Conformational Sieving Effect of Organic Structure-Directing Agents during the Synthesis of Zeolitic Materials

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Abstract. In this work we find a novel conformational sieving effect during the structure-direction of two chiral organic diastereoisomers, (1R,2S)-benzyl-ephedrine and (1S,2S)-benzyl-pseudoephedrine, during the synthesis of zeolitic aluminophosphates. Protonation of each diastereoisomer can take place through two different stereochemical configurations, giving place to a new stereogenic N center that results in two stereoisomers for each molecule, with (1R,2S,NS) or (1R,2S,NR) configurations for benzyl-ephedrine or (1S,2S,NR) or (1S,2S,NS) configurations for benzyl-pseudoephedrine. Through a combination of ¹H and ¹³C NMR spectroscopies and DFT+D

computational calculations we are able to distinguish the two stereoisomers derived from benzyl-pseudoephedrine: results show a higher occurrence of the (1S,2S,NS) isomer in aqueous solution, displaying a folded molecular configuration, while the less abundant (1S,2S,NR) isomer displays instead a conformation with an elongated shape. Crystallization of microporous aluminophosphates in the presence of benzyl-pseudoephedrine results in materials with AFI structure based on one-dimensional channels with a surprising higher occurrence of the (1S,2S,NR) isomer, in sharp contrast with the behavior in aqueous solution. Such notable difference is ascribed to the elongated shape of the (1S,2S,NR) stereoisomer that can better fit within the AFI one-dimensional nano-channels. On the other hand, assignment of the ^1H and ^{13}C NMR bands to the different protonated stereoisomers of (1R,2S)-benzyl-ephedrine is not as clear due to the smaller splitting of the signals upon protonation through the two stereochemical configurations. This work demonstrates that confinement in nano-spaces can alter the relative stability of stereoisomers in open spaces, leading to the occurrence of species that would not be possible otherwise.

Keywords: Aluminophosphate, zeolite, chirality, diastereoselective, structure-directing agent, template, conformers.

1. Introduction

The characteristic properties of nanoporous materials, in particular zeolite and zeolite-related materials, where chemical reactions take place in a confined space of molecular dimensions, combined with their characteristic cationic-exchange, molecular sieving and catalytic capacities, have triggered a wide range of different applications in the chemical industry [1-5]. Confinement effects are a direct consequence of the specific nanoporous

structure of zeolites, with channels and/or cavities of molecular dimensions that enable the discrimination between guest species (sorbates, reactants, transition states or products) with small steric differences [6]. The family of zeolite materials, traditionally based on a Si tetrahedral network, is further complemented by zeolitic microporous aluminophosphates (AlPO₄), where SiO₄ tetrahedra are substituted by alternated AlO₄ and PO₄ tetrahedra, giving place to analogous framework structures but with particular chemical properties different from those of silica-based zeolites [7,8].

Confinement effects are intrinsically dependent on the particular zeolite framework structure and the topology and dimensions of the channels, cavities and windows which host the guest species. Hence, in order to gain advantage of confinement effects in diverse applications it is crucial to adequately control the zeolite porous architecture that is to be used. In this context, the main control that zeolite scientists have gained over the outcome (in terms of topological framework) of a zeolite hydrothermal synthesis is through the use of the so-called organic structure-directing agents (SDAs) [9-13]. These are typically ammonium-based organic cations that are added to the synthesis gels, and provide a control on the crystallizing zeolite framework by host-guest size- and shape-relationships. These organic agents are said to order the inorganic precursors around in a particular geometry which determines the final framework that crystallizes, with usually (but not always) a structural relationship between the molecular shape of the organic cation and that of the void space of the zeolite framework [14]. In recent years, zeolite researchers have been able to control the zeolite architecture by carefully-designing the molecular size and shape of the organic species to be used as SDAs [15].

One of the biggest challenges in zeolite science where the careful design of organic SDAs is the best tool available is to promote the crystallization of an enantiomerically-pure (or at least enriched) chiral zeolite material [16-18]; these materials could provide robust

enantioselective adsorbents and catalysts which would have a great impact, especially on the pharmaceutical industry [19-23]. Several chiral zeolite frameworks do actually exist [17,24-28], which usually contain helicoidal channels; however, they usually crystallize as racemic mixtures, either as racemic conglomerates where each crystal is enantiopure but the polycrystalline sample has 50:50 proportion of the two enantiomorphous crystals, like the STW case (SU-32 or HPM-1 materials), or as racemic compounds where mixtures of enantiomorphous polymorphs are intergrown, like the beta zeolite where polymorph A is chiral (in this case in addition there is also polymorph B which is achiral giving a complex mixture of intergrown polymorphs). Because of the geometrical and spatial relationship that is usually established between the organic SDAs and the surrounding zeolite network that crystallizes, chiral organic molecules have been traditionally used as SDAs in an attempt to promote the crystallization of chiral zeolite frameworks, where the asymmetric nature of the SDA would be transferred to the nascent zeolite framework [29]. In fact, there is a recent successful example of enantio-enrichment of a chiral zeolite (STW) through the use of a rationally-designed chiral organic SDA [30], which clearly demonstrates the validity of this strategy as long as a rational choice of the SDA fulfilling several conditions is performed. In this context, a molecular understanding of the structure-directing role of chiral SDAs is crucial for the successful transfer of chirality from the organic component to the zeolite framework.

In order to properly understand the structure-directing behavior of chiral SDAs, in our group we have been working for some time with derivatives of chiral alkaloids (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine during the synthesis of zeolitic nanoporous materials, especially in AlPO_4 composition using secondary or tertiary amines [31-38]. These molecules were rationally selected as chiral SDAs since they contain two stereogenic centers, they are commercially available, they resist hydrothermal treatments,

and they contain aromatic rings and H-bond forming and accepting groups that impart a very rich supramolecular chemistry to these species. In particular, we have found that the presence of such H-bond donor and acceptor groups within the molecule provides a very rich conformational space, which in turn alters the resulting supramolecular chemistry and the structure-directing behavior of these chiral SDAs [35,37,39-42]. Moreover, we have shown that ^{13}C NMR spectroscopy can be very useful for monitoring the conformational space of these organic species upon confinement in nanoporous spaces [35], revealing stabilization of particular conformations under confinement that are unstable in open spaces (in solution). On the other hand, the occurrence of diastereoisomerism can also notably alter the outcome of a crystallization route [43-45]. These observations about conformational chemistry and diastereoisomerism have motivated us to study the structure-directing behavior of other derivatives of (1R,2S)-ephedrine and (1S,2S)-pseudoephedrine, in particular of the benzyl-containing derivatives (1R,2S)-benzyl-ephedrine and (1S,2S)-benzyl-pseudoephedrine (Scheme 1). These derivatives are particularly interesting since the addition of a benzyl substituent to N gives place to a new stereogenic center, the N atom, that upon protonation under the synthesis conditions can produce two different isomers (for each SDA) as a function of the stereochemical attack of the proton. This leads to a new degree of freedom which could potentially affect the structure-directing behavior of these molecules. In this work we perform a combined study by ^{13}C NMR and quantum mechanics calculations in order to identify the presence of the different isomer species for each SDA, the associated conformational space and the influence on the structure-directing behavior during the synthesis of nanoporous aluminophosphates.

2. Experimental and Computational Details

A. Synthesis of (1R,2S)-benzylephedrine and (1S,2S)-benzylpseudoephedrine

(1R,2S)-benzylephedrine and (1S,2S)-benzylpseudoephedrine were prepared from (1R,2S)-ephedrine (Sigma-Aldrich, 98 %) and (1S,2S)-pseudoephedrine (Sigma-Aldrich, 98 %), respectively, through alkylation in dimethylformamide (DMF, Fisher Scientific 99 %) with benzyl bromide (Alfa Aesar, 99 %) in the presence of K_2CO_3 (Sigma-Aldrich 99 %), following standard procedures [46]. In a typical synthesis of (1R,2S)-benzylephedrine, 15.0 g of (1R,2S)-ephedrine were added to 200 mL of DMF, followed by the careful (drop by drop) addition of 36.0 g of benzyl bromide and 37.0 g of K_2CO_3 . The mixture is kept overnight at 90°. DMF is then removed in a rotatory evaporator, and 100 mL of water are added to the resulting product, which is extracted with diethyl ether (Fisher Scientific, 99.5 %). The organic layer is then collected, dried with K_2CO_3 , and the organic solvent is finally evaporated. (1R,2S)-benzylephedrine is obtained with acceptable purity (without further purification) with a yield of ~90%. 1H NMR ($CDCl_3$): 1.07 (d, 3H, CH_3C), 2.26 (s, 3H, CH_3N), 2.97 (qd, 1H, CHN), 3.57 (broad band, 1H, OH), 3.68 (d, 2H, CH_2N), 4.92 (d, 1H, $CHOH$), 7.25-7.50 (10H, m, aromatics). ^{13}C NMR ($CDCl_3$): 10.0 (CH_3C), 38.7 (CH_3N), 59.2 (CH_2N), 63.5 ($CHCH_3$), 73.8 ($CHOH$), 126-129 (unsubstituted aromatics), 139-143 (substituted aromatics). Synthesis of the diastereoisomer (1S,2S)-benzylpseudoephedrine was carried out exactly in the same way, giving a similar yield of ~90%. 1H NMR ($CDCl_3$): 0.89 (d, 3H, CH_3C), 2.31 (s, 3H, CH_3N), 2.84 (qd, 1H, CHN), 3.60-3.83 (2H, CH_2N), 4.41 (d, 1H, $CHOH$), 7.31-7.48 (10H, m, aromatics). ^{13}C NMR ($CDCl_3$): 7.40 (CH_3C), 35.8 (CH_3N), 58.3 (CH_2N), 65.0 ($CHCH_3$), 74.9 ($CHOH$), 126-129 (unsubstituted aromatics), 139-143 (substituted aromatics).

B. Synthesis of MgAPO-5 microporous materials

Microporous aluminophosphate materials were prepared by hydrothermal methods using (1R,2S)-benzylephedrine (BEP) and (1S,2S)-benzylpseudoephedrine (BPS) as SDAs. The molar composition of the synthesis gels was $xR:1P_2O_5:0.2MgO:0.9Al_2O_3:50H_2O$, where R stands for the organic SDA (BEP or BPS), and x was 1 or 2. In a typical preparation, the corresponding amounts of H_2O , H_3PO_4 (Sigma-Aldrich, 85 % in water), pseudoboehmite (Pural SB-1 77.5% Al_2O_3 , Sasol) and $Mg(CH_3COO)_2 \cdot 4H_2O$ (Sigma-Aldrich, 99.5 %) were stirred for 1 hour, after which the corresponding SDA is added and the mixture is further stirred for 2 hours. The gels were introduced into 60 ml Teflon lined stainless steel autoclaves and heated statically at 140 or 180 °C under autogenous pressure for 24 h. The resulting solids were separated by filtration, washed with ethanol and water and dried at room temperature overnight.

C. Characterization of microporous 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 registered using a Perkin-Elmer TGA7 instrument (heating rate = 20°C/min) under air flow. The crystal morphology of the materials was studied by scanning electron microscopy (SEM) using a Hitachi TM-1000 Tabletop microscope. Liquid 1H and ^{13}C NMR spectra were recorded with a Bruker Avance III-HD Nanobay 300MHz spectrometer, using a 5mm HBO 1H/X probe. Solid State MAS-NMR spectra of the solid samples were recorded with a Bruker AV 400 WB spectrometer (details are given in the Supporting Information). The aggregation state of the molecules in the solid samples was studied by fluorescence spectroscopy, using a RF-5300 Shimadzu fluorimeter in front face configuration.

D. Computational Details

Molecular simulations based on a combination of molecular mechanics and quantum mechanics (DFT) were performed in order to understand the structure-directing role of the two chiral diastereoisomers. As confirmed by ^{13}C NMR, in order to compensate for the negative charge induced by the isomorphic substitution of Al^{3+} by Mg^{2+} , both SDAs were protonated when confined within the nanoporous materials, and hence protonated BEP and BPS cations were studied.

The conformational space of the molecules was scanned by means of the Conformers Calculation Module in Materials Studio [47], optimizing the molecular structures for each set of dihedral angles. For these molecular-mechanics calculations, we used the pcff force-field [48,49] and force-field-assigned atomic charge distributions. Calculations of the stability of these conformers in vacuum were also performed at *ab-initio* level with the CASTEP code [50], using DFT+D and plane waves (with an energy cut off of 571.4 eV), and the PBE functional (including the Grimme dispersion term) [51]. All energies are expressed relative to the most stable conformer in kcal/mol.

Calculation of the NMR chemical shielding of the different isomers was carried out with the gauge-including projector augmented-wave method (GIPAW) developed by Pickard and Mauri [52], as implemented in the CASTEP code. The chemical shift for a nucleus in a given position ($\delta(\text{r})$) is defined as: $\delta(\text{r}) = \sigma_{\text{ref}} - \sigma(\text{r})$, where $\sigma(\text{r})$ is the isotropic shielding obtained in the calculations. In order to compare with experimental ^{13}C chemical shifts, a σ_{ref} value of 176 ppm was used, the same as in our previous works [35]. The conformational behavior of the SDA cations in water as a function of their stereochemical configuration was studied by Molecular Dynamics (MD) simulations, in the same way as reported in our previous works [39], using the same force-field conditions as before (pcff). 16 SDA cations, 16 Cl^- anions (for charge-compensation) and 800 water molecules were included in the simulation cell (in the same ratio as in the gels used for

the synthesis of MgAPO-5), and 1000 ps of MD simulations in the NVT ensemble were run at 298 K. The conformational behavior of the cations was studied by analyzing the Radial Distribution Functions (RDF) of selected sets of atoms in the 500-1000 ps time interval.

3. Results and Discussion

A. Stereoselective protonation of BPS

Due to the acidic pH of the synthesis gels and the strong basicity of these tertiary amines, the SDAs are expected to be protonated during the crystallization process. Upon protonation of the two diastereoisomers, (1R,2S)-benzyl-ephedrine and (1S,2S)-benzyl-pseudoephedrine, the N atom becomes a stereogenic center, and as a consequence two possible isomers result from each molecule, (1R,2S,NR) and (1R,2S,NS) isomers for benzyl-ephedrine (BEP) (where 'N' refers to the N atom, and will be denoted as RSR and RSS), and (1S,2S,NR) and (1S,2S,NS) isomers for benzyl-pseudoephedrine (BPS) (which will be denoted as SSR and SSS). Due to the different stereochemical configuration, distinct ^1H and ^{13}C NMR shifts are expected for each isomer. Therefore, aqueous solutions (in D_2O) of the protonated cations were prepared by adding equimolar amounts of DCl (from a solution of DCl in D_2O , 35%, Sigma-Aldrich) and the liquid NMR spectra were collected.

Figure 1 (left) shows the ^1H liquid NMR spectra of protonated BPS; clear shifts of the bands are observed, confirming the protonated state of BPS (notably the band corresponding to H3 is shifted from 2.31 ppm in neutral state). Remarkably, protonation of BPS lead to splitting of the bands, which is especially notable for H1, H3 and H2 (see Figure 1), due to the proximity of these H atoms to the N atom and the lack of other overlapping bands. Such splitting of the bands is due to the formation of the two isomers

upon protonation of N, SSR and SSS. H1 gives two doublet signals at 0.96 (with a relative area, 'a', of 2.92) and 1.09 (a=2.20) ppm, H3 gives two singlet signals at 2.75 (a=2.18) and 2.90 (a=2.91), and H2 gives two doublet quadruplet signals at 3.34 (a=1.00) and 3.66 (a=0.77). Because of the relative intensity of the split signals, we can group the bands at 0.96, 2.90 and 3.34 ppm (those with higher intensity) and assign them to H1, H3 and H2 of one (more abundant) isomer, and the bands at 1.09, 2.75 and 3.66 ppm (lower intensity) to the H atoms of the other isomer. The relative ratio of the two isomers is 1.33:1 (by comparing areas); however, at this point we cannot assign the different species to one or the other isomer of BPS (SSS or SSR).

A similar picture is observed from the ^{13}C NMR spectrum of the same D_2O solution (Figure 1-right). In this case, the bands that are most notably split are those corresponding to C3, giving signals at 34.8 (a=1.37) and 38.7 (a=0.99) ppm, C9 giving signals at 53.1 (a=0.99) and 58.4 (a=1.26) ppm, and C2 giving signals at 61.9 (a=1.15) and 66.7 (a=0.95) ppm. Again, if we compare the relative intensities, we can assign the bands at 34.8, 58.4 and 61.9 ppm to C3, C9 and C2 of one (more abundant) isomer, and those at 38.7, 53.1 and 66.7 ppm to the C atoms of the other (less abundant) isomer. Indeed, the averaged relative ratio of the two isomers (calculated by comparing the areas of the same type of C) is 1.29:1, very close to the value obtained by ^1H NMR. The relative areas of the rest of C atoms with smaller splitting are compatible with the calculated proportion of the two isomer species. Hence, these results clearly show that the two possible isomers upon protonation (SSR and SSS) are formed in aqueous solution, with one of them being more abundant (1.33:1); however, at this point we cannot assign the two species to each isomer. In order to identify the two species, we performed a computational study based on DFT+D and molecular mechanics (pcff force-field), and calculated the stabilities and theoretical ^{13}C NMR shifts. We first identified the most stable conformers for each isomer (SSR and

SSS), and calculated the relative stability (relative energies in kcal/mol with respect to the most stable case); energies of the three most stable conformers as well as ^{13}C theoretical shifts are given in Table 1, and Figure 2 shows the structure of the conformers for each isomer (Table S1 in the Supporting Information provides the same data for all the conformers studied).

The relative conformational energies calculated by pcff and DFT methodologies are in general very similar, thus evidencing that the pcff model is able to reproduce well the conformational behavior of BPS. In the case of the SSR isomer, there is one conformer which is more stable than the others (SSR-A, see Figure 2, top-left), where the molecular structure is in an extended configuration stabilized by the formation of an intramolecular H-bond between the H(N) proton and O. In the other two conformers (SSR-B and SSR-C), the cation is in a folded configuration (Figure 2-top). On the other hand, SSS isomer displays three conformers with small energy differences (see Table 1 and Figure 2-bottom); in two of them (SSS-A and SSS-B), the cation is in a folded configuration, while conformer C displays an extended configuration.

The previous DFT calculations were performed in vacuum; we now wanted to analyze the conformational behavior in aqueous solution, which will be reminiscent of that occurring during their structure-directing action. In this case, we use the pcff model which has been shown to properly model the conformational behavior of BPS. Results of the MD simulations of aqueous solutions of SSR- and SSS-BPS are displayed in Figure 3. If we look at the energy results (normalized per BPS cation), we observe a higher stability (lower energy) of the SSS isomer (Figure 3-left, blue line). With respect to the occurrence of the different conformations, a very strong peak between H(N) and O(H) atoms at 2.3 Å is observed (not shown), clearly evidencing a prominent formation of intramolecular H-bonds, and hence discarding the presence of SSR-B and SSS-A conformers that do not

develop intramolecular H-bonds (see Figure 2). The intramolecular RDF between the substituted aromatic C atoms (cp0cp0) (Figure 3-right) allowed us to identify the different remaining conformers of SSR ('A' with a $d_{cp0} = 5.9 \text{ \AA}$ and 'C' with a $d_{cp0} = 4.7 \text{ \AA}$) and SSS ('B' with a $d_{cp0} = 5.1 \text{ \AA}$ and 'C' with a $d_{cp0} = 6.0 \text{ \AA}$). In the case of SSR (red line), we observe a higher presence of conformer SSR-A (peak at $\sim 6.0 \text{ \AA}$), with the extended configuration, and a minor presence of conformer SSR-C (peak at $\sim 4.7 \text{ \AA}$), with a folded conformation. In contrast, in the case of the SSS isomer, we observe a higher occurrence of conformer SSS-B with the folded configuration (peak at $\sim 5.3 \text{ \AA}$) and a lower occurrence of conformer SSS-C with the extended configuration (peak at $\sim 6.4 \text{ \AA}$).

Once identified the most stable conformers for each BPS isomer, we look at the theoretical ^{13}C NMR chemical shifts in an attempt to assign the experimental peaks observed to the two protonated BPS species. In principle we will focus on the most abundant conformers SSR-A (extended configuration) and SSS-B (folded configuration). By looking at the experimental ^{13}C NMR data (Figure 1), we note that the most prominent difference between the two species is in the C9 and C2 atoms: in one species (the less abundant one), this gives bands at 53.1 and 66.7 ppm, with a large difference of 13.6 ppm, while in the most abundant species the bands appear at 58.4 and 61.9 ppm, with a much smaller difference of 3.5 ppm. If we now look at the theoretical NMR data (Table 1), we can clearly see that SSS-isomer displays a much smaller difference between those C9 and C2 signals (63.0 and 66.1 ppm for the most stable conformer SSS-B, as found in aqueous solution), while the same C9 and C2 signals are much more separated for the SSR-isomer (56.2 and 75.6 ppm for the most stable conformer SSR-A). Moreover, the C3 band of SSR-A (36.1 ppm) appears at a higher shift than that of SSS-B (33.2 ppm), which is also in line with the experimental observations. Hence, by comparing with the theoretical data, we can now assign the species displaying experimental bands at 34.8, 58.4 and 61.9 ppm

to the SSS isomer, and the species with bands at 38.7, 53.1 and 66.7 ppm to the SSR isomer. Interestingly, a higher proportion (1.33:1) of the SSS isomer is observed experimentally, which is in line with the higher stability of the SSS-isomer in aqueous solution found in our MD simulations (Figure 3-left).

We also calculated theoretically the ^1H NMR chemical shifts of the most stable conformers (Table 2). Following the previous assignment, we identified the most abundant species (with H1, H3 and H2 signals at 0.96, 2.90 and 3.34 ppm) with the SSS isomer, and the less abundant species (with ^1H δ at 1.09, 2.75 and 3.66 ppm) with the SSR isomer. If we look at the theoretically calculated values, we find a very good agreement of the experimental ^1H δ values with those of the corresponding isomer in the most stable conformation, SSR-A and SSS-B (see Table 2). However, the agreement is not as good with the less stable conformers SSR-C and SSS-C, which suggests that indeed the conformations that occur in aqueous solutions are SSR-A and SSS-B.

Therefore, through this combined experimental and computational study, we are now able to monitor the occurrence of the different stereochemical configurations of BPS upon protonation during their structure-directing effect, both from ^1H and ^{13}C NMR results. Our study indicates that a mixture of the two modes of protonation of BPS takes place in aqueous solution, giving a higher concentration of the SSS isomer in a folded conformation, and a lower concentration of SSR in an extended conformation.

B. Stereoselective protonation of BEP

We then performed the same study for (1R,2S)-benzylephedrine (BEP). In this case, the two possible modes of protonation give place to RSR- and RSS-isomers. Figure 4 shows the ^1H (left) and ^{13}C (right) NMR spectra of aqueous (in D_2O) solutions of protonated (upon addition of equimolar amounts of DCl) of BEP. In this case, we observe that the

splitting of the ^1H NMR signals is not as large as for BPS: signals assigned to H1, H3 and H2 are not adequately resolved (Figure 4-left). The only band that is properly resolved is that corresponding to H4, which gives signals at 5.12 (with higher intensity) and 5.34 ppm (with lower intensity), giving a ratio of the two species of 1.6:1; this ratio is similar to that estimated from H1 (1.6:1), although in this case the splitting is not well-resolved. Note that an additional band observed at 2.64 could not correspond to a splitting of H3 due to the ratio between the two species that would give (5.2:1), much higher than the one observed for the rest of protons; at this moment, we are not sure of the origin of such band (marked with asterisk in Figure 4).

A similar picture is observed from the ^{13}C NMR spectrum (Figure 4-right). In this case, the splitting of the C1, C3 and C4 bands are resolved, although the separation is very small. The bands that are most separated are those corresponding to C9 and C2. If we group the split signals as a function of their intensity (there is always one that is ~ 1.6 times more intense than the other), we can assign the bands at 7.1, 37.1, 58.7, 63.3 and 71.8 ppm to C1, C3, C9 and C2 atoms of one more abundant isomer, and bands at 7.7, 38.0, 56.9, 65.7 and 70.9 ppm to the same C atoms of the other less abundant isomer, with a relative ratio between the two species of 1.6:1 (the same as the one observed from ^1H NMR). Due to the smaller splitting of the signals for BEP, in this case the most noticeable ^{13}C NMR feature is that corresponding to C9 and C2, which should give two bands more separated (56.9 and 65.7 ppm) for one BEP isomer (less abundant), and two closer bands (58.7 and 63.3 ppm) for the other isomer (more abundant).

In order to identify the two species, we performed DFT+D calculations of the different conformers for the two possible isomers of BEP, RSS and RSR; as previously, data for the three most stable conformers of each isomer is collected in Table 3 and their molecular structure in Figure 5, while data for all the studied conformers are given in the Supporting

Information (Table S2). If we look at the theoretical ^{13}C δ of C9 and C2 (which are the ones mostly distinguishable in the experimental NMR data), we observe that the data for the RSR isomer gives values which are more separated than those for isomer RSS. Indeed, if we focus on the most stable conformers (as determined by DFT+D), RSR-H and RSS-G, calculations predict signals for the former at 38.5, 59.8 and 70.2 ppm for C3, C9 and C2, respectively, and at 32.6, 67.5 and 69.9 ppm for the same Cs of RSS. These values are in relatively good agreement with an assignment of the experimental ^{13}C NMR data with RSS for the most abundant species (giving signals at 7.1, 37.1, 58.7, 63.3 and 71.8 ppm), and RSR for the less abundant species (giving signals at 7.7, 38.0, 56.9, 65.7 and 70.9 ppm); however, we note that the differences in the BEP case are not as clear as in the case of BPS, and therefore this assignment should be treated as tentative. In the case of the most abundant RSS, the most stable conformer (G) involves an elongated shape with an intramolecular H-bond, while for the RSR- isomer, the most stable conformer displays a folded configuration, also stabilized by intramolecular H-bonds. We note here that for this BEP isomer, relative conformational energy results determined by pcff differ from those calculated by DFT+D, especially regarding the stability of the H-bonded conformers (see Table 3). Keeping in mind such differences, we performed the same MD simulations for these isomers (see Figure S1 in the Supporting Information). Results show a higher stability of the RSS isomer in aqueous solution (Figure S1, top-left), and that no intramolecular H-bonds are formed. Regarding the type of conformation, RSS isomer shows a single peak at ~ 4.6 Å indicative of a folded conformation, similar to that of RSS-A, while RSR isomer shows a certain variation of conformations during the simulations, probably due to the lack of intramolecular H-bonding. Nevertheless, we again note that these results obtained with pcff should be treated with care for BEP, as previously mentioned.

We also calculated the ^1H NMR chemical shifts (Table S3 in the Supporting Information); however, as previously pointed out, in this case the differences in the split signals are much smaller, and no clear conclusions could be reached by comparing with the theoretical predictions. In summary, while results for BPS isomers are in excellent agreement with the experimental observations, and we can be confident in the assignment to the different species, those for BEP are less convincing, and the corresponding assignment made here with ^{13}C NMR should be treated as tentative.

C. Structure-directing effect of BPS and BEP

We next analyzed the structure-directing behavior of both molecules during the synthesis of aluminophosphate-based microporous materials, using a composition of $x\text{R}:1\text{P}_2\text{O}_5:0.2\text{MgO}:0.9\text{Al}_2\text{O}_3:50\text{H}_2\text{O}$, where R was 1 or 2, and the crystallization temperature was 140 or 180 °C. XRD results (Figure S2 and S3 in the Supporting Information) show that both BPS (Figure S2) and BEP (Figure S3) leads to the crystallization of MgAPO-5 (AFI type structure) in all conditions; the AFI structure is composed of one-dimensional 12-ring cylindrical channels with a diameter of 7.3 Å [53]. Dense AlPO-cristobalite is observed from gels heated at 180 °C in the presence of BPS (Figure S2-right), while traces of MgAPO-36 are observed in the sample obtained with 1 BEP at 140 °C (Figure S3-top-left). TGA results (Figure S4) show desorption peaks corresponding to the release of water (at T below 200 °C, giving 3.6 and 2.5 H_2O molecules per AFI u.c. for samples obtained with 2R at 140 °C in the presence of BPS and BEP, respectively), and several peaks at T above 200 °C assigned to the release and combustion of the organic cations, resulting in 0.85 BPS and 0.80 BEP cations per AFI unit cell.

The presence of two aromatic rings on the SDA molecules results in the possibility of developing supramolecular aggregation when confined within the nanopores of the AFI

framework. For this reason, we applied UV-Visible fluorescence spectroscopy in order to unravel the supramolecular aggregation state of the molecules (Figure 6); bands at 280 nm indicates the incorporation of the molecules as monomers, and bands between 350 and 500 nm correspond to the presence of aggregates with π - π stacking between the aromatic rings. In the same line as in our previous works [32], we observe a higher incorporation of aggregates in samples obtained at higher crystallization temperatures (Figure 6-red lines). Two bands assigned to aggregate species are observed, at 375 and 425 nm, which we previously tentatively assigned to different orientations of the π - π stacked aggregates, with aromatic rings parallel to the direction of the channels (375 nm) or bent (425 nm). A notably higher presence of aggregates (relative to monomers) is observed for BEP molecules (Figure 6-right) than for BPS (left) at both crystallization temperatures; similar behavior was previously found for materials obtained in the presence of ephedrine and pseudoephedrine [32,39].

^{31}P MAS NMR (Figure S5 in the Supporting Information) demonstrated the incorporation of Mg in the AFI framework due to the presence of a resonance signal at -24 ppm assigned to P(1Mg,3Al) environments, being slightly more intense for the material obtained with BPS, in accordance with the slightly higher organic content required for charge-compensation. SEM pictures (Figure S6 in the Supporting Information) show the formation of crystalline aggregates, being larger for the samples obtained with BEP.

We then studied the incorporation of BPS and BEP species within the AFI materials by ^{13}C MAS NMR (Figure 7). First we study the material obtained with BPS (with 2SDA and 140 °C crystallization temperature, top-black line); first of all, we note that all the bands corresponding to the different C atoms of BPS are observed in the ^{13}C MAS NMR spectrum, thus confirming the integral incorporation of the BPS species within the framework. We now focus on bands corresponding to C3, C9 and C2, which are the ones

that are split upon protonation depending on the stereochemical configuration of N. Following the assignment previously shown for SSS and SSR species, by comparison with the bands in aqueous solution (blue lines), we can assign the bands at 32 and 39 ppm to C3 of SSS and SSR isomers, with the latter being much more intense (see assignment in Figure 7-top). In the same line, we assign the bands at 54 and 69 ppm to C9 and C2 of the SSR isomer, while the corresponding bands for the SS isomer appear at ~62 ppm (with a rather lower intensity, and in fact are not resolved). Interestingly, in all cases (for C3, C9 and C2 atoms) the bands assigned to SSR species are much more intense than those corresponding to SSS species, which is the opposite trend to that observed in aqueous solution. In fact, by comparing the areas under the corresponding bands, we estimate that the SSR species is 2-3 times more abundant than SSS isomer (note that the types of C atoms compared are the same, as hence the cross-polarization effect should be comparable). This clearly means that SSR isomers are much more effective for directing the crystallization of the AFI framework.

We collected also the ^1H NMR spectra for this solid, and compared with the liquid ^1H NMR (see Figure S7 in the Supporting Information). Although in this case the bands are very broad and not well-resolved, if we compare with the corresponding bands assigned previously to SSR and SSS species (see Figure 1-left), we can observe a good agreement with a higher occurrence of the SSR isomer (Figure S7) as detected by ^{13}C NMR, though as previously mentioned the assignment from ^1H NMR is not as clear as from ^{13}C NMR due to the broadness of the bands.

It is interesting to note the alteration of the relative occurrence of the two isomer species of BPS in solution (we can consider it as an open-space) and occluded within the AFI nanochannels (in a confined space). In the former case, the occurrence of the two isomers is dictated by their relative stability: SSS isomers are more stable, and consequently these

predominate in solution, though of course, due to the reversibility of the protonation reaction, both SSS and SSR isomers are in equilibrium in solution. As suggested by our calculations, the SSS isomers adopt a folded conformation, while SSR-isomers adopt an elongated shape. Interestingly, only elongated conformations can fit within the one-dimensional channels of the nascent AFI framework, and as a consequence, only SSR-isomers will direct the crystallization of the zeolite material, thus resulting in AFI materials which are enriched in the SSR isomer, despite this being less abundant in aqueous solution. This is a clear indication that we can stabilize species that are not stable in open spaces through confinement in an adequate pore or cavity. In this way, the porous framework would exert along its building-up process a conformational sieving effect among the several organic chemical species present in the synthesis gel.

Next we studied the BEP isomer (Figure 7-bottom); we note that the assignment to RSS and RSR species in this case is more dubious, as previously explained. Again all the bands corresponding to the different C atoms are present, confirming the resistance of BEP molecules to the hydrothermal treatment and their integral incorporation within the AFI framework. We note however that the bands are broader than in the previous case (despite the spectra were performed under the same conditions), which might point to a lower ordering of the BEP cations in the AFI channels. First of all, we note that the band assigned to C1 (where the two isomers resulting from protonation of N are not distinguishable) is shifted from 7.2-7.7 ppm in aqueous solution to 10.1 ppm when occluded within the AFI framework, which might suggest a change of conformation (probably to a more elongated shape) upon confinement. If we now focus on the region corresponding to C9 and C2, we observe in this case a broad band where it is not easy to assign the bands to the different RSR or RSS isomeric species (^1H NMR in Figure S7 did not help either to solve the assignment of the two isomers). By comparison with the bands

in aqueous solution, we observe the profile of the band is relatively similar, and hence this suggests that at least RSS seems to be incorporated, possibly with a higher occurrence than the RSR isomer, the same as occurred in aqueous solution. This seems to indicate that in contrast to BPS, the BEP isomer most abundant in solution is also incorporated in a higher proportion within the AFI channels, probably as a consequence of its elongated shape that can fit in one-dimensional channels (see RSS-G conformer, Figure 5). However, we note again that conclusions regarding the BEP isomers should be taken as tentative due to the ambiguity of the bands assigned to RSR and RSS species and the broadness of the MAS NMR spectrum for this sample.

Conclusions

In this work we study the stereoselective protonation of chiral (1R,2S)-benzyl-ephedrine and (1S,2S)-benzyl-pseudoephedrine during the structure direction of nanoporous aluminophosphates. Through a combination of ^1H and ^{13}C NMR spectroscopy and DFT+D calculations, we are able to monitor the occurrence of the different diastereoisomers of each molecule upon protonation from two different sides that result in distinct diastereomeric configurations. In aqueous solution, protonation of (1S,2S)-benzyl-pseudoephedrine results in a mixture of (1S,2S,NS) and (1S,2S,NR) isomers, with a higher occurrence of the former. Conformational analyses by molecular mechanics methods reveal that (1S,2S,NS) displays a folded conformation, while (1S,2S,NR) shows an elongated extended configuration. When used as structure-directing agents, materials with AFI topology, based on one-dimensional channels, are produced; interestingly, a much higher occlusion of (1S,2S,NR) isomers is observed in the AFI materials, in sharp contrast with the observations in aqueous solution. This is explained in kinetic terms, since only the elongated shape of the most stable conformers of (1S,2S,NR) can fit within

the one-dimensional nanochannels of the nascent AFI material. On the other hand, the assignment of the different NMR signals to the distinct isomers of (1R,2S)-benzylephedrine is not as clear as for benzyl-pseudoephedrine, but our tentative assignment indicates that in this case the most abundant isomer in solution has the (1R,2S,NS) configuration and an elongated shape that can fit within the AFI channels, as suggested by ^{13}C CP MAS NMR.

This work demonstrates that confinement effects can be advantageously used in order to stabilize isomers or conformers that are not stable in open-space, such as in solution, which can be useful for materials science research in host-guest systems.

Declarations of interest: none

Supporting Information

NMR details, additional theoretical data, RDF plots, XRD patterns, TGA, additional ^{31}P and ^1H MAS NMR, SEM pictures, are included as Supporting Information.

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Tables

Table 1. Relative energies (as calculated by pcff molecular-mechanics and DFT+D methods), and theoretical ^{13}C NMR chemical shifts of the three most stable conformers of the two BPS isomers; the formation of H-bonds, as well as the relative orientation along the $\text{C2}\cdots\text{N}$ bond, are also given.

SSR-BPS											
Conformer	RE (pcff)	RE (DFT)	C1	C3	C9	C2	C4	Aromatics	H-bond	C1/HN	C1/C9
SSR-A	0.0	-0.1	4.4	36.1	56.2	75.6	80.7	126.7-138.9	Yes	Anti	Sin
SSR-B	1.0	1.5	5.8	37.2	60.9	73.9	82.2	127.2-140.0	No	Anti	Sin
SSR-C	1.2	1.2	4.8	43.2	61.2	77.7	79.5	126.6-139.2	Yes	Anti	Sin
SSS-BPS											
Conformer	RE (pcff)	RE (DFT)	C1	C3	C9	C2	C4	Aromatics	H-bond	C1/HN	C1/C9
SSS-A	0.0	0.0	3.7	38.9	63.9	63.8	82.7	123.6-141.8	No	Anti	Sin
SSS-B	0.4	0.0	2.1	33.2	63.0	66.1	80.1	126.6-138.6	Yes	Anti	Sin
SSS-C	0.5	0.3	4.8	27.9	66.2	76.7	81.0	126.6-138.7	Yes	Anti	Sin

Table 2. Theoretical ^1H NMR chemical shifts of the most stable conformers of SSR- and SSS-BPS isomers, and comparison with the experimental values.

Isomer	Conformer	H1	H3	H2	H4	H9	Aromatics
SSR	A	1.19	2.65	3.56	5.07	4.26	7.4-7.9
	C	1.19	3.09	3.24	3.08	4.38	6.7-7.9
<i>SSR</i>	<i>Exp.</i>	<i>1.09</i>	<i>2.75</i>	<i>3.66</i>			
SSS	B	0.86	3.04	3.20	4.59	4.36	6.8-8.0
	C	1.17	2.59	3.78	4.70	4.24	7.4-8.0
<i>SSS</i>	<i>Exp.</i>	<i>0.96</i>	<i>2.90</i>	<i>3.34</i>			

Table 3. Relative energies (as calculated by pcff molecular-mechanics and DFT+D methods), and theoretical ^{13}C NMR chemical shifts of the three most stable conformers of the two BEP isomers; the formation of H-bonds, as well as the relative orientation along the $\text{C2}\cdots\text{N}$ bond, are also given.

RSR-BEP											
Conformer	RE (pcff)	RE (DFT)	C1	C3	C9	C2	C4	Aromatics	H- bond	C1/HN	C1/C9
RSR-A	0.0	0.0	6.2	36.3	56.1	73.0	83.0	126.1-139.7	No	Anti	Sin
RSR-H	2.4	-0.4	6.7	38.5	59.8	70.2	80.1	124.9-17.5	Yes	Anti	Sin
RSR-K	2.9	1.4	6.1	40.6	57.6	71.4	80.2	123.9-136.8	Yes	Anti	Sin
RSS-BEP											
Conformer	RE (pcff)	RE (DFT)	C1	C3	C9	C2	C4	Aromatics	H- bond	C1/HN	C1/C9
RSS-A	0.0	0.0	3.8	34.5	63.1	64.7	82.5	128.6-138.1	No	Anti	Sin
RSS-E	2.4	0.2	4.9	37.7	65.7	60.8	78.8	123.9-138.8	Yes	Anti	Sin
RSS-G	2.6	-0.1	7.4	32.6	67.5	69.9	80.0	124.1-138.1	Yes	Anti	Sin

Captions

Scheme 1. Molecular structure of the SDAs used in this work.

Figure 1. ^1H (left) and ^{13}C (right) liquid NMR spectra of an aqueous solution (in D_2O) of protonated BPS (using $\text{DCl}\cdot\text{D}_2\text{O}$ to give acidic pH)

Figure 2. Molecular structure of the three most stable conformers of SSR-BPS (top) and SSS-BPS (bottom), as calculated by DFT+D. The arrow indicates the distance (shown below) between cp0 aromatic C atoms used to identify the conformers during the MD simulations.

Figure 3. Molecular Dynamics results: total energy of the systems (left), and RDF (calculated in the 500-1000 ps time interval) between the substituted aromatic C atoms (right), indicative of the different conformations.

Figure 4. ^1H (left) and ^{13}C (right) liquid NMR spectra of an aqueous solution (in D_2O) of protonated BEP. *: unidentified bands.

Figure 5. Molecular structure of the three most stable conformers of RSR-BEP (top) and RSS-BEP (bottom), as calculated by DFT+D.

Figure 6. UV-Visible Fluorescence spectroscopy of MgAPO-5 materials obtained with BPS (left) or BEP (right) with 2 (molar composition of SDA) at 140 (black lines) or 180 (red lines) °C crystallization temperatures.

Figure 7. ^{13}C NMR spectra of MgAPO-5 materials (obtained with 2SDA and 140 °C crystallization temperature) prepared in the presence of BPS (top) and BEP (bottom); aqueous solutions of the protonated species are also shown for comparison. *: rotation bands.

Scheme 1

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

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