8) R. E. Morris, X. H. Bu, Induction of Chiral Porous Solids Containing only Achiral Building Blocks, *Nat. Chem.* 2 (2010) 353-361.
- (9) J. Yu, R. Xu, Chiral Zeolitic Materials: Structural Insights and Synthetic Challenges, *J. Mat. Chem.* 18 (2008) 4021-4030.
- (10) M. M. J. Treacy, J. M. Newsam, 2 New 3-Dimensional 12-Ring Zeolite Frameworks of which Zeolite Beta is a Disordered Intergrowth, *Nature* 332 (1988) 249-251.
- (11) N. Rajic, N. Z. Logar, V. Kaucic, A Novel open Framework Zincphosphate - Synthesis and Characterization, *Zeolites* 15 (1995) 672-678.

-
- (12) J. Sun, C. Bonneau, A. Cantín, A. Corma, M. J. Díaz-Cabañas, M. Moliner, D. Zhang, M. Li, X. Zou, The ITQ-37 Mesoporous Chiral Zeolite, *Nature* 458 (2009) 1154-1157.
- (13) A. Rojas, M. A. Camblor, A Pure Silica Chiral Polymorph with Helical Pores, *Angew. Chem. Int. Ed.* 51 (2012) 3854-3856.
- (14) L. Q. Tang, L. Shi, C. Bonneau, J. L. Sun, H. J. Yue, A. Ojuva, B. L. Lee, M. Kritikos, R. G. Bell, Z. Bacsik, J. Mink, X. D. Zou, A Zeolite Family with Chiral and Achiral Structures Built from the Same Building Layer, *Nat. Mater.* 7 (2008) 381-385.
- (15) J. Pérez-Pariente, L. Gómez-Hortigüela. The role of templates in the synthesis of zeolites, in *Zeolites: From model materials to industrial catalysts*. (eds J. Čejka, J. Pérez-Pariente, W. J. Roth). ISBN: 978-81-7895-330-4.
- (16) L. Gómez-Hortigüela, F. Corà, C. R. A. Catlow, J. Pérez-Pariente, Computational Study of a Chiral Supramolecular Arrangement of Organic Structure Directing Molecules for the AFI Structure, *Phys. Chem. Chem. Phys.* 8 (2006) 486-493.
- (17) L. Gómez-Hortigüela, F. Corà, J. Pérez-Pariente, Chiral Distributions of Dopants in Microporous Materials: A New Concept Of Chirality, *Micropor. Mesopor. Mater.* 155 (2012) 14-15.
- (18) T. Álvaro-Muñoz, F. López-Arbeloa, J. Pérez-Pariente, L. Gómez-Hortigüela, (1R,2S)-Ephedrine: A New Self-Assembling Chiral Template for the Synthesis of Aluminophosphate Frameworks, *J. Phys. Chem. C* 118 (2014) 3069-3077.
- (19) B. Bernardo-Maestro, M. D. Roca-Moreno, F. López-Arbeloa, J. Pérez-Pariente, L. Gómez-Hortigüela, Supramolecular chemistry of chiral (1R,2S)-ephedrine confined

within the AFI framework as a function of the synthesis conditions, *Catal. Today*, published in web; DOI: 10.1016/j.cattod.2015.10.010.

(20) L. Gómez-Hortigüela, T. Álvaro-Muñoz, B. Bernardo-Maestro, J. Pérez-Pariente, Towards Chiral Distributions of Dopants in Microporous Frameworks: Helicoidal Supramolecular Arrangement of (1R,2S)-Ephedrine and Transfer of Chirality, *Phys. Chem. Chem. Phys.* 17 (2015) 348-357.

(21) Y. Wang, J. Yu, Y. Li, Z. Shi, R. Xu, Chirality Transfer from Guest Chiral Metal Complexes to Inorganic Framework: The Role of Hydrogen Bonding, *Chem. Eur. J.* 9 (2003) 5048-5055.

(22) B. Bernardo-Maestro, F. López-Arbeloa, J. Pérez-Pariente, L. Gómez-Hortigüela, Supramolecular Chemistry Controlled by Conformational Space during Structure-Direction of Nanoporous Materials: Self-Assembly of Ephedrine and Pseudoephedrine, *J. Phys. Chem. C* 119 (2015) 28214–28225.

(23) P. Dauber-Osguthorpe, V. A. Roberts, D. J. Osguthorpe, J. Wolff, M. Genest, A. T. Hagler, Structure and Energetics of Ligand-Binding to Proteins-Escherichia-Coli Dihydrofolate Reductase Trimethoprim, a Drug-Receptor System, *Proteins: Struct., Funct., Genet.* 4 (1988) 31-47.

(24) L. S. Schanker, P. A. Shore, B. B. Brodie, C. A. M. Hogben, Absorption of Drugs from the Stomach. 1. The Rat. *J. Pharmacol. Exp. Ther.* 120 (1957) 528-539.

(25) Forcite Module, Materials Studio 2016. Biovia.

(26) S. J. Clark, M. D. Segall, C. J. Pickard, P. J. Hasnip, M. J. Probert, K. Refson, M. C. Payne, First principles methods using CASTEP, *Z. Kristallogr.* 220 (2005) 567-570.

(27) J. Šponer, J. Čejka, J. Dědeček, B. Wichterlová, Coordination and properties of cobalt in the molecular sieves CoAPO-5 and -11, *Micropor. Mesopor. Mater.* 37 (2000) 117-127.

-
- (28) J. Yu, R. Xu, Insight into the construction of open-framework aluminophosphates, *Chem. Soc. Rev.* 35 (2006) 593-604.
- (29) H. O. Pastore, E. C. de Oliveira, G. B. Superti, Reaction at Interfaces: The Silicoaluminophosphate Molecular Sieve CAL-1, *J. Phys. Chem. C* 111 (2007) 3116-3129.
- (30) M. Strauss, G. A. V. Martins, G. Berlier, S. Coluccia, L. Marchese, H. O. Pastore, [M]-CAL-2: MeAPSO-34-like molecular sieves using a lamellar aluminophosphate as precursor, *Microporous Mesoporous Mater.* 187 (2014) 135-144.
- (31) R. W. Dorner, M. Deifallah, D. S. Coombes, C. R. A. Catlow, F. Corà, Synthesis and Structure Determination of a Novel Layered Aluminophosphate Material Templated with 1-Phenylethylamine: $[\text{AlPO}_4(\text{OH})](\text{NH}_3\text{C}_2\text{H}_4\text{C}_6\text{H}_5)$, *Chem. Mater.* 19 (2007) 2261-2268.
- (32) L. Gómez-Hortigüela, A. Sanz, T. Álvaro-Muñoz, F. López-Arbeloa, J. Pérez-Pariente, Un-assemblable layered aluminophosphates from self-assembling structure-directing agents: effect of fluorine, *Microporous Mesoporous Mater.* 183 (2014) 99-107.
- (33) L. Gómez-Hortigüela, C. Márquez-Álvarez, M. Grande-Casas, R. García, J. Pérez-Pariente, "Tailoring the acid strength of microporous silicoaluminophosphates through the use of mixtures of templates: control of the silicon incorporation mechanism", *Microporous Mesoporous Mater.* 121 (2009) 129-137.