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Graphical Abstract

Supramolecular Chemistry Controlled by Packing Interactions during Structure-Direction of Nanoporous Materials: Effect of the Addition of Methyl Groups on Ephedrine Derivatives

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Abstract. A combined experimental and computational study has been applied in order to understand the effect of the addition of subsequent methyl groups to chiral (1R,2S)-(-)-ephedrine on its structure-directing behavior during crystallization of the nanoporous

AFI aluminophosphate. Results show that bare ephedrine and the double-methylated N,N-dimethyl-ephedrinium display the most efficient structure-directing abilities, while the mono-methylated derivative shows a poor structure-directing capacity towards this framework. Fluorescence spectroscopy indicates that confinement of the mono- and dimethylated derivatives within the nanopores of the AFI channels involves a preferential incorporation of the SDA molecules as monomers. In contrast, occlusion of the bare ephedrine can lead to a strong supramolecular aggregation, depending on the synthesis conditions. Molecular simulations suggest that the stronger trend of ephedrine to form supramolecular aggregates when confined within the AFI channels is due to the formation of two intermolecular H-bonds between consecutive molecules in the dimers interface, which balances the strong electrostatic repulsion between closely-located positive charges of the N atoms under this supramolecular arrangement. The addition of subsequent methyl groups reduces the possibility of establishing these interdimer H-bond interactions that stabilize dimers while provoking steric repulsions, thus reducing the supramolecular aggregation.

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

1. Introduction

Chirality, the property by which objects are not superimposable to their mirror-images, is essential for life [1]. Living organisms are built up by particular enantiomers of the biological molecular building-blocks, L-aminoacids and D-sugars. The crucial consequence of this asymmetric construction of life is that the metabolism of living organisms works in an asymmetric fashion, distinguishing between enantiomers of

chiral compounds [2]. In fact, different enantiomers of a chiral compound usually lead to different biological responses upon exposure to our asymmetrically-working metabolism, with only one enantiomer being active in a particular (desired) reaction, and the other being less active, inactive or even harmful. However, enantiomers of a chiral compound have, by definition, exactly the same physical properties, and therefore it is an extremely difficult task to discriminate between them. The way to induce enantio-differentiation is by subjecting the chiral compound to an asymmetric confined environment, where different enantiomers of the compound will interact differently with the environment. In this context, one of the greatest challenges nowadays is the development of homochiral solids able to discriminate between the enantiomers of chiral compounds [3,4]. Indeed, chiral surfaces (like those in *d*- or *l*-quartz) are in principle able to transfer their chirality to a particular separation/catalytic process and perform enantioselective operations [5].

Crystalline nanoporous materials represent very promising candidates to achieve chiral enantio-differentiating solids since they provide a rigid and crystalline environment of molecular-size, and therefore their characteristic shape-selectivity could enhance a potential enantioselectivity [6-8]. Indeed, molecular simulations have shown that homochiral frameworks are able to enantioselectively adsorb chiral molecules as long as appropriate relationships between the pore geometry and the molecular dimensions are satisfied [9-11]. Homochiral nanoporous metal-organic frameworks (MOFs) have been built by using asymmetric ligands, and in fact they have successfully performed particular asymmetric operations [12,13]. However, although these represent extremely interesting examples of inducing chiral environments, MOFs materials still present some problems associated to the stability of the frameworks upon solvent removal. The classical type of crystalline nanoporous materials, which are widely-used in the

industry, is provided by zeolite (or zeotype) materials. One of the most intensively-searched types of zeolite materials is represented by homochiral zeolite frameworks where chirality is directly imprinted into the zeolite structure itself [14]. Indeed, zeolite-type chiral frameworks do exist, as polymorph A of zeolite BEA [15], which has been recently enriched in the chiral polymorph A [16,17], the chiral zincophosphate CZP [18], or the recently-discovered ITQ-37 [19] and HPM-1 [20], the silica-form of the chiral SU-32 silicogermanate [21], among others [14]. In fact, several zeolites have only recently been recognized as being chiral, with their consequent potential use for chiral discrimination [22]. However, unless particular strategies are developed for the enrichment of these crystals in a particular enantiomorph [23], the main limitation in the enantio-differentiation capacity of these chiral zeolites is that they almost invariably crystallize as racemic crystals, with half of them of each handedness. Nevertheless, although extremely rare, and in fact not well-understood, homochirality does sometimes spontaneously and unpredictably occur through chiral symmetry breaking effects [24,25]. In this context, the challenge in producing solids able to discriminate between enantiomers is not only to produce a chiral zeolite framework, but to do so in an asymmetric fashion so that crystals in only one absolute configuration grow.

The most straightforward way to induce chirality during the crystallization of a zeolite framework is through the use of homochiral organic molecules as structure-directing agents (SDAs). These SDAs organize the inorganic building units in a particular geometry giving place to hybrid organo-inorganic precursors from which crystallization of a particular framework type will take place [26]. The organic SDAs develop strong intermolecular (Van der Waals and electrostatic) interactions with the nascent zeolite frameworks, whereby a transfer of the chirality from the organic molecule to the inorganic network could take place. The use of chiral organic molecules has indeed led

to the crystallization of chiral zeolite frameworks [7,19]; however, these zeolite frameworks crystallized as racemic crystals, evidencing that no transfer of chirality from the molecular component occurred. Such a failure on the transfer of chirality must be related to, on the one hand, the lack of strong and localized interactions between SDAs and the inorganic network, resulting in a mobility of the molecules that would cancel the asymmetric nature, and on the other, to the incommensurate nature of chirality in the SDA, at a molecular level, and in the zeolite framework, at a long-range level.

In this context, we have recently proposed a new concept of chirality in zeolite frameworks, which is represented by the development of chiral spatial distribution of dopants (tetrahedral atoms substituting for the typical T atoms in zeolites and zeotypes) embedded in otherwise achiral zeolite frameworks [27]. The substitution of a small number of T atoms by dopants (typically Si by Al, B or Ge in zeolites, or Al by Mg, Zn, Co, etc in AlPO networks) brings about a new degree of freedom, the spatial distribution of these dopants in the zeolite network, to which chirality could be potentially transferred in the sense of asymmetric (chiral) distributions of dopants (helical for instance) (see Figure S1 in the Supporting Information, bottom-left). Our rationale for proposing this new concept is that rather than achieving a chiral ordering of all the atoms in a framework under a chiral spatial group (like in BEA, CZP or STW chiral frameworks), it should more easily be achievable to only arrange in a chiral fashion a particular subset of atoms, in our case the dopants, especially taking into account that these dopants develop the strongest (electrostatic) interactions with the chiral precursors, the SDA molecules. In this context, in order to develop helical distributions of the dopants, a supramolecular helical ordering of the SDA molecules

that could be transferred to the spatial distribution of dopants should be achieved (see Figure S1).

In an attempt to enhance the probability of chiral SDAs to transfer their asymmetry into a helicoidal distribution of dopants, we propose the use of aromatic chiral amines as SDAs. The motivation for this choice is that the aromatic moiety of these molecules would induce a self-assembly to form supramolecular dimers through π - π type interactions [28-31], leading to asymmetric supramolecular entities (Figure S1). Indeed, their asymmetric nature makes that the packing of these dimers within the zeolite channels should involve a particular more stable rotation between consecutive dimers. Hence all consecutive dimers will be rotated by the same angle, leading to an (enantiomerically-pure) helicoidal ordering of these dimers throughout the nanopores of the framework, and resulting in a long-range chirality that could be more easily transferred into the periodic zeolite network [32,33] (Figure S1). The strongest and most localized interactions of the SDAs with zeolite frameworks is developed with dopants (since the most common dopant substitutions in zeolitic materials involve the generation of a net negative charge, inducing a strong electrostatic interaction with the positively-charged SDA cations), and hence such supramolecular long-range helicoidal distribution of SDA dimers could be transferred into a spatial helicoidal distribution of dopants [33]. In this context, nanoporous aluminophosphates (AIPO) are preferred candidates (compared to zeolites) since their crystallization allows an easier and more versatile dopant incorporation, usually takes shorter times (reducing the possibility of racemization of the chiral SDA under the harsh crystallization conditions), and enables the use of organic (protonated) amines as SDAs (which are not very effective SDAs for zeolites) with the consequent presence of H-bond-forming groups that could drive the asymmetric long-range supramolecular ordering [34]. Besides, in contrast to the

synthesis of zeolites which usually takes place at high pHs, the synthesis of nanoporous aluminophosphates typically occurs under acidic conditions where amines are mostly protonated, thus increasing the electrostatic interactions with dopants through H-bond interactions. Furthermore, the strict alternation of Al and P atoms in the AlPO network, and the unique isomorphic incorporation of M^{2+} in Al^{3+} positions (and not in P^{5+} positions, i.e. only in half of the total tetrahedral positions) would also facilitate the long-range spatial ordering of the dopant distributions.

Based upon these grounds, we have been recently working with (1R,2S)-(-)-ephedrine (Figure 1) as a chiral SDA for the synthesis of crystalline nanoporous aluminophosphates; this molecule directed the crystallization of the AFI framework doped with different elements [35], which is composed by 12-MR one-dimensional cylindrical channels with a diameter of 7.3 Å. Ephedrine, which is an alkaloid found in nature [36] in the *Ephedra* species of plants, and is commercially available at a moderate cost, was selected as SDA since it contains i) an aromatic ring which enables π - π -driven supramolecular aggregation, ii) two stereogenic centers that impart a strong asymmetric nature to the molecule, iii) H-bond donor ($\underline{H}(N)$) and acceptor ($\underline{O}(H)$) groups that enable a rich H-bond-driven supramolecular chemistry, and iv) positively-charged (when protonated under the acidic pH of AlPOs synthesis) NH_x^+ groups that would strongly-interact and spatially-direct the incorporation of the dopants. Previous works showed that (1R,2S)-(-)-ephedrine tend to form dimers when confined within the AFI channels only under particular synthesis conditions [37]. Indeed, molecular-mechanics-based simulations showed that ephedrine supramolecular aggregates tend to pack within the one-dimensional channels of the AFI framework with a particular rotation angle between consecutive dimers ($+30^\circ$), thus developing a long-range helicoidal, and hence chiral, supramolecular organic ordering. Interestingly, these

simulations also showed that Mg dopants (substituting Al positions) tend to locate close to the NH_x^+ groups of ephedrine molecules in order to maximize electrostatic interactions. As a consequence, the helicoidal arrangement of the ephedrine dimers can be transferred to a helicoidal spatial distribution of the Mg dopants embedded in the (achiral) AFI network.

In a recent work we observed that the conformational space of (1R,2S)-(-)-ephedrine and its diastereomer (1S,2S)-(+)-pseudoephedrine controls the supramolecular chemistry of these molecules during structure-direction [38]; indeed, it seems that the presence of intermolecular H-bonds between hydroxyl-groups tend to strongly affect the supramolecular behavior [39]. The control of supramolecular chemistry is fundamental for developing long-range chirally-ordered supramolecular organic arrangements that could be potentially transferred into chiral spatial distributions of dopants embedded in zeolite frameworks. For this reason, in this work we analyze the effect of adding subsequent methyl groups to (1R,2S)-(-)-ephedrine (EPH), giving place to (1R,2S)-(-)-N-methyl-ephedrine (MeEPH) and (1R,2S)-(-)-N,N-dimethyl-ephedrinium (DMeEP) (see Figure 1), on their structure-directing ability towards crystalline nanoporous aluminophosphates as well as, in particular, on their supramolecular behavior when confined within these nanoporous structures. In order to promote the transfer of chirality from the molecular component to the spatial distribution of dopants, Mg-doped aluminophosphates have been studied.

2. A. Experimental Details

A) Synthesis of Ephedrine derivatives:

(1R,2S)-(-)-ephedrine (Ia) was used as received (Sigma-Aldrich, 98 %).

(1R,2S)-(-)-N-Methyl-ephedrine (Ib) was prepared from Ia according to reported methods through the Leucart reaction. 25.0 g of Ia were carefully added (with cooling) to a solution of 15.1 g of formaldehyde (Sigma-Aldrich, 37 wt % solution in water) and 23.0 g of formic acid (Sigma-Aldrich, 95 %), and the mixture was refluxed for 4 hours. 18.2 g of 37 wt % HCl (Panreac) were then added, and the excess formic acid and formaldehyde were evaporated by heating. The residue was dissolved in 30 mL of water, and 60 g of 25 wt % NaOH aqueous solution were added, giving place to a white precipitate, which was recrystallized from diethyl-ether. Ib was obtained in ~70 % yield. ¹H NMR (CDCl₃): 0.84 (d, 3H, CH₃C), 2.37 (s, 6H, CH₃N), 2.55 (dq, 1H, CHN), 3.60 (broad signal, 1H, OH), 4.96 (d, 1H, CHOH), 7.2-7.4 (m, 5H, aromatics). ¹³C NMR (CDCl₃): 10.2 (CH₃C), 43.1 (CH₃N), 65.3 (CHN), 72.3 (CHOH), 125.9-128.0 (unsubstituted aromatic C), 142.2 (substituted aromatic C).

(1R,2S)-(-)-N,N-Dimethyl-ephedrinium (Ic) iodide was prepared from Ib by direct alkylation with excess iodomethane (Sigma-Aldrich, 99 %) in acetonitrile. 17.5 g of Ib were dissolved in 700 mL of acetonitrile, and 24.3 g of iodomethane were carefully added (with cooling), and the mixture was kept at room temperature overnight. The solvent was then evaporated, and the resulting white precipitate was washed with diethyl ether. The iodide salt of Ic was obtained in ~95 % yield. ¹H NMR (MeOD): 1.27 (m, 3H, CH₃C), 3.36 (m, 9H, CH₃N), 3.74 (dq, 1H, CHN), 5.72 (s, 1H, CHOH), 7.3-7.5 (m, 5H, aromatics). ¹³C NMR (MeOD): 6.0 (CH₃C), 47.3 ((CH₃)₃N), 69.4 (CHOH), 74.7 (CHN), 125.5-128.2 (unsubstituted aromatic C), 141.2 (substituted aromatic C).

Ic iodide was finally converted into the hydroxide form through ion-exchange with an anionic resin (Amberlite IRN-78, Aldrich); the solution was titrated with HCl (0.1 N, Panreac) using phenolphthalein as an indicator, and concentrated by evaporation up to ~25 wt % of Ic hydroxide.

B) Synthesis of MgAPO-5 materials:

Mg-doped AFI aluminophosphate materials (MgAPO-5) were synthesized by hydrothermal methods using (1R,2S)-(-)-ephedrine (EPH), (1R,2S)-(-)-N-methyl-ephedrine (MeEPH) and (1R,2S)-(-)-N,N-dimethyl-ephedrinium hydroxide (DMeEP) as SDAs. The gel molar composition was 1 SDA : x MgO : (1-x/2) Al₂O₃ : 1 P₂O₅ : 50 H₂O, where x was 0.11 or 0.22. Pseudoboehmite (Pural SB-1 77.5% Al₂O₃, Sasol), H₃PO₄ (Sigma-Aldrich, 85%) and Mg(CH₃COO)₂·4H₂O (Sigma-Aldrich, 99.5%) were used as sources of Al, P and Mg, respectively. Preparation of the gels involved the initial addition of Al₂O₃, H₃PO₄ and H₂O, which were stirred for 2 hours; then the SDA was added, and the stirring was kept for 30 minutes, after which Mg(CH₃COO)₂·4H₂O was added, and the final mixture was stirred for 30 additional minutes. 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.

C) Characterization of MgAPO materials:

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 carried out in air flow using a Perkin-Elmer TGA7 instrument (heating rate = 20 °C/min). UV-Visible diffuse reflectance absorption spectra were registered using a UV-Vis Cary 5000 Varian spectrophotometer equipped with an integrating sphere using the synthetic polymer Spectralen as a reference. The crystal morphology of the materials was studied by scanning electron microscopy (SEM) using a Hitachi TM-1000 Tabletop microscope.

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. 10 kHz.

The aggregation state of the molecules in 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 dichloromethane suspension of the solid samples.

2. B. Computational Details

Molecular simulations were performed in order to analyze the supramolecular arrangement of the different ephedrine derivatives occluded within the 12-MR channels of the AFI framework, as a function of their molecular structure. Due to the strong basicity of ephedrine ($\text{pK}_a = 9.6$) [40] and the low pH of the synthesis medium, protonated ephedrine and N-methyl-ephedrine molecules, in addition to quaternary cationic N,N-dimethyl-ephedrinium, were considered. The presence of rotatable bonds and H-bond donor and acceptor groups, with the consequent possibility of developing intramolecular H-bonds, drives the conformational space of these molecules, which can

strongly affect the supramolecular behaviour [38]; therefore, an initial conformational analysis was performed. The conformational space of the molecules was scanned by means of the Conformers Calculation Module in Materials Studio [41] using a systematic grid scan search method and optimising the molecular structures for each set of dihedral angles. Calculations of the stability of the different conformers in vacuum were repeated at *ab-initio* level with the Gaussian09 code [42] using DFT+D and the hybrid B3LYP functional (including the D3 Grimme dispersion term); a 6-311G++(d,p) basis set was employed.

As in our previous works [32,37,33], the molecular structures and packing of the different ephedrine derivatives and their interactions with the AFI framework were described with the cvff forcefield [43]. The AFI structure was kept fixed during the calculations. These molecular-mechanics calculations were performed using the Forcite module, as implemented in Material Studio 7.0 [44]; all calculations were performed under periodic boundary conditions (PBC). The atomic charge-distributions of the (+1) cationic molecules were obtained from DFT+D calculations, using the B3LYP hybrid functional and the ESP charge calculation method, setting the total net charge to +1. The framework charges were initially fixed to -1.2 for O, 3.4 for P and 1.4 for Al. The positive charge of the ephedrine derivatives was compensated by the framework by uniformly reducing the Al atomic charge until neutrality. Depending on the packing value (in terms of number of SDA molecules per AFI unit cell), different AFI supercells were used (4 molecules in 1x1x3 or 1x1x4 AFI supercells for packing values of 1.33 and 1.0 molecules/u.c., respectively). The molecules were manually docked in the required configuration and geometry optimized; the most stable configuration was then obtained by simulated annealing calculations (NVT ensemble). The interaction energies were calculated by subtracting the energy of the molecules in vacuum to the total energy

of the systems; interaction energies are reported in kcal/mol. Dimerisation energies (per molecule) are expressed as the difference between the interaction energy when the molecules are arranged as dimers (with a packing value of 1.33) or as monomers (with a packing value of 1.0).

3. Results and Discussion

A. Structure-directing effect of ephedrine derivatives towards the Mg-AFI structure.

EPH, MeEPH and DMeEP were employed as SDAs for the synthesis of Mg-doped nanoporous aluminophosphates for various Mg contents (0.11 and 0.22 in molar composition) and crystallization temperatures (140, 160 and 180 °C). Mg-AFI materials (MgAPO-5) were identified in all the solids prepared, although some other phases appeared in particular cases; XRD patterns of the samples obtained with EPH, MeEPH and DMeEP are reported in the Supporting Information in Figures S1, S2 and S3, respectively; phase selectivity results are reported in Table S1. MgAPO-5 (AFI-type structure) was the major phase in all the obtained materials. Minor amounts of the dense AIPO-trydimite phase (T) were also observed in some cases, especially for low concentrations of Mg (0.11).

When using EPH as the SDA (Figure S2) with low Mg content (0.11), apart from MgAPO-5 as the major phase, a low-dimensional-type material (L) with a characteristic diffraction at ~ 4.5 was observed as an impurity at all temperatures (though its intensity decreases with higher temperatures); such diffraction was slightly shifted towards lower angles upon an increase of the crystallization temperature. In addition, very minor amounts of AIPO-C (a dense hydrated aluminophosphate) and AIPO-trydimite were also observed. These competing phases disappeared when the Mg content was increased to 0.22 (except at 140 °C where a minor presence of the low-dimensional phase was still

present), giving place to pure and very-crystalline MgAPO-5 materials (see Figure S5 in the Supporting Information for SEM pictures). These results evidenced the strong ability of EPH to direct the crystallization of MgAPO-5, and the preference of this phase to crystallize under high Mg contents.

When MeEPH was used as SDA, the crystallization of MgAPO-5 was much more difficult (Figure S3). Low-crystalline MgAPO-5 was obtained with the low Mg content of 0.11, and accompanied with competing dense phases AlPO-C (especially at 140 °C) or AlPO-tridymite (especially at 180 °C). Crystallization of the AFI phase was enhanced when the amount of Mg was increased to 0.22, though still competing crystalline phases (APC and ATS) were observed at 140 and 160 °C. Instead, the unique conditions that afforded MgAPO-5 as the sole crystalline phase with this SDA involved high Mg content and high (180 °C) temperature. Nevertheless, SEM (Figure S5) revealed that MgAPO-5 was accompanied by amorphous material.

Finally, the quaternization of ephedrine to give the quaternary ammonium cation (DMeEP) facilitated the crystallization of the AFI framework, since in this case crystalline MgAPO-5 materials were obtained both with low and high Mg contents at 140 and 160 °C (Figure S4); samples obtained with both Mg contents at 160 °C were highly pure and crystalline (Figure S5). However, apart from MgAPO-5, some other crystalline phases were observed with both Mg contents at the high temperature of 180 °C. These new phases were identified as AlPO-20 (SOD) and AlPO-EN (AEN), and are typically obtained in the presence of small molecules, such as tetramethylammonium [45] or methylamine [46], and therefore their crystallization only at high temperature points to a degradation of the DMeEP cations, being the resulting fragments responsible for the crystallization of these other frameworks. These phases were more abundant

with the low Mg content, suggesting a less favoured crystallization of AFI under these conditions, as observed with the other SDAs.

We then analysed the incorporation of the chiral organic molecules within the Mg-doped AFI framework. The organic content could not be determined by CHN analysis since the strong acidity and large crystal size of the samples did not allow a complete combustion of the organic matter during the CHN analysis. Therefore, we performed TGA of the different samples (a selection of TGAs of AFI samples is shown in Figure 2). A first weight loss from room temperature up to 215 °C was observed in all the samples, which corresponds to desorption of water; the high dehydration temperature of these samples is a consequence of the strong interaction with the negatively-charged Mg defects and/or the large crystal size. The amount of occluded water was much higher for the samples obtained with MeEPH (5.86 %) than that of the materials obtained with EPH (3.06 %) or DMeEP (2.67 %). The organic molecules were removed from 215 up to almost 900 °C, in different desorption steps depending on the molecule. The first weight loss at around 270 °C (for samples obtained with EPH and MeEPH) must correspond to desorption of the molecule (after deprotonation) (taking into account the boiling point of ephedrine of 255 °C); this desorption occurs at higher temperatures for DMeEP, possibly because it already involves a degradation. Two other strong weight losses were observed at ~500 and 700-800 °C, corresponding to oxidative combustion of the organic matter. In contrast with the observed water contents, the organic contents followed the opposite trend, being higher for the materials obtained with EPH (12.26 %) and DMeEP (12.83 %) than with MeEPH (7.08 %). SEM pictures (Figure S5) showed that the samples obtained with EPH and DMeEP are pure MgAPO-5; hence, it becomes clear that MgAPO-5 materials obtained with EPH and DMeEP were filled with organic molecules, with a higher packing value for EPH (1.3 EPH/u.c.) than for DMeEP (1.1

DMeEP/u.c.); 2.9 and 2.6 H₂O/u.c. (for EPH and DMeEP samples, respectively) are additionally occluded, probably in the 6-MR channels. In contrast, the sample obtained with MeEPH incorporated a lower amount of organic molecules and a higher water content. This was ascribed to the amorphous material accompanying the AFI phase in this sample (Figure S5), suggesting that this amorphous material was rich in water but poor in organics.

¹³C CP MAS-NMR was used to analyze the resistance of the molecules to the hydrothermal treatment and their incorporation within the MgAPO-5 solids (Figure 3). MgAPO-5 obtained with EPH (black line) showed the characteristic resonances of EPH at 11 ppm (CH₃C), 32 ppm (CH₃N), 62 ppm (CHN) and 73 ppm (COH), and several bands between 120 and 140 corresponding to the aromatic C atoms. The sample obtained with MeEPH (red line) showed bands at 9 ppm (CH₃C), 44 ppm ((CH₃)₂N), a broad band between 60 and 80 ppm which included (CHN) and (COH), and several bands between 122 and 142 characteristic of the aromatic C atoms. These results evidenced the resistance of these amines, EPH and MeEPH, to the harsh conditions of the hydrothermal treatment at 180 °C and their integral incorporation in the framework. MgAPO-5 obtained with DMeEP showed the characteristic resonances of this cation at ~10 ppm (CH₃C), 53 ppm ((CH₃)₃N), 72 (COH) and 77 ppm (CHN), as well as the typical aromatic bands at 126 (ortho-C), 130 (meta- and para-C) and 140 ppm (substituted aromatic C), evidencing the incorporation of DMeEP in the material. Worth is noting the presence of two differentiated bands around 10 ppm, at 13 and 7 ppm; the occurrence of the two bands could be ascribed to different arrangements of the DMeEP molecules within the AFI channels, giving place to distinct signals of the CH₃C terminal C. Another explanation would be that the signal at 13 ppm is due to a minor presence of some non-identified degradation products. Besides, an additional signal is observed at

45 ppm; trimethylamine (with a typical resonance at 46 ppm) would be the product of the Hofmann degradation of DMeEP, and hence this signal at 45 ppm could be assigned to a partial degradation of the SDA. In an attempt to clarify the origin for these additional signals at 13 and 45 ppm, we collected the ^{13}C CP MAS NMR spectra of other samples obtained with DMeEP at 140, 160 and 180 °C (Figure S6 in the Supporting Information); similar bands (~10, 53, 72, 77 and around 130 ppm) coming from the presence of DMeEP are observed, evidencing the incorporation of the integral SDA. Nonetheless, sample DMeEP-0.22Mg-140, prepared at a lower crystallization temperature, where degradation of DMeEP is expected to be lower, did not show the band at 45 ppm, evidencing that this was indeed due to trimethylamine from degradation of DMeEP. However, the band at 13 ppm was still present, suggesting that the two bands at 7 and 13 ppm are indeed due to the terminal methyl group, possibly in different conformations. Sample DMeEP-0.22Mg-160 showed the additional band slightly shifted (47 ppm) with respect to DMeEP-0.11Mg-160 and with a higher intensity (note however that these are ^{13}C CP NMR, and therefore intensities are not directly comparable). When the crystallization temperature was increased to 180 °C, where XRD showed the presence of SOD and AEN phases which pointed to a degradation of the SDA, several new bands were observed at 45, 47, 49 and 58 ppm, apart from the DMeEP typical bands. The occurrence of these bands at higher temperatures in samples which lead to denser phases is again due to the presence of degradation products (through Hofmann elimination and/or other reactions) like trimethylamine (45-49 ppm) or even tetramethylammonium (58 ppm) (after transalkylation reactions; we note here that prior to this work we had already unambiguously observed the presence of tetramethylammonium from degradation of DMeEP during zeolite syntheses). Instead, the two bands at 7 and 13 ppm have in all

the samples the same position and intensity regardless of the crystallization temperature (and hence of the degree of degradation of DMeEP), evidencing that they are due to $\underline{\text{CH}_3\text{C}}$ of DMeEP in different configurations.

^{31}P MAS-NMR (Figure 4) showed the incorporation of Mg within tetrahedral positions of the AlPO network because of the presence of a resonance at -24 ppm, corresponding to P(1Mg,3Al) tetrahedral environments, in addition to the P(4Al) resonance at -30 ppm [47]. The sample obtained with MeEPH (0.22Mg at 180 °C) (Figure S7 in the Supporting Information) showed additionally two intense resonances at -18 and -13 ppm with too high intensities that ruled out their origin from the AFI materials, but rather they must come from the amorphous material accompanying the solid (P in low degree of condensation). Hence we focus on the most pure and crystalline samples obtained with EPH and DMeEP (Figure 4). MgAPO-5 materials obtained with EPH (at 180 °C) showed the two bands at -30 and -24 ppm, with a notably higher incorporation in the sample with higher Mg content in the gel (0.22Mg); however, no bands characteristic of P(2Mg,2Al) or P(3Mg,1Al) environments were observed. In contrast, samples obtained with DMeEP (at 160 °C) showed, apart from the 30 and -24 ppm bands, resonances at -17 (P(2Mg,2Al)) and -10 ppm (P(3Mg,1Al)). Again a higher Mg incorporation was found for the sample obtained with a higher content in the gel (0.22Mg). Worth is noting the difference observed between samples obtained with the primary amine (EPH) or the quaternary ammonium (DMeEP). In the former case, only one type of Mg incorporation was observed (P(1Mg,3Al)); in contrast, samples obtained with DMeEP led to P(2Mg,2Al) and even P(3Mg,1Al) environments; this different behavior could be ascribed to the minor presence of trimethylamine after a partial degradation of DMeEP, as evidenced by ^{13}C CP MAS NMR, which could increase the

incorporation of Mg due its small size (high charge/volume ratio leading to a high charge density in the framework).

SEM pictures of the pure MgAPO-5 samples (Figure S5 in the Supporting Information) showed the typical crystal morphology of Mg-AFI materials, with very large hexagonal prisms. Samples obtained with DMeEP at 160 °C with both Mg contents as well as with EPH at 180 °C with 0.22Mg were highly pure. AFI crystals obtained with 0.22Mg with MeEPH were much larger (~115 μm) than those with EPH (~35 μm) or DMeEP (~30 μm), possibly associated to a more difficult nucleation in the presence of this molecule, in agreement with the presence of amorphous unreacted material in this sample. As previously mentioned, crystals of the sample obtained with DMeEP with low Mg content in the gel were smaller (~13 μm) than those with high Mg content.

B. Aggregation of ephedrine derivatives within Mg-AFI materials

UV-Visible fluorescence spectroscopy was used to monitor the formation of supramolecular aggregates (Figure 5) [28,37,38]. Phenyl-containing molecules arranged within the solids as monomers gives rise to an emission band with a vibronic structure centered around 280 nm after excitation at the first absorption band at around 260 nm; when these molecules form supramolecular aggregates through π - π interactions of their aromatic systems, there is a rearrangement of the π electronic levels that involves a red-shift to higher wavelengths. In the fluorescence spectra of our materials, we observed bands below 350 nm, which were assigned to the SDAs arranged as monomers, and two differentiated bands above 350 nm, centered at 370 and 430 nm, assigned to supramolecular dimers of the molecules, although the origin for the two distinct bands is not clear at the moment.

We first analyzed the fluorescence results for the materials obtained with EPH (Figure 5-top). As already observed in our previous work [37], an increase of the crystallization

temperature involved a progressive decrease of the relative intensity of the monomer band and an increase of the band associated to dimers; this occurred with samples obtained both with low and high Mg contents. Furthermore, lower Mg contents led to a stronger aggregation of EPH. Nevertheless, EPH molecules were mostly aggregated in both samples obtained at 180 °C, where fluorescence of monomers was hardly noticed.

In contrast, a much stronger presence of monomers was observed in samples obtained with MeEPH as SDA (Figure 5-middle). As for EPH samples, again we observed an increase of the bands associated to supramolecular dimers upon an increase of the crystallization temperature, as well as upon a decrease of the Mg content in the gels. Nonetheless, aggregation of MeEPH molecules confined within the AFI materials was much weaker compared to EPH. For instance, the sample obtained with low Mg content at 180 °C, which showed a high aggregation with EPH, in this case showed the presence of both aggregates and monomers. Furthermore, the sample obtained also at 180 °C but with a higher Mg content showed a major presence of monomers, although dimers were also observed, in contrast with the corresponding sample with EPH which showed a very strong aggregation of the confined SDA molecules.

Finally, fluorescence spectra of AFI materials obtained with DMeEP are shown in Figure 5-bottom. In line with MeEPH results, the attachment of an additional methyl group in the SDA involved a reduction of the supramolecular aggregation of the molecule. In this case, all samples displayed a major presence of monomers. If we compare samples obtained at 160 or 180 °C with high Mg contents (which consist mostly of MgAPO-5), we observe a much weaker aggregation for those obtained with DMeEP than with EPH.

The aggregation of the materials was also studied by UV absorption spectroscopy (Figure S8 in the Supporting Information). In this case, the presence of aggregates was

evidenced by the appearance of a shoulder between 300 and 500 nm, which was red-shifted with respect to the main absorption of the phenyl ring (at ~260 nm). Although not so evident as in fluorescence results, similar conclusions can be drawn from absorption spectra: a stronger aggregation behavior is observed for samples obtained with the bare molecule, EPH, especially those prepared at 180 °C.

Our experimental results so far indicate that the three molecules are able to direct the crystallization of the Mg-doped AFI framework; however, a notably lower structure-directing ability is observed for MeEPH. On the other hand, the progressive attachment of methyl groups on the N atom of ephedrine involves a progressive reduction of the supramolecular aggregation of the SDA molecules when confined within the 12-MR channels of the AFI framework. Furthermore, the hydrothermal stability of DMeEP has been found to be lower than those of EPH and MeEPH.

C. DFT Conformational analysis of ephedrine derivatives

In our previous work [38] we observed that the conformational space of (1R,2S)-(-)-ephedrine and (1S,2S)-(+)-pseudoephedrine, which is in turn controlled by the formation of intramolecular H-bonds, determines the supramolecular aggregation of these molecules in water, and as a consequence, within the nanopores of AFI materials. Due to the presence of H-bond acceptor and donor groups in the ephedrine derivatives, an analysis of the conformational space of these molecules in vacuum was performed; the relative energies of the different conformers were calculated at the DFT/B3LYP+D3 level (see Table 1). The three most stable conformers for each cation are displayed in Figure 6.

The conformational space of EPH is dominated by the development of intramolecular H-bonds between the protons attached to the N atom of the amino group and the O atom of the hydroxyl group (Figure 6-top). The three most stable conformers involve the

presence of these H-bonds; A and B conformers, which are related by a 120° rotation around the bond between the two stereogenic centers, are in an extended configuration, while conformer C is in a folded conformation and is less stable, probably due to steric repulsions between the methyl group and the aromatic ring. Conformers D, E and F (Figure S9 in the Supporting Information) are much less stable since the relative orientation of the N-H bonds does not allow any intramolecular H-bond with the hydroxyl group.

The conformational space of N-methyl-ephedrine is also dominated by the formation of similar intramolecular H-bonds, although in this case the H-bond possibilities are reduced since there is only one H-bond-donor group. The two most stable conformers, A and B, also involve the development of intramolecular H-bonds (Figure 6-middle). Conformers C (and H) do not have H-bonds, but are instead stabilized by interactions between the H(N) atom and the π -electron density. The rest of conformers (D, E, F and G) are less stable again because of the lack of intramolecular H-bonds.

Finally, the lack of H-bond donor atoms in DMeEP involves that the conformational space of this molecule is only determined by steric interactions, and as a consequence only three different conformers (stable in the potential energy surface) were found, two of them (A and B) being clearly more stable than C (Figure 6-bottom). In sum, these results indicate that the conformational behaviors of EPH and MeEPH are determined by the formation of intramolecular H-bonds, whilst that of DMeEP is only governed by steric interactions.

D. Molecular simulations of ephedrine derivatives within the AFI framework.

We finally studied the incorporation of the three molecules in the different supramolecular arrangements (as monomers or as dimers) confined within the 12-MR of the AFI framework. Dimers were studied in principle under a packing value of 1.33

molecules per u.c., by loading 4 molecules (arranged as dimers) in 1x1x3 AFI supercells. Instead, the arrangement of these molecules as monomers did not allow such a high packing value because of steric repulsions, and in this case a lower packing value of 1.0 molecules per u.c. was used by loading 4 molecules (without π - π overlapping) in 1x1x4 AFI supercells. We should remark here that the interaction between the negative charge of localized Mg dopants and the organic molecules is not taken into account in our model (since the negative charge associated to Mg is modelled as a uniform charge-background, representing a random distribution of Mg). The interaction energies (reported in Table 2) are expressed as energies per molecule, which provides an estimation of the comfortability of the molecules under a particular supramolecular arrangement and packing value. The most stable arrangement for the molecules as dimers (packing of 1.33) or monomers (packing of 1.0) are given in Figures 7 and 8, respectively.

The arrangement of EPH molecules as dimers (Figure 7-top) gave an interaction energy (per molecule) of -120.0 kcal/mol, while when they arrange as monomers (Figure 8-top) the energy was higher (meaning more negative) (-127.5 kcal/mol) (Table 2), giving a dimerization energy (defined as the energy difference between the dimer and monomer arrangements) of 7.5 kcal/mol per molecule. The higher stability of EPH monomers is associated to a lower electrostatic repulsion between the positively-charged EPH molecules under the lower packing of 1.0; indeed, the distance between positively-charged N atoms in the monomer configuration is 8-9 Å, whilst this distance between N atoms in the dimer interface is ~4 Å (and ~11 Å between N in the same dimer). However, the space-filling of the AFI channels under the monomer configuration was of course lower, and if we normalize the interaction energy per molecule, as a measure of the molecular comfortability, to interaction energy per unit cell, as a measure of the

density of interaction energy, we observed a much higher interaction of EPH dimers (-160.0 kcal/mol, packing of 1.33 EPH/u.c.) than of monomers (-127.7 kcal/mol, packing of 1.0 EPH/u.c.). These energy trends suggest that in principle, EPH molecules should arrange as monomers or dimers depending on the synthesis conditions, which is experimentally confirmed since both types of arrangements were observed in MgAPO-5 materials obtained using EPH as SDA, synthesis conditions, which is experimentally confirmed since both types of arrangements are observed in MgAPO-5 materials obtained using EPH as SDA, depending on the synthesis conditions used during the crystallization of the framework, and hence on thermodynamic and also kinetic factors. For instance, MgAPO-5 materials with EPH molecules arranged as dimers were only obtained at high crystallization temperatures (180 °C, see Figure 5) and high EPH concentrations (1EPH:50H₂O) [37]. The higher molecular comfortability of the monomer arrangement is associated to the lower packing value (1.0) which reduces the electrostatic repulsion between closely-located net positive charges; in this arrangement, EPH monomers are stabilized by the development of intra-molecular (but not intermolecular) H-bonds (Figure 8-top). Under the dimer supramolecular arrangement (Figure 7-top), strong inter-molecular H-bonds between H(N) and O atoms of consecutive dimers are established, as illustrated in detail in Figure 7-top (right). This molecule in particular allows for such special inter-dimer H-bond connection which stabilizes the formation of dimers and balances the electrostatic repulsion caused by the occurrence of two closely-located positively-charged ammonium groups in the dimer configuration.

The stability of MeEPH molecules under the dimer arrangement (1.33 MeEPH/u.c., Figure 7-middle) was much lower, with an interaction energy of -112.6 kcal/mol (Table 2); in contrast, in this case the monomer arrangement (Figure 8-middle) was much more

stable, giving an interaction energy of -130.5 kcal/mol; the calculated dimerization energy was much higher than for EPH, of 17.9 kcal/mol per molecule. The low stability of MeEPH dimers is associated, on the one hand, to the steric repulsion caused by the incorporation of an additional methyl group under such a high packing of 1.33 (Figure 7-middle); on the other hand, this methyl group prevents the establishment of the particularly stable double-H-bond interface between consecutive dimers as occurred for EPH, hence notably reducing the stability of MeEPH dimers. In contrast, MeEPH molecules are much more comfortable under a monomer arrangement (Figure 8-middle), where all the molecules are periodically arranged in the same position stabilized by the formation of non-sterically-impeded intramolecular H-bonds.

The addition of a second methyl group in DMeEP involved again a very low stability of the dimer arrangement (Figure 7-bottom) under the high packing value of 1.33, giving an interaction energy of -114.8 kcal/mol; again the arrangement of these molecules as monomers (Figure 8-bottom) under a lower packing was much more stable, with an energy of -135.2 kcal/mol, resulting in a very high dimerization energy of 20.4 kcal/mol (Table 2). The low stability of DMeEP dimers confined within the AFI channels is again due to the steric repulsion caused by the attachment of a second bulky methyl group, and in this particular case by the lack of H-bond donor groups and hence the non-occurrence of stabilizing inter-dimer H-bonds (Figure 7-bottom). DMeEP molecules are much more comfortable under the monomer arrangement (Figure 8-bottom), where they arrange periodically in a very similar configuration as MeEPH monomers, where no close-contacts between the methyl groups of adjacent molecules occur.

The low stability of MeEPH and DMeEP dimers are a consequence of the steric repulsion between the methyl groups of the highly-packed molecules under the packing of 1.33. The only possibility of forming dimers with these molecules would involve a

longer distance between consecutive dimers to avoid such steric repulsions, i.e. a lower packing value. For this reason, we also analyzed the stability of these MeEPH and DMeEP dimers under a packing value of 1 molecule per u.c. (by loading 4 molecules, 2 dimers, in a 1x1x4 AFI supercell, see Figure S10 in the Supporting Information). The interaction energies (per molecule) were in this case -121.7 and -129.7 kcal/mol for MeEPH and DMeEP, respectively, which were larger than the corresponding energies in the dimer configuration under a packing of 1.33 (-112.6 and -114.8 kcal/mol). However, even despite the lower packing of 1.0, the monomer configuration is still more stable (-130.5 kcal/mol and -135.2 kcal/mol for MeEPH and DMeEP, respectively) than the supramolecular arrangements for these two molecules, providing an explanation for the experimental observation about the low presence of dimers in AFI materials obtained with these molecules.

Conclusions

Our combined experimental and computational study has allowed us to understand the effect of adding subsequent methyl groups to (1R,2S)-(-)-ephedrine derivatives on their supramolecular chemistry when confined within the 12-MR channels of the AFI framework. The synthesis and characterization of the Mg-AFI materials clearly suggest that the three molecules are able to direct the crystallization of the AFI framework, being the monomethyl-derivative MeEPH, the least efficient structure-directing agent towards the AFI framework. Fluorescence spectroscopy clearly shows that while EPH molecules can arrange as monomers or dimers within the 12-MR channels of the AFI framework, depending on the synthesis conditions (dimers are only the most abundant species when the crystallization temperature is the highest, 180 °C), the addition of subsequent methyl groups to give MeEPH and DMeEP provokes a notable reduction of

the formation of supramolecular aggregates. Besides, a lower stability of the quaternary ammonium DMeEP during the hydrothermal treatment has been observed.

Our computational study shows that the conformational space of these molecules is governed by the development of intramolecular H-bonds, causing strong differences in the conformational behavior upon the addition of methyl groups. The study of the packing of the molecules within the AFI channels shows that the monomer configuration is always more stable since it involves a lower electrostatic repulsion between the positively-charged ammonium groups. However, the formation of EPH dimers is favored by the development of a particular strongly-stabilizing interface between consecutive dimers where two intermolecular H-bonds are established between H(N) and O atoms; this particular arrangement is not possible for MeEPH due to steric repulsions, and possibly also to the presence of only one (rather than two in EPH) H(N) atom, and neither for DMeEP due to the lack of H-bond donor groups and to steric repulsions.

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Supporting Information

Additional synthesis results, XRD, ^{13}C and ^{31}P MAS-NMR, SEM, UV-Vis Absorption and molecular pictures are reported as Supporting Information.

Tables

Table 1. Relative energies (with respect to the most stable conformer) of the different conformers (in kcal/mol), as calculated by DFT/B3LYP+D3 and CVFF, and the occurrence of intramolecular H-bonds.

Molecule	Conformer	B3LYP+D	Intramolecular H-bond
EPH	A	2.6	Yes
	B	0.0	Yes
	C	2.9	Yes
	D	4.4	No
	E	6.3	No
	F	5.3	No
MeEPH	A	0.0	Yes
	B	2.1	Yes
	C	2.1	No
	D	4.4	No
	E	5.8	No
	F	6.1	No
	G	4.4	No
	H	2.2	No
DMeEP	A	2.5	---
	B	0.0	---
	C	4.1	---

Table 2. Different systems studied under distinct supramolecular arrangements, and their corresponding interaction energies (given in kcal/mol per molecule, as a measure of the molecular comfortability); dimerization energy is calculated as the difference between dimer (at packing of 1.33) and monomer (packing of 1.00) interaction energies.

Molecule	Arrangement	Packing	Int. E. per molecule	Dimerization E
EPH	Dimer	1.33	-120.0	7.5
	Monomer	1.00	-127.5	
MeEPH	Dimer	1.33	-112.6	17.9
	Monomer	1.00	-130.5	
DMeEP	Dimer	1.33	-114.8	20.4
	Monomer	1.00	-135.2	

Figures

Figure 1. Molecular structure of the chiral molecules used as SDAs in this work.

Figure 2. TG and DTG of pure MgAPO-5 samples obtained with a high Mg content with the different molecules.

Figure 3. ^{13}C CP MAS NMR of representative samples obtained with the different SDA molecules.

Figure 4. ^{31}P MAS NMR of samples obtained with EPH (black) or DMeEP (blue) with high (dashed lines) and low (solid lines) Mg contents.

Figure 5. UV-Visible Fluorescence spectra of samples obtained with EPH (top), MeEPH (middle) and DMeEP (bottom), with 0.11 (left) or 0.22 (right) Mg contents in the gel, at crystallization temperatures of 140 (black), 160 (red) and 180 (blue) °C.

Figure 6. Most stable conformers (calculated at the DFT/B3LYP+D3 level) of EPH (top), MeEPH (middle) and DMeEP (bottom); the rest of conformers are reported in the Supporting Information (Figure S9).

Figure 7. Arrangement (after simulated annealing) of EPH (top), MeEPH (middle) and DMeEP (bottom) cations as dimers under a packing of 1.33 SDA/u.c.

Figure 8. Arrangement (after simulated annealing) of EPH (top), MeEPH (middle) and DMeEP (bottom) cations as monomers under a packing of 1.0 SDA/u.c.

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