Supramolecular Chemistry Controlled by Conformational Space during Structure- Direction of Nanoporous Materials: Self- Assembly of Ephedrine and Pseudoephedrine

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Abstract. In an attempt to produce chiral solids, where chirality arises from an asymmetric ordering of the spatial distribution of dopants, we have studied the supramolecular aggregation by π - π type interactions between aromatic rings of two closely related diastereoisomers, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, during structure-direction of the microporous AFI large-pore aluminophosphate framework. Despite their very similar molecular structure, only differing in the stereochemistry of the hydroxyl substituent, fluorescence spectroscopy clearly shows a completely different aggregation behavior of the two isomers, with ephedrine displaying a much stronger aggregation trend than pseudoephedrine in aqueous solution; interestingly, this supramolecular behavior is reproduced when the molecules are occluded within the AFI framework during crystallization. A molecular-mechanics study of the conformational behavior of the two chiral flexible molecules, both in vacuum and in aqueous solution, revealed that the lower trend of pseudoephedrine to form supramolecular aggregates is caused by the occurrence of a particular conformation with a folded molecular structure. Such conformation, which is stable for pseudoephedrine but not for ephedrine, provokes a steric hindrance that prevents the approaching of a neighboring molecule to form the aggregate, hence providing an explanation for the experimental observations. Our work represents the first example where the conformational space of a molecule determines its supramolecular aggregation behavior during structure-direction, and could play a role in molecular-recognition phenomena in host-guest systems.

Keywords: zeolite, ephedrine, supramolecular, self-assembly, chirality, conformation.

1. Introduction

Molecular recognition phenomena are fundamental for life. In this context, chirality is particularly crucial since life, from its origin, decided to work in an asymmetric fashion, with only certain enantiomers of the molecular building-blocks, aminoacids or sugars, making up the essential biological macromolecules, proteins and nucleic acids. Hence, molecular recognition of asymmetric (chiral) molecules is vital in living organisms; indeed, different enantiomers of the same molecular compound usually lead to a different biological response depending on their absolute configuration, with only one enantiomer having the desired therapeutic effect, and the other one being less-active, inactive or even harmful. Therefore, a fundamental area of research in contemporary chemistry is the quest for materials that can perform enantioselective operations, being asymmetric catalysts or adsorbents, so that one can have only the desired enantiomer of the targeted compound.¹

In this context, current trends in green chemistry suggest the use of solid materials that can easily be recovered as supports for the production of enantioselective materials.² Indeed, it was soon recognized that chiral solid materials such as enantiopure crystals of quartz were able to transfer their chirality to a particular separation/catalytic process and perform enantioselective operations.³ One of the main candidates to achieve enantioselective heterogeneous catalysts/adsorbents is represented by crystalline microporous (zeolite-type) materials, since they can combine their characteristic molecular shape-selectivity and hydrothermal stability with a potential enantioselectivity.⁴⁻⁷ Among the different ways of inducing chirality in these materials, such as the anchoring of chiral additives or the immobilization of homogeneous chiral catalysts,⁸ the production of intrinsically chiral frameworks, where chirality is directly imprinted into the inorganic network, is preferred.⁹ Indeed, several zeolite-type chiral

frameworks do exist, as was reported in polymorph A of zeolite BEA¹⁰ or the chiral zincophosphate CZP;¹¹ interesting examples have been recently discovered, including the mesoporous chiral ITQ-37 zeolite¹² and HPM-1,¹³ the silica-form of the chiral SU-32 silicogermanate,¹⁴ and a Beta zeolite partially enriched in polymorph A.¹⁵ In fact, the chiral nature of several zeolites has been recently recognized, and calorimetric measurements suggest a potential use for chiral discrimination.¹⁶ However, the main drawback associated to these chiral microporous materials for their application in enantioselective operations is that they almost invariably crystallize as racemic mixtures, with crystals in both enantiomorphic forms (racemic conglomerates). Homochirality during synthesis of microporous materials is very rarely found, although some examples do spontaneously (and normally unpredictably) occur through chiral symmetry breaking effects.^{17,18} An interesting strategy to achieve a certain enantio-enrichment of chiral zeotype racemic crystals has been developed by using nucleotides as chiral inductors,¹⁹ although extension of this strategy to other systems is difficult to envisage. Therefore, the great challenge here is not only to produce chiral microporous frameworks, but to do so in an asymmetric fashion so that crystals in only one absolute configuration grow.

Zeolite frameworks are built from achiral tetrahedral TO₄ units, and therefore their potential chirality comes from the long-range asymmetric arrangement of these units to compose the framework, usually in the form of helicoidal channels.⁹ When thinking in how to induce chirality during the hydrothermal synthesis of these materials, one first looks at the organic molecules that are usually added to the synthesis gels. These molecules, typically referred to as structure-directing agents (SDA) or templates, organize the inorganic units into a particular geometry around themselves, leading the crystallization pathway towards a particular framework type.²⁰ In this context, the most

straightforward strategy to induce chirality would be the use of chiral molecules as SDAs, in an attempt to induce an asymmetric environment around the molecule that prompts a transfer of the chirality from the molecular component into the inorganic framework that crystallizes around. However, although chiral molecules have effectively directed the crystallization of different frameworks,⁶ even some of them being chiral,¹² failure of such a transfer of chirality was evident from the fact that racemic conglomerates invariably crystallized. This must be probably associated to the typical lack of strong and localized non-bonded interactions between the organic SDA molecules and the oxide inorganic networks. Indeed, the important role of H-bonds during the transfer of chirality to an inorganic chiral framework was recognized by Yu and coworkers.²¹

In an attempt to overcome such problems during transfer of chirality, we have recently proposed a new concept of chirality in microporous frameworks, which consists in a chiral order of the dopants embedded in zeolite frameworks. Our purpose is not to obtain chiral frameworks with helicoidal channels where all the atoms are arranged in a helicoidal fashion, but frameworks where only dopants are chirally ordered.^{22,23} We believe this should be more easily achievable since in frameworks where low-valent dopants replace trivalent atoms by isomorphic substitution (typically Al^{+3} for Si^{+4} in zeolites or M^{2+} for Al^{3+} in aluminophosphates, with $\text{M} = \text{Mg}, \text{Co}, \text{Zn}$, preferentially), a negative charge is generated in the network that is compensated for by the positive charge of the organic molecule employed as SDA, and hence a strong and localized electrostatic interaction between both net charges is established, especially when using protonated amines as SDAs where the positive charge is well-localized on the protons bonded to N atoms. As a consequence, such a strong and localized interaction might lead to a direction over the spatial incorporation of dopants by the

SDA molecules, as was observed during the synthesis of ferrierite with secondary amines,²⁴ thus potentially enabling a transfer of chirality from the SDA molecules to the spatial distribution of dopants.

In this context, we emphasize that typical organic molecules act as SDA in an individual fashion, in the sense that no self-assembly between the SDA molecules occur when occluded within a particular framework. Such individual (non-connected) SDAs are incompatible with a potential long-range ordering of the incorporation of dopants (relative to each other), since each SDA would direct the incorporation of a single dopant but there would be no connection in the relative distribution between different dopants. For an ordered (chiral) distribution of dopants to occur, the organic molecules have to be supramolecularly connected in some way in order to transfer such feature to the spatial relative distribution of dopants. As a consequence, the SDA molecules to be used need to have the ability to self-assemble within the nascent microporous framework, and at the same time develop a strong interaction with the negative charge associated to the incorporation of dopants.

One of the most common driving-forces for the self-assembly of organic molecules in aqueous media, as the synthesis of microporous materials usually takes place, is the establishment of π - π type interactions between aromatic rings, leading to π - π stacked supramolecular aggregates.²⁵ On the other hand, the most common driving-force for molecular-recognition phenomena is the development of intermolecular H-bonds; the possibility of forming H-bonds would in principle enhance a potential supramolecular ordering among the SDA molecules occluded within nanoporous frameworks. Based upon these grounds, we have selected the chiral flexible molecules (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine (Figure

1) as SDAs for the synthesis of Mg-doped aluminophosphate (AlPO) nanoporous frameworks. AlPO networks have been selected since these materials crystallize more effectively in the presence of protonated amines at low pHs. Ephedrine and pseudoephedrine are alkaloid molecules found in nature,²⁶ specifically in the Ephedra species of plants, with biological activity on the sympathetic nervous system, although their pharmacological behavior differs as a function of their absolute configuration. These isomers have been rationally selected as SDAs based on i) the presence of aromatic rings which enable a supramolecular self-assembly through π - π type interactions, ii) the presence of two stereogenic centers that impart a strong asymmetric nature to the molecule, iii) the presence of flexible -NH_x and -OH groups susceptible of developing inter/intra-molecular H-bonds, and iv) the presence of NH_x⁺ groups that may lead to a strong and localized electrostatic interaction with dopants, hence potentially driving the spatial distribution of dopants during crystallization of the framework.²⁷ The rationale behind the choice of these chiral SDA molecules is that if they form supramolecular aggregates (dimers) during the crystallization of the framework, then these aggregates will also be chiral, and they will drive the connected incorporation of at least 2 dopants (one for each molecule composing the dimer) possibly in a chiral fashion (relative to each other) following the asymmetric nature of the aggregate.

In a recent work, we demonstrated that (1R,2S)-ephedrine directs the crystallization of the AFI aluminophosphate (AlPO) framework in the presence of different dopants, displaying a strong trend to self-assemble when occluded within the framework;²⁸ the AFI framework is composed by 12-membered-ring one-dimensional channels with a large-pore size of 7.3 Å. In addition, a computational study suggested that ephedrine

dimers tend to develop a helicoidal ordering within the AFI channels, where consecutive dimers are rotated by an angle of $+30^\circ$; interestingly, a strong interaction between the NH_2^+ groups and the divalent dopants is established, and consequently such helicoidal supramolecular organic ordering can be transferred to a helicoidal spatial distribution of dopants.²⁷ Due to the interest in this type of chiral flexible self-assembling SDA molecules during structure-direction, in this report we analyze the supramolecular aggregation behavior of the two isomers, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, during the crystallization of the AFI framework (Figure 1-right).

Figure 1. Left: molecular structures of (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine used as structure-directing agents in this work, and definition of the rotatable bonds that define the conformational space (arrows); right: AFI structure (top) and 12-MR channels (bottom).

2. A. Experimental Details

Mg-doped AFI aluminophosphate materials were synthesized by hydrothermal methods using (1R,2S)-Ephedrine (EPH) (Sigma-Aldrich, 98 %) or (1S,2S)-Pseudoephedrine (PsEPH) (Sigma-Aldrich, 98 %) as SDAs. The gel molar composition was $1\text{SDA}:x\text{MgO}:(1-x/2)\text{Al}_2\text{O}_3:1\text{P}_2\text{O}_5:100\text{H}_2\text{O}$, where x was 0.11, 0.22, 0.27 or 0.32 (Table S1 in the Supporting Information). Pseudoboehmite (Pural SB-1 77.5% Al_2O_3 , Sasol), H_3PO_4 (Sigma-Aldrich, 85%) and $\text{Mg}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ (Sigma-Aldrich,

99.5%) were used as sources of Al, P and Mg, respectively. The gels were transferred into Teflon-lined stainless steel autoclaves with a capacity of 14 cm³, 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.

Aqueous solutions of the hydrochlorides of the SDA amines were prepared by adding equimolar amounts of the amine and HCl. In this way, 0.1, 0.01 and 0.001 M aqueous solutions were obtained and studied by fluorescence spectroscopy.

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. MAS-NMR spectra were recorded with a Bruker AV 400 WB spectrometer, using a BL7 probe for ¹³C and a BL4 probe for ³¹P. ¹H to ¹³C Cross-Polarization spectra were recorded using $\pi/2$ rad pulses of 4.5 μ s for ¹H, a contact time of 5 ms and a recycle delay of 3 s. For the acquisition of the ¹³C spectra, the samples were spun at the magic angle (MAS) at a rate of 5-5.5 kHz. For ³¹P, $\pi/2$ rad pulses of 4.25 μ s and recycle delays of 80 s were used; these spectra were recorded while spinning the samples at ca. 11 kHz.

The aggregation state of the molecules in liquid solution and in the solid samples was studied by fluorescence spectroscopy. Liquid and 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. Fluorescence spectra in liquid solution were recorded using 1 cm quartz cells.

2. B. Computational Details

Molecular-mechanics simulations were performed in order to understand from a molecular level the different supramolecular behavior of (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine molecules. Molecular structures of the organic and water molecules were described with the cvff forcefield.²⁹ Due to the strong basicity of ephedrine ($\text{pK}_a = 9.6$)³⁰ and the low pH of the synthesis medium, 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 positive charge of the EPH/PsEPH molecules was compensated by including an equal number of Cl^- anions in the simulations. The atomic charges for the O and H atoms of water molecules were -0.82 and $+0.41$, respectively.³¹

Due to the presence of rotatable bonds, and the importance of molecular flexibility when studying structure-direction and supramolecular aggregation issues,^{32,33} an initial conformational analysis was performed. The conformational space of the protonated molecules was scanned by means of the Conformers Calculation Module in Materials Studio,³⁴ 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,³⁵ using the HF-MP2 method, and using DFT+D and the hybrid B3LYP functional (including the D3 Grimme dispersion term); in both cases, a 6-311++G(dp) basis set was employed.

The aggregation behavior of the molecules in water was studied by means of Molecular Dynamics (MD) simulations, under Periodic Boundary Conditions (PBC), using the Forcite code.³⁶ 16 protonated molecules and 16 Cl^- anions were included in the

simulation cell together with 1600 water molecules (in the same ratio as in the synthesis gels). An initial equilibration period was allowed, consisting of 100 ps of MD simulations in the NPT ensemble at 25 °C. The density of the systems along this initial MD simulation was averaged, and a frame in the last steps of the MD trajectory with a density close to the averaged value was selected as the starting configuration for the subsequent NVT study. 1000 ps of MD simulations were then run, keeping the temperature constant at 298 K. Of this simulation time, the first 500 ps were assumed as the equilibration period, and only the last 500 ps of the MD simulations were used for production. The aggregation behaviour of the molecules was studied by analysing the Radial Distribution Functions (RDF) of different sets of atoms [$g_{\alpha\beta}(r)$]; concentration profiles were calculated according to the following equation:

$$n_{\alpha(\beta)}(r) = 4\pi\rho_{\beta}\int_0^r g_{\alpha\beta}(r) r^2 dr$$

where $n_{\alpha(\beta)}(r)$ is the number of β species surrounding α at less than a given distance (r), ρ_{β} is the bulk number density of atom β and $g_{\alpha\beta}(r)$ is the α - β RDF.

3. Results

A. Aggregation of EPH and PsEPH in aqueous solution

We first analyzed the supramolecular aggregation behavior of the two molecules in aqueous solutions by means of fluorescence spectroscopy. As the molecules will be protonated within the Mg-doped AFI materials in order to compensate for the negative charge associated to the isomorphic substitution of Al^{3+} by Mg^{2+} , ephedrine and pseudoephedrine hydrochlorides were studied (by adding equimolar amounts of the free amines and HCl); solutions with increasing concentrations were prepared (0.001, 0.01 and 0.1 M) and fluorescence spectra were recorded in the front-face mode (Figure 2).

Figure 2. Fluorescence spectra of ephedrine·HCl (blue lines) and pseudoephedrine·HCl (red lines) aqueous solutions of increasing concentrations (in mol/L, M)

Molecular aggregation would cause a quenching in the intensity of the monomer emission band and the observation of new emission bands in the case that the association leads to fluorescent aggregates. As observed in our previous work for EPH,²⁸ a band at 282 nm predominates at low concentrations (0.001 M), which corresponds to EPH arranged as monomers. The relative intensity of this band decreases, and a new band centered at around 360 nm appears as the concentration progressively increases to 0.01 and especially to 0.1 M, where this band predominates (Figure 2, blue lines). This is a clear indication that such fluorescence band comes from the presence of EPH aggregates, which are present at 0.01 M and are the dominant species at 0.1 M. Surprisingly, an entirely different picture is observed for PsEPH (Figure 2, red lines). In this case, a single band at 282 nm dominates in all the cases, corresponding as previously to the molecules arranged as monomers, but no fluorescence band at higher wavelengths is observed upon an increase in the

concentration, at least up to 0.1 M. The slight bathochromic shift observed in the monomer emission band with the PsEPH concentration could be assigned to reabsorption/reemission effects in high concentration samples. These results clearly indicate a much lower aggregation trend for PsEPH compared to that of EPH, in contrast to what one could expect.

B. Hydrothermal synthesis and characterization of nanoporous aluminophosphates

EPH and PsEPH were employed as SDAs for the synthesis of Mg-doped nanoporous aluminophosphates for various Mg contents and crystallization temperatures. Mg-AFI materials (MgAPO-5) were identified in all the solids synthesized (see Figure 1-right for a picture of the AFI framework), although in some cases secondary phases were also observed; phase selectivity results are reported in Table S1 in the Supporting Information (XRD patterns and some SEM pictures are displayed in Figure S1 and S2 in the Supporting Information). MgAPO-5 was the major phase in all the obtained materials. Minor amounts of the dense AlPO-tridymite phase were also often observed, especially for low concentrations of Mg; the presence of tridymite was slightly more abundant when EPH was used as SDA. At 140 °C and with low Mg concentrations, a low-dimensional phase with a low-angle diffraction at $4.6\ 2\theta$, which possessed a very high organic content, was observed only when EPH was the SDA; interestingly, such phase was never observed with PsEPH. In addition, traces of the hydrated AlPO-C (a dense AlPO network) were also observed at 140 °C and low Mg concentrations. In summary, both EPH and PsEPH effectively directed the crystallization of Mg-doped AFI materials under a wide range of conditions, although higher Mg concentrations led to more crystalline AFI materials and less secondary phases.

^{13}C CP MAS-NMR (Figure S3 in the Supporting Information) demonstrated the resistance of the molecules to the hydrothermal treatment and their integral incorporation within the AFI solids. On the other hand, ^{31}P MAS-NMR showed the incorporation of Mg within tetrahedral positions of the AlPO network because of the presence of a resonance at -24 ppm, corresponding to $\text{P}(\text{1Mg},4\text{Al})$ tetrahedral environments, in addition to the $\text{P}(4\text{Al})$ resonance at -30 ppm (Figure S4 in the Supporting Information).

Figure 3. UV-Visible fluorescence spectra of Mg-AFI materials obtained using ephedrine (blue lines) or pseudoephedrine (red lines) as SDAs at a crystallization temperature of 165 (left) or 180 (right) °C, for various Mg contents (Figure S5 in the Supporting Information includes materials obtained with a Mg content of 0.32).

C. Aggregation of EPH and PsEPH within nanoporous aluminophosphates

We then studied the aggregation state of the molecules occluded within the AFI materials (Figure 3); only solids obtained at 165 and 180 °C are included since these were more crystalline; nevertheless, similar conclusions were reached for materials obtained at 140 °C. As in the aqueous solutions, a fluorescence band centered at 282 nm

(with a vibronic structure) is indicative of the SDA molecules arranged as monomers, while red-shifted bands between 330 and 500 nm indicate the presence of supramolecular aggregates; this red-shift is caused by a reorganization of the π electronic levels due to the π - π interaction between the stacked aromatic rings in the aggregates. In all the series of materials obtained, a stronger supramolecular aggregation (lower intensity of the monomer band at 282 nm and higher intensity of the aggregates band between 330 and 500 nm) within the AFI channels was observed for EPH (Figure 3-blue lines) compared (under the same synthesis conditions) to PsEPH (red lines). Two aggregates bands are distinguished (one more intense between 350 and 400 nm and another broader less intense between 400 and 500 nm), although the origin for these two, beyond the fact that are due to aggregates, is not clear at the moment. In any case, such higher aggregation of EPH, which was reproduced in the aqueous solutions, occurs at both crystallization temperatures (165 and 180 °C), and at the different Mg concentrations. A systematic influence of the synthesis conditions over supramolecular aggregation is also appreciated: for both SDA molecules, higher temperatures (180 °C) led to a stronger aggregation of the molecules; on the other hand, supramolecular aggregation progressively decreased upon an increase in the Mg content (Figure 3; see also Figure S5 in the Supporting Information for $x = 0.32$).

D. Computational study of the aggregation behavior of EPH and PsEPH

Experimental results clearly show a much stronger trend of ephedrine to aggregate through $\pi \cdots \pi$ self-assembly compared to that of pseudoephedrine, both in aqueous solution and within the nanoporous aluminophosphate frameworks. Indeed, our observations suggest that the lower aggregation of pseudoephedrine within the AFI framework is a direct consequence of its poorer aggregation in aqueous solution. This is

rather surprising due to the very similar molecular structure of both diastereoisomers, which only differs in the relative position of the hydroxyl substituent. Indeed, one would not expect that such hydroxyl groups should play a role on the $\pi\cdots\pi$ -driven self-assembly of these molecules between the aromatic rings to form supramolecular aggregates. Thus, molecular simulations were carried out in an attempt to understand from a molecular level such notably different supramolecular behavior.

Figure 4. Stable and most relevant conformations (as calculated by cvff) of ephedrinium, and their corresponding Newman projections; A/G notation refers to the anti or gauche arrangement of the $C_{\text{arom}}\text{CCN}$ and OCCN chains, respectively.

D1. Conformational analysis in vacuum.

We first analyzed the conformational space of both molecules in vacuum; three rotatable bonds determine the conformational space (see arrows in Figure 1-left). The conformational search of protonated EPH showed the existence of 6 different conformations which are minima on the Potential Energy Surface (after Geometry

Optimisation); Figure 4 shows the four most stable ones, and their corresponding Newman projections and *A/G* (for *anti* or *gauche*) configurations (the first and second label refers to the C_{arom}CCN and OCCN chains, respectively). The two most stable conformers (A and B) correspond to configurations where the H-bond-forming groups (NH₂ and OH) are in *gauche* configuration (of the OCCN chain) since this enables the formation of an intramolecular H-bond between O(H) and H(N) atoms (in both cases with the same H(N) atom), minimizing at the same time the steric hindrance with methyl groups. These two stable conformers have an *extended* configuration of the long alkyl chain (see Figure 5-left), and are related by anticlockwise rotation of the CC bond (between the two chiral C atoms) by 120°. Indeed, the same type of *AG* configuration in an extended configuration of conformer A is also found in the crystal structure of ephedrine hydrochloride; besides, these types of *AG* and *GG* configurations were found for ephedrinium in aqueous solution by NMR studies.^{37,38} Conformer C, which is related to B by rotation of the CN bond, also has the H-bond-forming groups in *gauche* configuration to enable the formation of the same type of H-bond; however, in this case the long alkyl chain has a *folded* configuration, where the final methyl group points towards the aromatic side of the molecule (see Figure 5-left). This conformer is less stable by more than 5 kcal/mol with respect to the most stable conformer A. Conformer D has the H-bond-forming groups in *anti* configuration, thus preventing the intramolecular H-bond, resulting in a rather unstable conformation. Two other conformers were found (see Figure S6 in the Supporting Information), both without intramolecular H-bonds, also leading to very unstable conformations (with relative energies higher than 10 kcal/mol).

The conformational search for protonated PsEPH gave 6 different conformations which are minima on the PES. There are two stable conformers (A and B), whose

Figure 5. Configuration of the alkyl chain (*extended* or *folded*) (left), Van der Waals surface (middle, in blue) and potential of π - π overlapping leading to supramolecular aggregation (right) as a function of the molecular conformation. Dashed white lines indicate the structure of the long alkyl chain. H atoms have been omitted for clarity.

stability is rather similar (Figure 6) with an energy difference of only 0.1 kcal/mol.

Conformer A has an *anti-gauche* (AG) configuration for the $C_{\text{arom}}\text{CCN}$ and OCCN chains, respectively, which is similar to that of conformer A of ephedrinium, stabilized by the formation of an intramolecular H-bond with the long alkyl chain in an *extended*

configuration. However, pseudoephedrinium possesses another stable conformation, conformer B, which is stable only for this diastereoisomer (but not for EPH), with a *gauche-gauche* configuration that enables a strong intramolecular H-bond, where the long alkyl chain is in a *folded* configuration (Figure 5-left). Such type of *GG* folded conformation is very unstable for ephedrine (corresponding to EPH-C conformer, +5.8 kcal/mol). PsEPH conformer C is similar to conformer PsEPH-A where the CN bond has been rotated, leading to the formation of the intramolecular H-bond with the other H atom, resulting in a much less stable conformer. In conformer D, the OH and NH₂ groups are in *anti* configuration, preventing the formation of the H-bond, resulting in an unstable conformer. Two other much less stable conformations were found (shown in Figure S7 in the Supporting Information), with no intramolecular H-bond. Attempts to produce a conformer similar to that of EPH-B (in a *GG* configuration with an *extended* molecular structure) for PsEPH reverted in folded conformer PsEPH-B after geometry optimization. In summary, the conformational analysis of protonated ephedrine and pseudoephedrine suggests the existence of different conformers for both molecules stabilized by intramolecular H-bonds: the two most stable conformers of EPH display an *extended* configuration of the long alkyl chain, while those of PsEPH display an *extended* and a *folded* configuration. This distinct conformational behavior could be related to the different supramolecular behavior of both diastereoisomers observed experimentally. In fact, if we think of the potential of π - π overlapping of the conformers with *extended* or *folded* configurations of the long alkyl chains, which will drive the supramolecular aggregation, we hypothesize that conformers with *extended* configurations should allow for an effective overlapping of the aromatic rings, thus allowing the formation of supramolecular aggregates (see Figure 5-right-top). In contrast, conformers with a *folded* configuration should raise a steric hindrance upon an

approaching molecule due to the presence of the terminal methyl group that could prevent supramolecular aggregation (Figure 5-right-bottom). However, we note that at

Figure 6. Stable and most relevant conformations (as calculated by cvff) of pseudoephedrinium, and their corresponding Newman projections; A/G notation refers to the anti or gauche arrangement of the $C_{arom}CCN$ and $OCCN$ chains, respectively.

this point, this represents just a mere hypothesis; evidence will be given below.

D2. Aggregation behavior in water.

We then analyzed through Molecular Dynamics simulations the supramolecular behavior of both molecules in aqueous solution (in the same concentration as in the synthesis gels, 1R:100H₂O) by looking at the RDFs between different sets of atoms; Figure 7 shows some representative RDFs. The RDF between aromatic C atoms (cp) (Figure 7, top-left) shows a maximum at around 4 Å which is indicative of the π - π stacking between molecules forming dimers, and therefore can be taken as an indication of the aggregation behavior. In good agreement with the experimental observations, a

much higher aggregation is observed for EPH (blue line) compared to PsEPH (red line) (evidenced by the higher intensity of the RDF peak), showing that our computational model seems to correctly reproduce the experimental observations. This can also be concluded from the concentration profile curves (Figure 7, top-right), which indicate the number of aromatic rings around a given one at particular distances, where a higher concentration of molecules is observed for EPH. Once we had a correct reproduction of the experimental observations, we now wanted to unravel the reason, from a molecular level, for such different aggregation behavior, by analyzing RDFs between different sets of atoms.

First we looked if the hydrophilic groups of the molecules (NH_2 and OH) showed a different interaction with water molecules; Figure 7 (middle-left) shows the intermolecular RDFs between $\underline{\text{H}}(\text{N})$ atoms of the organic molecules and $\underline{\text{O}}$ atoms of water. The formation of H-bonds between these atoms is clearly observed at a distance of 1.91 Å, evidencing a strong interaction of the charged NH_2 groups with water molecules (through O atoms). However, no difference in such hydrophilic interactions between the two molecules is appreciated. A similar picture is found for the interaction between $\text{O}(\text{H})$ atoms of the organic molecules and H atoms of water, where the formation of even stronger H-bonds (at a distance of 1.77 Å) is observed (Figure 7 (middle-right), but again with no appreciable differences between both diastereoisomers (although a slightly higher order of water molecules in the second shell is appreciated for PsEPH). These results suggest a similar interaction of the hydrophilic groups of the two organic molecules with water, hence discarding a different interaction with water as the cause for the distinct supramolecular behavior observed.

Figure 7. Intermolecular (inter, top-left and middle) and intramolecular (intra, bottom) RDFs between different sets of atoms of ephedrinium (blue lines) and pseudoephedrinium (red lines). Top-right: concentration profile, as calculated from the cp-cp RDF.

We then analyzed the intramolecular RDFs, which in turn are indicative of the conformational behavior. In this case, we indeed found notable differences between both isomers (Figure 7-bottom). The intramolecular RDF between $\underline{\text{H}}(\text{N})$ and $\underline{\text{O}}$ atoms of

the organic molecules shows the formation of a stronger intramolecular H-bond for PsEPH (around 2.2 Å) than in EPH (around 2.4 Å); in addition to such shift, the peak is narrower and more intense for PsEPH, all indicative of a higher H-bond strength. Such difference in the intramolecular H-bonds could cause a different conformational behavior, as observed in vacuum. Therefore, we studied the occurrence of different conformations during the simulations. For this analysis, we took the distance between the methyl C atom bonded to N (c3n) and the aromatic C atom (cp1) with the substituent attached (see Figure S8 in the Supporting Information for definition of the distances used) to monitor the presence of the different types of conformers: in an *extended* configuration (conformers A and B for EPH, with c3n-cp1 distances of 4.8 and 4.7 Å, respectively, and conformer A for PsEPH, with c3n-cp1 distance of 5.0 Å), or in a *folded* configuration (conformer C for EPH and B for PsEPH, with c3n-cp1 distances of 3.6 and 3.7 Å, respectively). Figure 7 (bottom-right) shows a band with two peaks at 4.7 and 5.0 Å for EPH (blue line), but no band at around 3 Å, indicating that EPH is always in the *extended* (A or B) configuration; the presence of the two peaks is probably associated to an oscillation of the terminal methyl group caused by the weakness of the H(N)···O(H) intramolecular interaction for EPH (Figure 7-bottom-left). In contrast, two peaks are observed for PsEPH at 3.7 and 4.9 Å (red line), which corresponds to the presence of conformers B (in a *folded* configuration) and conformer A (in an *extended* configuration) of PsEPH, respectively, with the intensity for the latter, and therefore its concentration, being slightly higher. Analysis of the intramolecular RDFs between the same aromatic C (cp1) and the methyl substituent bonded to C (c3c), and between this and the O atom (oh) (Figure S9 in the Supporting Information) leads to a similar conclusion: only conformers in *extended* configuration are present for EPH (with unique cp1-c3c and c3c-oh distances at 3.2 and 3.0 Å) and both types of conformers, in

extended and *folded* configurations, are present for PsEPH (with two cp1-c3c distances at 3.2 and 3.9 Å and two c3c-oh distances at 3.1 and 3.8 Å) during the simulations in water. These results indicate that EPH molecules adopt *extended* configurations in

Figure 8. Intermolecular distance between methyl $\underline{\text{C}}$ atoms bonded to N (c3n) and aromatic $\underline{\text{C}}$ atoms with the substituent (cp1) along the simulation (500 to 1000 ps) for the two PsEPH molecules in the simulation box (top-left), distance distribution along different intervals of time (top-right), and intermolecular RDF between aromatic $\underline{\text{C}}$ atoms (cp) along different intervals of time (bottom).

aqueous solutions, while PsEPH adopts a mixture of *extended* and *folded* configurations. Such distinct conformational behavior might be the reason for the different supramolecular aggregation of both molecules. As previously mentioned, *extended* configurations (EPH-A and EPH-B, and PsEPH-A) have a molecular structure such that should allow an effective π - π stacking with another molecule to form a dimer, while *folded* conformers (PsEPH-B) have a structure that might prevent such π - π stacking because of the proximity of the methyl and phenyl groups and the steric hindrance generated (see Figure 5).

We now wanted to unambiguously connect the lower aggregation trend found in the MD simulations for PsEPH with the occurrence of that conformer in a *folded* configuration (PsEPH-B). In this case, simulations of 2 molecules (and 2 Cl⁻ anions) in 200 water molecules were performed, and the RDF between the aromatic C atoms was analyzed at different time intervals, depending on the occurrence of *folded* (PsEPH-B) conformers during the particular period of simulation time. Figure 8 shows the evolution of the c3n-cp1 distance (as defined above) (top-left) that shows the presence of the *extended* conformer PsEPH-A (with a distance of 4.9 Å) and of the *folded* conformer PsEPH-B (distance of 3.7 Å). Analysis of the evolution of these distances for the two PsEPH molecules with time clearly indicates a higher presence of the *extended* conformer A during the 500-800 ps interval (Figure 8, top-right, red line), and a higher presence of the *folded* conformer B during the 800-1000 ps interval (green line). Interestingly, calculation of the RDF between the aromatic C atoms (indicative of supramolecular aggregation) in those time intervals (Figure 8-bottom) showed a strong π - π stacking of the aromatic rings in the 500-800 ps interval where the *extended* conformer A predominated (red line) and no π - π stacking in the 800-1000 ps interval where at least one of the two PsEPH molecules was in the *folded* configuration B (green

line). These results provide a strong evidence for the presence of the molecules in the *folded* conformation, which occurs only for pseudoephedrinium, as being the cause for its lower supramolecular aggregation trend observed experimentally.

Discussion

In this work we have analyzed the structure-directing behavior of two chiral diastereoisomers, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, during the synthesis of microporous aluminophosphates. Despite their very similar chemical structure, only differing in the stereochemistry of the hydroxyl-bearing C atom, a notably different supramolecular behavior has been observed. In aqueous solution, the aggregation of ephedrine (hydrochloride) through π - π type interactions is much stronger than that of pseudoephedrine (hydrochloride). Interestingly, this difference is also reproduced when the inorganic aluminophosphate network crystallizes around the organic molecules, and hence the AFI materials synthesized with ephedrine as SDA incorporate a much higher amount of supramolecular aggregates, as evidenced by fluorescence spectroscopy. The incorporation of aggregates is also influenced by the synthesis conditions, especially the crystallization temperature and the dopant concentration.

Our computational study has been decisive for providing a chemical explanation for the different supramolecular aggregation observed between the two molecules. Despite their similar chemical structure, ephedrine and pseudoephedrine have very different pharmacological behaviors, and this is usually ascribed to the different conformational behavior of both diastereoisomers as a consequence of their distinct intramolecular interactions. MD simulations clearly show that the lower supramolecular aggregation of pseudoephedrinium is due to the occurrence of a *folded* conformation which impedes (by steric hindrance) the approach of another molecule to form the aggregate (see

Figure 5). Such *folded* conformation is unstable for ephedrinium, and hence this molecule is always in an *extended* configuration that enables the supramolecular aggregation. Indeed, molecular beam Fourier transform microwave spectroscopy revealed the presence of a similar folded conformer only for (neutral) pseudoephedrine but not for (neutral) ephedrine, although in a minor amount.³⁹

In order to test the reliability of our computational model and the conclusion reached about the different supramolecular behavior, the stabilities of the different conformers were evaluated by ab-initio methods. MP2/6-311++G(dp) method has been shown to correctly describe the conformational behavior of the neutral molecules;³⁹ apart from this, we have also employed the DFT/B3LYP method, including the D3 dispersion correction (Table 1). Results show that the two most stable conformers of protonated ephedrine predicted by the MP2 method are the same as those predicted originally by cvff (Figure 4), although the order of stability is the reverse (EPH-B is in this case more stable than EPH-A); anyway, it is important to remark that both of them are in the *extended* configuration which should enable the formation of supramolecular aggregates, and hence MP2 would predict also a high aggregation trend for EPH. In the case of pseudoephedrine, there are three more stable conformers (PsEPH-A, PsEPH-B and PsEPH-C), with a similar stability among them (the difference being less than 1 kcal/mol). Two of these stable conformers (A and B) were those predicted as the most stable ones by cvff (Figure 6). We want to remark here that MP2 level of theory also predicts PsEPH-B, the *folded* conformer, as being rather stable (0.9 kcal/mol relative to the most stable one), at least in vacuum. Again, the stability of this *folded* configuration in PsEPH which prevents the formation of aggregates would predict a lower aggregation trend for this isomer, as experimentally observed. Conformer C is very similar, in terms of steric hindrance, to conformer A (related by rotation of the CN bond

by 120°), and therefore should not alter the aggregation trend. Repetition of these calculations at the B3LYP-DFT level (without including the dispersion term) gives similar results for the stability of EPH conformers, but predicts a lower stability of the folded conformer in PsEPH, and thus would not agree with the experimental observations. However, B3LYP results match perfectly with those of MP2 and the experimental observations when the D3 dispersion term is included in the calculations, showing the importance of the dispersion interactions to correctly model the conformational behavior. In sum, the ab-initio computational results agree with the molecular mechanics conclusion that the different aggregation behavior observed for the two isomers is due to a different conformational space, in which the most stable conformers of ephedrine are in an *extended* configuration that enables supramolecular aggregation, while pseudoephedrine has one stable conformer in a *folded* configuration that prevents by steric hindrance the approach of a neighboring molecule to form the aggregate.

Table 1. Relative energies of the different conformers (in kcal/mol), as calculated by the different methods, and their corresponding type of conformation (A/G notation refers to the anti or gauche arrangement of the C_{arom}CCN and OCCN chains, respectively).

Ephedrine						
Conformer	cvff	HF-MP2	B3LYP	B3LYP+D3	Conformation	Configuration
A	0.0	2.6	1.8	2.6	AG1	Extended
B	1.9	0.0	0.0	0.0	GG1	Extended
C	5.8	3.1	3.4	2.9	GG2	Folded
D	8.1	4.2	3.8	4.4	GA1	Folded
E	10.7	6.7	5.9	6.3	AG2	Extended
F	12.6	5.0	5.3	5.3	GA2	Extended
Pseudoephedrine						
A	0.0	0.0	0.0	0.0	AG1	Extended
B	0.1	0.9	2.6	1.2	GG1	Folded
C	6.7	0.6	1.2	0.8	AG2	Extended
D	10.0	4.7	6.8	5.2	GA1	Extended
E	11.4	1.8	3.6	1.9	GG2	Extended
F	17.4	7.1	10.3	7.9	GA2	Folded

Conformational flexibility is crucial for molecular recognition phenomena, and this is determined by the intramolecular interactions that can be established throughout the conformational space. The present work represents the first example, at least to the best of our knowledge, where the conformational space determines also the supramolecular aggregation of aromatic molecules through the establishment of π - π type interactions between the aromatic rings during structure-direction of microporous materials. It is interesting to remark that such distinct supramolecular behavior is reproduced when the molecules are occluded within the AFI frameworks, suggesting that the organic molecules, being in the synthesis gels as monomers or aggregates, are the true structure-directing agents during the synthesis of the framework, and hence that their supramolecular state in the gel will determine their incorporation within the microporous solid. This issue is crucial for a potential transfer of the molecular chirality into the spatial distribution of dopants within the framework. Our previous computational study suggested that the SDA molecules will drive the incorporation of dopants through the establishment of strong electrostatic interactions between the negatively-charged divalent dopants (isomorphically substituting trivalent Al) and the positive charge of the protonated molecules. If one wants to achieve a particular chiral ordering of the relative spatial distribution of dopants, there needs to be a spatial connection between at least two dopants. As the incorporation of dopants is driven by the protonated ammonium groups of the SDA molecules, these have also to be spatially connected in order to transfer their particular spatial arrangement into the spatial distribution of the dopants. Indeed, as the molecules are chiral themselves, the dimers that they will form within the AFI channels are also asymmetric, and hence the relative distribution of the two dopants that will be incorporated driven by the SDA dimer could also be chiral. Our work shows a great trend of ephedrine to aggregate within the AFI

framework, and a lower trend, but still remarkable, for pseudoephedrine, and hence a potential chiral ordering of the dopants within the AFI frameworks.

Conclusions

In an attempt to produce chiral microporous solids through a transfer of chirality from supramolecular organic chiral arrangements into chiral spatial distributions of dopants, we have analyzed the supramolecular behavior during structure-direction of two chiral flexible isomers, (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, for the crystallization of Mg-doped AFI frameworks. Surprisingly, UV-Vis fluorescence results clearly show a much higher trend of ephedrine isomers to form supramolecular aggregates compared to pseudoephedrine. Molecular simulations suggest that the lower trend of pseudoephedrine to form supramolecular aggregates is due to the stability of a particular conformation with a folded molecular structure that provokes a steric hindrance, preventing the approach of a neighboring molecule to form the aggregate. Such aggregation-preventing folded conformation is only stable for pseudoephedrine, but not for ephedrine, due to their different intramolecular interactions, hence explaining the higher trend of ephedrine to form aggregates observed experimentally.

Interestingly, the supramolecular behavior of the molecules in aqueous solution is reproduced when occluded within the AFI channels, with occluded ephedrine dimer species being more abundant than pseudoephedrine dimers, hence evidencing that the supramolecular behavior of the molecules in the gels determine their incorporation within the microporous frameworks. To our knowledge, this represents the first report where the conformational space of chiral molecules, which is in turn controlled by the intramolecular interactions, determines the π - π driven self-assembly of the molecules

through the aromatic rings during structure-direction, and in consequence their supramolecular state when occluded within microporous frameworks.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Supporting Information

Additional XRD, ^{13}C and ^{31}P MAS-NMR, fluorescence, RDFs and molecular pictures are reported as Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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