Ibuprofen Loading in Surfactant-Templated Silica: Role of the Solvent According to the Polarizable Continuum Model

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Ibuprofen (an anti-inflammatory drug) has been loaded onto two different surfactant-templated silicas (SBA-15 and MCM-48). To evaluate the effect of the drug−solvent combination on the loading capacity of the silica, we have performed ibuprofen adsorption experiments using 10 different solvents; we have interpreted our experimental results assuming a chemical equilibrium between the ibuprofen adsorbed on the silica and that remaining in solution. To estimate the equilibrium constant for different solvents, we have calculated the free energy in solution for the ibuprofen molecule using the polarizable continuum model (PCM) to take the solvent into account. The results have been analyzed statistically to eliminate the effects of the dispersion of experimental data; results reveal a statistically significant (95−99%) linear relationship between the ibuprofen loading capacity and its free energy in solution calculated with the PCM solvation model. In addition, useful relationships between loading capacity and dielectric constant and molecular size of the solvents are established.

Introduction

In recent years, surfactant-templated silica materials, known as molecular sieves, have been the focus of research as drug delivery systems.[1,2] The surfactant, added in a concentration above its critical micellar concentration, acts as the structure-directing agent during polymerization. Finally, the surfactant aggregates are removed, leaving an ordered mesoporous material with a uniform size, which is determined by the size of the surfactant aggregate.[3,4] These materials present two main advantages as drug carrier devices: (1) since they are mesoporous materials with a high specific pore volume, relatively large amounts of the drug can be loaded; (2) their narrow pore size distribution allows the rate of drug release to be controlled.

The loading capacity of mesoporous templated materials has been extensively studied. Specifically, several papers have evaluated effects of the features of the silica used, such as its pore size,[5,6] its specific surface area,[6] or its pore array structure.[7] Other research studies have evaluated the effect of the drug loaded, such as its chemical composition,[8] its pore size,[5] or its physical state.[9] Nevertheless, the role played by the drug solvent used in the impregnation process has hardly been studied at all. In the literature there is only one study, which reports the performance of ibuprofen adsorption onto mesoporous silica using solvents of different polarities.[10] In that study, Charnay et al. reported that, when ibuprofen is dissolved in highly polar solvents, such as dimethylformamide, dimethyl sulfoxide, and dimethylacetamide, it is only weakly adsorbed in the silica pores, or the adsorption may even be negligible. In contrast, when less polar solvents, such as hexane or ethanol, were used, ibuprofen was adsorbed. Therefore the drug loading varies as a function of the solvent polarity. However no explanations of this tendency were included in that study.

The aim of this study is to evaluate the drug-loading capacity of surfactant-templated silica considering the molecular characteristics of the solvent used in the impregnation process as the main parameters. Specifically, the dielectric constant values and the molecular sizes of the solvents used in the impregnation are believed to play a key role in the drug-loading process. In the present work two different silica matrices have been used, denoted SBA-15 and MCM-48. SBA-15[11] contains a hexagonal array of pores of around 8 nm diameter. In contrast with the unidirectional channel present in SBA-15, MCM-48 has a cubic structure with space group *Ia3d* and pore size of around 3 nm.[12]

The drug chosen as the loading model in this study is ibuprofen $C_{13}H_{18}O_2$, an anti-inflammatory drug; the small size of the molecule makes it suitable, because these can fit easily into the pores of smaller radius of the MCM-48 matrix. Its low molecular size also simplifies the quantum chemistry calculations including solvent effects. In addition, ibuprofen is commonly used as a drug model, thus allowing the results obtained to be compared with data already available in the literature.

For the interpretation of our experimental results, utilized in this study, we have made two assumptions:

(a) The quantity of drug adsorbed by the molecular sieve from a given solvent is determined mainly by an equilibrium between the drug dissolved and that adsorbed

$$X(\text{dissolved}) \rightleftarrows X(\text{adsorbed})$$

(b) Any other factor (for example, the heterogeneity of the molecular sieve, the differences of temperature between samples, etc.) has a random influence; such influences can be taken into account using standard statistical procedures (least-squares fits and analysis of errors).

Because the characteristics of the equilibrium are determined, for each solvent, by the difference between the free energy corresponding to the ibuprofen adsorbed, ΔG_0, and that corresponding to the ibuprofen dissolved, ΔG_k ($k = 1, 2, ..., 10$), it is necessary to calculate ΔG_k. We performed this calculation using ab initio quantum chemistry methods, taking into account the solvent effects by means of the polarizable continuum model (PCM) proposed by Tomasi et al.[13−24] All calculations have been

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TABLE 1: PCM and Experimental Solvation Free Energies for Representative Examples[a]

	solvent = water		solvent = *n*-hexane		$\Delta G_{water} - \Delta G_{hexane}$	
solute	ΔG^{PCM}	ΔG^{exp}	ΔG^{PCM}	ΔG^{exp}	PCM	exp
CH_3OH	−4.4	−5.1	−1.9	−1.4	−2.5	−3.7
C_2H_5OH	−4.5	−5.0	−2.4	−2.0	−2.1	−3.0
CH_3COCH_3	−3.3	−3.8	−3.2	−2.5	−0.1	−1.3
C_6H_6	−0.9	−0.9	−3.6	−4.0	+2.7	+3.1

[a] ΔG^{PCM} is the solvation free energy calculated using the PCM model; ΔG^{exp} is the experimental value (data taken from ref 13).

carried out using the standard Gaussian software[25] at the Hartree−Fock level, and the stability of the method against the choice of the basis set has been confirmed by comparing the results obtained with different bases.

It has not been necessary to calculate the free energy of the molecule of the ibuprofen adsorbed, ΔG_0, because, as will be seen later, this can be left as an empirical parameter, characteristic of the particular molecular sieve utilized. This assumption has been found to be extremely useful, since a direct quantum chemical calculation of ΔG_0 with sufficient accuracy for ($\Delta G_k - \Delta G_0$) to be significant would have proved extraordinarily difficult.

Experimental Section

Synthesis. MCM-48 material was obtained using the method proposed by Washmon and Kriel:[26] a solution of 10% w/w cetyltrimethylammonium bromide (CTAB) from Aldrich was prepared. With continuous stirring, 2 N sodium hydroxide solution and tetraethoxysilane (TEOS) were added, sequentially. The resulting solution was stirred at room temperature for 30 min. The gelation process took place after 5 min. The molar ratio of the gel was 1 SiO_2/0.23 Na_2O/0.55 CTAB/112 H_20. The resulting product was heated at 100 °C for 2 days and then collected by filtration. Finally, it was heated at 100 °C for 24 h after replacing the mother liquor with deionized water. MCM-48 was air-dried at room temperature overnight, and then the template was removed by calcination at 540 °C for 16 h.

SBA-15 was prepared according to the procedure described by Luan et al.[27] The amphiphilic triblock copolymer Pluronic type P10300, from BASF, with average molecular weight of 4950, was used. This is a block copolymer in which the central poly(propylene glycol) group is flanked by two poly(ethylene glycol) groups. The Pluronic copolymer was dispersed in water and 2 M chlorhydric acid solution while being stirred, followed by the addition of tetraethoxysilane (TEOS) from Aldrich. The molar ratio of the silica material was 1 SiO_2/5 HCl/41.66 H_2O/0.02 P10300. After gel transition, which took place in 10 min, the material was stirred continuously at 40 °C for 24 h and finally crystallized in an autoclave at 100 °C for 2 days. Then the solid product was filtered, washed, and air-dried at room temperature. The template was removed by calcination at 550 °C for 24 h.

Characterization. Powder X-ray diffraction (XRD) patterns were obtained using a Bruker D8 advance diffractometer equipped using Cu Kα radiation.

For transmission electron microscopy (TEM) observation, powder specimens were ground and deposited on a grid with a holey carbon film. These samples were visualized using a JEOL 2011 electron microscope with an accelerating voltage of 200 kV.

Nitrogen adsorption−desorption isotherms were measured at 77 K using a Sorptomatic 1990 analyzer. The specific surface area was determined from the linear part of the BET equation ($P/P_0 = 0.05-0.31$). The volume of adsorbed nitrogen was normalized to standard temperature and pressure. The pore size distribution was calculated from the desorption branches of the adsorption isotherm using the Barret−Joyner−Halenda model.[28]

Loading the Ibuprofen. The calcined powders were conformed into disks of 0.1 g by uniaxial pressure (1.7 Tm). Quantities of 100 mg of each of the powders were soaked in an ibuprofen solution containing 100 mg of ibuprofen in 3 mL of one of the solvents under study. The following 10 solvents, with a wide range of dielectric constants, were studied: cyclohexane (cyclo-C_6H_{12}) from Panreac, carbon tetrachloride (CCl_4) from Aldrich, toluene ($CH_3C_6H_5$) from Aldrich, diethyl ether ($C_2H_5OC_2H_5$) from Aldrich, chloroform ($CHCl_3$) from Panreac, tetrahydrofuran (C_4H_8O) from Aldrich, acetone (CH_3COCH_3) from Aldrich, ethanol (C_2H_5OH) from Aldrich, methanol (CH_3OH) from Merck, and acetonitrile (CH_3CN) from Aldrich. The purity of all the solvents under study was above 99%. The loading time was 3 days, and the loading temperature was 37 ± 1 °C. After loading, the materials were dried at 100 °C for 24 h.

Since the silica materials evaluated do not contain carbon, the determination of ibuprofen content in the MCM-48 and SBA-15 was based on the carbon content of the loading materials, determined through elemental analysis using a Leco CHNS-932 elemental analyzer.

The ibuprofen mass (mg) loaded in 100 mg of silica material is

$$\alpha_k = \frac{100 \cdot (\%C)}{75.69 - (\%C)} \tag{1}$$

where (%C) is the carbon percentage measured in the sample.

As the ibuprofen mass still dissolved is ($100 - \alpha_k$) mg, the moles number of ibuprofen dissolved (n_{IBU}) is

$$n_{IBU} = \frac{100 - \alpha_k}{206.28} \tag{2}$$

The moles number of the solvent ($n_{Solvent}$) is

$$n_{Solvent} = \frac{m_{Solvent}}{M_{Solvent}} = \frac{V_{Solvent} \cdot d_{Solvent}}{M_{Solvent}} = \frac{3 \cdot d_{Solvent}}{M_{Solvent}} \tag{3}$$

where m is mass (g), M is molar mass, d is density (g/mL), and V is volume (mL) of the solvent. According to the experimental data, the solvent volume used was 3 mL.

Thus, the molar fraction of ibuprofen dissolved in each solvent evaluated (x_k) could be calculated from

$$x_k = \frac{n_{IBU}}{n_{IBU}+n_{Solvent}} = \frac{1}{1 + \frac{3d_{Solvent}}{M_{Solvent}} \cdot \frac{206.28}{(100 - \alpha_k)}} \tag{4}$$

Computational Section

The polarizable continuum model (PCM) of Tomasi et al.[13−24] has been applied to perform the calculation of the energies in solution because, hypothetically, it permits the *differences* between the free energies in solution of ibuprofen in the solvents used to load the drug to be estimated with sufficient accuracy.

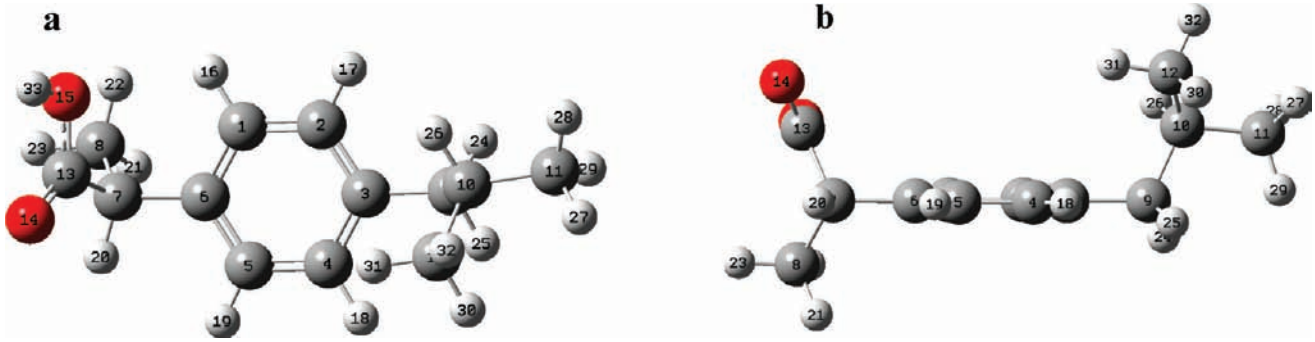

Figure 1. Ibuprofen HF/6-31G, view from top (a) and view from side (b).

TABLE 2: Efficiency of Various Alternative Basis Sets in the Calculation of in Vacuo Conformations of the Ibuprofen Molecule[a]

method	ΔE (eV)	V_0 (eV)	t/t_0
HF/6-311G(2d,p)	0.016	0.142	29
HF/6-31G(d,p)	0.014	0.152	5
HF/6-31G(d)	0.014	0.147	3.5
HF/6-31G	0.016	0.171	"1"
HF/STO-3G	0.082	0.150	0.06

[a] ΔE is the energy difference between conformers, V_0 is the height of the barrier between them, and t/t_0 is relative time required for calculating.

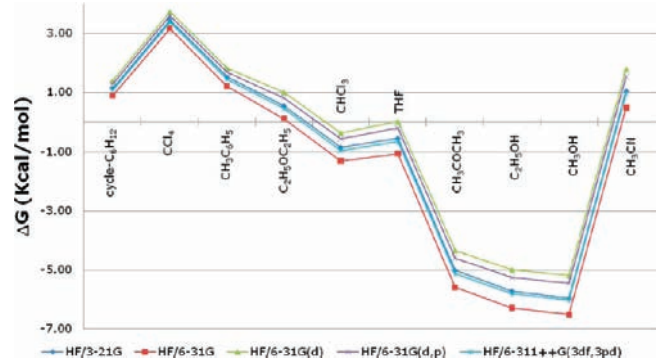

Figure 2. Free energies in solution of ibuprofen, obtained using the PCM and different basis sets, in 10 solvents ranked from lower to higher value of their dielectric constant.

This hypothesis is supported by data such as those provided by Tomasi in ref 13, and Table 1 has been produced with these data. It can be seen in this table that, although the theoretical calculations by means of the PCM do not reproduce exactly the experimental free energies in solution, the trend of these energies when the solvent is changed is adequately reproduced.

The ibuprofen molecule (Figure 1) possesses various conformations, determined principally by internal rotations around the links 6−7, 7−13, 3−9, and 9−10, of Figure 1. As a prior phase to the application of the PCM solvation model, the molecular geometry of ibuprofen has been obtained at the HF/6-31G level in vacuo, starting from the molecule designed with Gaussview, seeking one by one the minimum with respect to the four internal rotations cited, and finally optimizing all the distances and angles for the most stable conformation. The geometry represented in Figure 1 is obtained. This in vacuo geometry, of which the dihedral angles are $D(1-6-7-8) = -121.6°$; $D(2-3-9-11) = 73.9°$; $D(3-9-10-11) = -172.2°$, and $D(6-7-13-14) = -106.5°$, is the geometry that has been utilized for the calculations with all the solvents.

The employment of the HF/6-31G method seems to us to be preferable to a more sophisticated one, for several reasons. The first is that, in preliminary calculations, we had checked that employing more complicated basis sets does not appear to modify the results significantly, as can be seen in Tables 2 and 3 and Figure 2.

The data in Table 2 show the difference in energy between the two most stable conformations of the ibuprofen molecule (ΔE) and the height of the rotation barrier that separates them (V_0), obtained with basis sets better and worse than 6-31G.

The data in Table 3 show the solvation energies of ibuprofen obtained with the PCM method and various different basis sets, calculated with the in vacuo molecular geometry of ibuprofen. It can be seen that the differences between the results obtained with the different basis sets are not decisive, whereas the increased complexity of the task required to perform the calculations can be significant.

The second reason for the use of the 6-31G basis set is that, although wider basis sets can be employed with ibuprofen, most of the other drugs for which this type of study could be relevant possess much larger molecules; therefore, it is most unlikely that it would be feasible to use very complex basis sets for them.

TABLE 3: Solvation Energies of Ibuprofen Obtained Using Different Basis Sets[a]

solvent	$\epsilon(37°)$	HF/3-21G	HF/6-31G	HF/6-31G(d)	HF/6-31G(d,p)	HF/max[b]
cyclo-C_6H_{12}	1.997	1.15	0.90	1.39	1.30	1.08
CCl_4	2.204	3.45	3.17	3.72	3.61	3.38
$CH_3C_6H_5$	2.345	1.53	1.22	1.82	1.70	1.45
$C_2H_5OC_2H_5$	4.091	0.55	0.12	1.01	0.83	0.45
$CHCl_3$	4.506	−0.86	−1.31	−0.37	−0.56	−0.96
THF	7.130	−0.55	−1.06	0.02	−0.20	−0.67
CH_3COCH_3	19.234	−5.03	−5.59	−4.34	−4.60	−5.15
C_2H_5OH	23.544	−5.73	−6.28	−5.00	−5.26	−5.82
CH_3OH	30.939	−5.97	−6.51	−5.20	−5.46	−6.04
CH_3CN	33.591	1.05	0.49	1.80	1.54	0.96

[a] The molecular geometry of ibuprofen has been "frozen" at the in vacuo results (see Figure 1). [b] The abbreviation "max" refers to the basis set 6-311++G(3df,3pd).

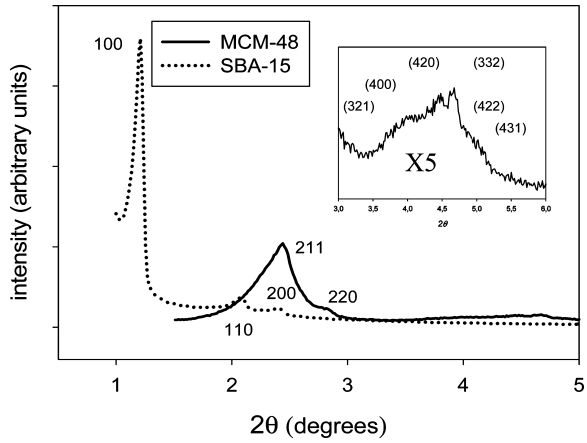

Figure 3. XRD patterns of the molecular sieves under study. For MCM-48, detail of reflections ranging from 321 to 431 is shown in the inset.

Results and Discussion

Experimental Results. The XRD patterns for the two surfactant-templated silicas synthesized in our laboratory are shown in Figure 3. For MCM-48, the two first peaks corresponding to (211) and (220) reflections and the broad feature resulting from 321 to 431 reflections (see inset in the Figure 3) are in good agreement with reported patterns from pure MCM-48 materials.[29] The $d_{(211)}$ spacing is 36.4 Å, compatible with the cubic *Ia*3*d* space group,[29] and the corresponding cubic cell parameter a is 89.1 Å based on the equation $a = d_{211}(6)^{-1/2}$. In contrast, the SBA-15 peaks can clearly be indexed to a hexagonal lattice[27] with a main reflection to 100 and two smaller reflections to 110 and 200. The $d_{(100)}$ spacing is 73.5 Å corresponding to $d_{(100)}$ spacing of 84.9 Å, corresponding to a large unit cell parameter a of 84.9 Å, with $a = 2d_{100}/3^{1/2}$.

The structural assignment based on the XRD patterns is corroborated by the TEM analysis. Figure 4 shows TEM images with the Fourier diffractograms. The MCM-48 image was recorded in the direction of the pore axis. The image shows a well-defined hexagonal arrangement, observed typically in MCM-48 material in the [111] direction. In the case of SBA-15, the image was captured in the direction perpendicular to the pore axis. The hexagonal array of uniform channels is directly visible.

The two nitrogen adsorption−desorption isotherms are shown in Figure 5. Both of them are typical type IV adsorption isotherms as defined by IUPAC. In the case of MCM-48, a sharp inflection between relative pressure 0.2 and 0.4 is observed, corresponding to capillary condensation within uniform mesopores. This steep step up reflects the uniform size of their pores. The SBA-15 isotherm is similar to those found for this material in the literature[27] and shows a pronounced pore filling step at P/P_0 0.5 and a significant hysteresis. A very narrow pore radius distribution is observed for the two materials. MCM-48 exhibits an average pore radius of 1.4 nm, whereas the average value for SBA-15 is 2.5 nm. For MCM-48, the BET surface area was 1556 m^2/g and the pore volume value was 1.14 cm^3/g. For SBA-15, these values are 756 m^2/g and 1.12 cm^3/g, respectively.

Experimental data from ibuprofen loading on SBA-15 and MCM-48, using the solvents studied, are given in Tables 4 and 5. Specific characteristics of the solvents are also included.

Relationship between the Ibuprofen Loading and the Free Energy of Solvation. If sufficient time is elapsed before the measurements of the quantity of ibuprofen loaded are made (in our experiments, 3 days), it can be assumed that equilibrium is reached between the ibuprofen loaded in the surfactant-templated silica and that which remains in solution:

$$C_{13}H1_8O_2(\text{silica}) \rightleftarrows C_{13}H_{18}O_2(\text{solvent}) \quad (5)$$

Consequently, the chemical potential of the ibuprofen that is loaded in the silica

$$\mu_{\text{silica}} = \mu^*_{\text{silica}} + RT\ln(x_{\text{silica}}/x^0_{\text{silica}}) \quad (6)$$

will be equal to the chemical potential of the ibuprofen that remains in solution

$$\mu_{\text{solution}} = \mu^*_{\text{solution}} + RT\ln(x_{\text{solution}}/x^0_{\text{solution}}) \quad (7)$$

where x_{solution} is the molar fraction of the ibuprofen in the solvent considered, and x_{silica} is that of the ibuprofen in the silica. In addition, taking advantage of the fact that the mass of the silica is much greater than that of ibuprofen, we will make the approximation $x_{\text{silica}} \approx x^0_{\text{silica}}$, such that $\mu_{\text{silica}} \approx \mu^*_{\text{silica}}$ will be considered a constant characteristic of the type of surfactant-templated silica employed. Thus the equilibrium condition to apply with the different solvents will be

$$\mu^*_{\text{solution}} + RT\ln(x_{\text{solution}}/x^0_{\text{solution}}) = \mu_{\text{silica}}\ (\approx\text{constant}) \quad (8)$$

The standard chemical potential of ibuprofen in each solvent, μ^*_{solution}, will depend on whatever molar fraction x^0_{solution} is chosen as reference, but can be assumed to be proportional to the free solvation energy of ibuprofen in the solvent considered

$$\mu^*_{\text{solution}} = K(x^0_{\text{solution}}) \cdot \Delta G_{\text{solution}} \quad (9)$$

The free energy in solution $\Delta G_{\text{solution}}$ is different for each solvent and can be calculated using the solute−solvent interaction models provided in the literature and available in programs such as GAUSSIAN.[13,31−33] Consequently, if our assumptions are correct, it should be

$$\ln(x_{\text{solution}}) = -\frac{K(x^0_{\text{solution}})}{RT}\cdot\Delta G_{\text{solution}} + \left(\ln(x^0_{\text{solution}}) - \frac{\mu^*_{\text{silica}}}{RT}\right) \quad (10)$$

and a linear relationship $y = A\cdot x + B$ should exist between the variable $x = \Delta G_{\text{solution}}$ and the variable $y = \ln(x_{\text{solution}})$, with coefficients A and B being constant for constant temperature. This linear relationship may be obscured by the dispersion of the experimental measurements, which is clearly demonstrated by comparing the data corresponding to "sample 1" and "sample 2" in Tables 4 and 5. However, this difficulty is easily removed using least-squares techniques as implemented in the standard statistical software packages. We have employed Statgraphics[34] to fit the data given in Table 6 and have obtained the results shown in Tables 7 and 8 and in Figures 6, 7, and 8.

The equilibrium molar fraction x_{solution} indirectly determines the drug-loading capacity from each solvent, since the smaller the fraction, the greater will be the quantity of ibuprofen

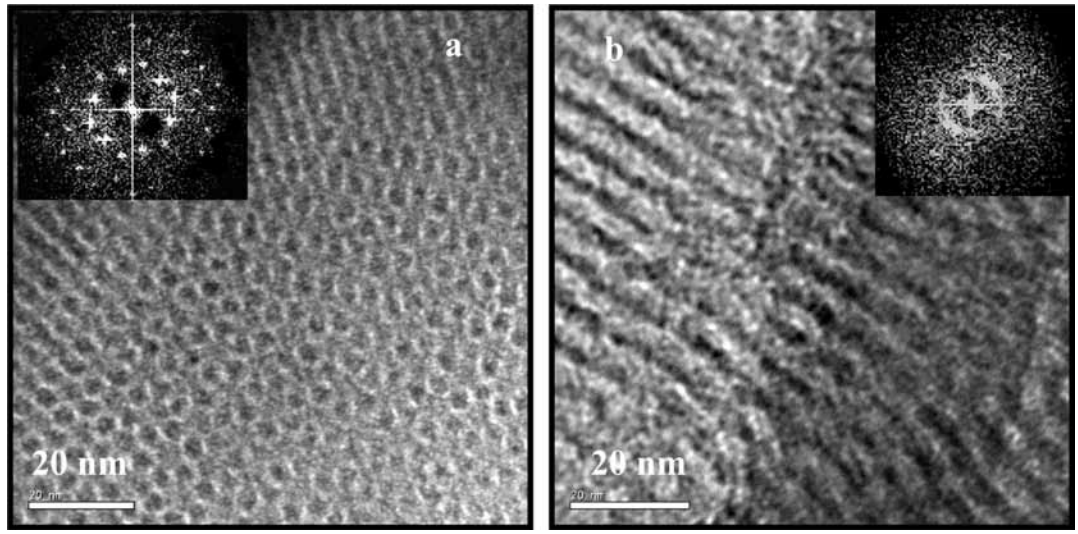

Figure 4. TEM images and Fourier diffractograms of MCM-48 (a) and SBA-15 (b).

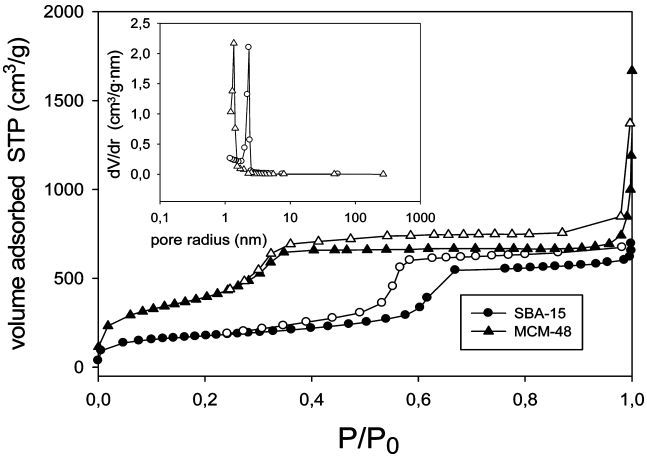

Figure 5. Adsorption−desorption isotherms for the molecular sieves under study. The inset shows the BJH pore radius distribution.

TABLE 4: Experimental Data from Ibuprofen Loading on SBA-15, Using the Solvents Studied[a]

solvent	dielectric constant (37 °C)	molecular mass	density (g/cm^3)	carbon content (%C) sample 1	carbon content (%C) sample 2
cyclo-C_6H_{12}	1.997	84.159	0.7739	6.22	9.05
CCl_4	2.204	153.8	1.594	12.54	11.30
$CH_3C_6H_5$	2.345	92.1	0.8668	6.04	7.12
$C_2H_5OC_2H_5$	4.091	74.1	0.7138	5.61	3.74
$CHCl_3$	4.506	119.4	1.4788	4.34	4.62
C_4H_8O	7.130	72.1	0.8833	3.26	2.82
CH_3COCH_3	19.234	58.1	0.7845	2.69	3.54
C_2H_5OH	23.544	46.1	0.7893	3.40	3.28
CH_3OH	30.939	32.042	0.7914	3.64	3.17
CH_3CN	33.591	41.052	0.7857	2.55	2.18

[a] Specific characteristics of the solvents were obtained from ref 30.

that has been loaded in the silica matrix. From the experimental data, the value of $x_{solution}$ corresponding to each solvent is determined by the formula

$$x_{solution} = \frac{10^{-3}(100 - \alpha_k)M_{IBU}^{-1}}{10^{-3}(100 - \alpha_k)M_{IBU}^{-1} + 3d_{solvent}M_{solvent}^{-1}} = \frac{1}{1 + z_{solvent}} \quad (11)$$

TABLE 5: Experimental Data from Ibuprofen Loading on MCM-48, Using the Solvents Studied

solvent	dielectric constant (37 °C)	molecular mass	density (g/cm^3)	carbon content (%C) sample 1	carbon content (%C) sample 2
cyclo-C_6H_{12}	1.997	84.159	0.7739	12.61	13.91
CCl_4	2.204	153.8	1.594	9.00	12.36
$CH_3C_6H_5$	2.345	92.1	0.8668	7.01	7.01
$C_2H_5OC_2H_5$	4.091	74.1	0.7138	2.34	3.03
$CHCl_3$	4.506	119.4	1.4788	3.72	5.01
C_4H_8O	7.130	72.1	0.8833	4.69	5.77
CH_3COCH_3	19.234	58.1	0.7845	1.96	2.16
C_2H_5OH	23.544	46.1	0.7893	2.83	1.93
CH_3OH	30.939	32.042	0.7914	2.54	2.30
CH_3CN	33.591	41.052	0.7857	1.75	2.33

where

$$z_{solvent} = \frac{3d_{solvent}M_{IBU}}{10^{-3}(100 - \alpha_k)M_{solvent}} \quad (12)$$

where $d_{solvent}$ = density of the solvent in g/cm^3, $M_{solvent}$ = molecular mass of the solvent in g/mol, and M_{IBU} = molecular mass of ibuprofen.

The variable α_k is the quantity, in milligrams, of ibuprofen adsorbed per 100 mg of silica when each solvent is used and is determined by eq 1.

PCM Calculation of the Ibuprofen Free Energies in Solution. Table 3 gives the free energies in solution of ibuprofen in the 10 solvents studied, calculated with five representative basis sets, and Table 6 gives the values of $\ln(x_{solution})$ determined from the experimental data of Tables 4 and 5 and eq 11. By employing two series of independent measurements of %C for each silica, we have been able to confirm that, as can be seen in Table 7, the differences between the values of %C experimentally determined are relatively unimportant for testing the hypothesis put forward. Moreover, by comparing the results obtained with materials SBA-15 and MCM-48, we are able to demonstrate the robustness of the approximation $\mu_{silica} \approx$ constant made in obtaining eq 10.

The results of fitting, by least-squares, the variable $y = \ln(x_{solution})$ to the variable $x = \Delta G_{solution}$ can be seen in Figures 6 and 7 and in Table 7. The only case represented in these figures, as an example, is that in which $\Delta G_{solution}$ is calculated by means of HF/6-31G(d), because all the other cases are

TABLE 6: Data Required To Apply Eq 10, Obtained from the Contents of Tables 4 and 5[a]

solvent	ln(x_{sol}) MCM-48 (sample 1)	ln(x_{sol}) MCM-48 (sample 2)	ln(x_{sol}) SBA-15 (sample 1)	ln(x_{sol}) SBA-15 (sample 2)
cyclo-C_6H_{12}	−4.2785	−4.3101	−4.1512	−4.2025
CCl_4	−4.3195	−4.3907	−4.3950	−4.3669
$CH_3C_6H_5$	−4.1877	−4.1877	−4.1709	−4.1897
$C_2H_5OC_2H_5$	−4.1365	−4.1465	−4.1866	−4.1570
$CHCl_3$	−4.4046	−4.4248	−4.4142	−4.4186
C_4H_8O	−4.4090	−4.4265	−4.3869	−4.3805
CH_3COCH_3	−4.4642	−4.4670	−4.4746	−4.4872
C_2H_5OH	−4.7118	−4.6988	−4.7203	−4.7185
CH_3OH	−5.0712	−5.0677	−5.0876	−5.0805
CH_3CN	−4.8067	−4.8149	−4.8182	−4.8127

[a] x_{sol} is the molar fraction of ibuprofen in the solvent considered.

TABLE 7: Results of Fitting $\ln(x_s) = A \cdot \Delta G_s + B$ from the Different Sets of Experimental Data and from Different Methods of Calculating ΔG

basis set	data	*A*	*B*	*p*-value	outliers	*p*-value (without outlier)
HF/3-21G	MCM-48 (1[a])	0.0571	−4.419	0.044	CH_3CN	0.008
	MCM-48 (2[a])	0.0521	−4.439	0.063	CH_3CN	0.015
	SBA-15 (1[a])	0.0576	−4.421	0.052	CH_3CN	0.011
	SBA-15 (2[a])	0.0579	−4.421	0.045	CH_3CN	0.008
HF/6-31G	MCM-48 (1[a])	0.0562	−4.395	0.041	CH_3CN	0.008
	MCM-48 (2[a])	0.0513	−4.417	0.059	CH_3CN	0.015
	SBA-15 (1[a])	0.0569	−4.396	0.048	CH_3CN	0.011
	SBA-15 (2[a])	0.0571	−4.397	0.042	CH_3CN	0.009
HF/6-31G(d)	MCM-48 (1[a])	0.0579	−4.449	0.054	CH_3CN	0.008
	MCM-48 (2[a])	0.0528	−4.466	0.075	CH_3CN	0.015
	SBA-15 (1[a])	0.0582	−4.451	0.065	CH_3CN	0.012
	SBA-15 (2[a])	0.0587	−4.451	0.056	CH_3CN	0.009
HF/6-31G(d,p)	MCM-48 (1[a])	0.0575	−4.438	0.051	CH_3CN	0.008
	MCM-48 (2[a])	0.0525	−4.456	0.071	CH_3CN	0.015
	SBA-15 (1[a])	0.0579	−4.439	0.061	CH_3CN	0.012
	SBA-15 (2[a])	0.0583	−4.440	0.053	CH_3CN	0.009
HF/"max"[a]	MCM-48 (1[a])	0.0568	−4.415	0.045	CH_3CN	0.008
	MCM-48 (2[a])	0.0519	−4.435	0.064	CH_3CN	0.015
	SBA-15 (1[a])	0.0574	−4.416	0.053	CH_3CN	0.012
	SBA-15 (2[a])	0.0577	−4.416	0.046	CH_3CN	0.009

[a] The abbreviation "max" refers to the basis set 6-311++G(3df,3pd).

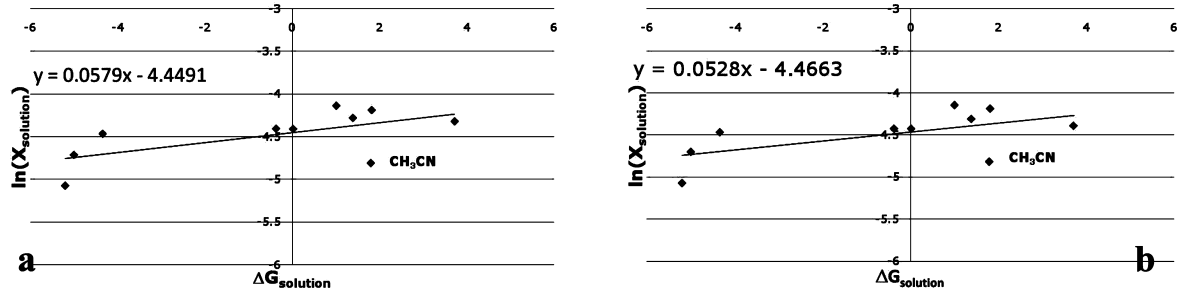

Figure 6. Result for the gel MCM-48: (a) first group of results; (b) second group of results. The single outlier detected by Statgraphics, CH_3CN, is pointed out in the graph.

TABLE 8: Slope *A* and Intercept *B* of the Fits Obtained from the Quantum Chemistry Calculations Performed with Basis Sets of Increasing Complexity

method	HF/3-21G	HF/6-31G	HF/6-31G(d)	HF/6-31G(d,p)	HF/"max"[a]
A	0.067 ± 0.009	0.065 ± 0.009	0.071 ± 0.009	0.069 ± 0.009	0.067 ± 0.009
B	−4.36 ± 0.03	−4.34 ± 0.03	−4.39 ± 0.03	−4.38 ± 0.03	−4.36 ± 0.03

[a] The abbreviation "max" refers to the basis set 6-311++G(3df,3pd).

completely analogous. According to Statgraphics,[34] the value of the statistical parameter "*p*" is close to 0.05 in all the fits of Table 7; therefore, there is a statistically significant relationship between $\ln(x_{solution})$ and $\Delta G_{solution}$ for a level of confidence close to 95%. This level increases to almost 99% (corresponding to $p < 0.01$) if the single outlier detected is eliminated.

Table 8 gives a comparison of the results of fitting all the experimental data, combined in one single set of data (four for each solvent) *excluding those referring to acetonitrile* because the result for that solvent is very clearly an outlier. It is clear that, at least in the cases that we have now studied, the basis set employed for performing the calculations is only of minor

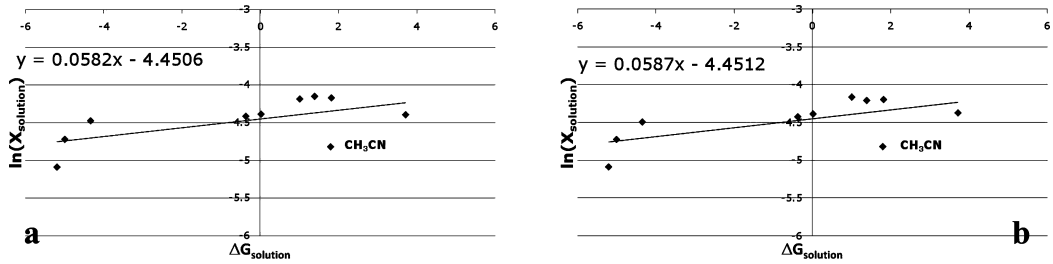

Figure 7. Result for the gel SBA-15: (a) first group of results; (b) second group of results.

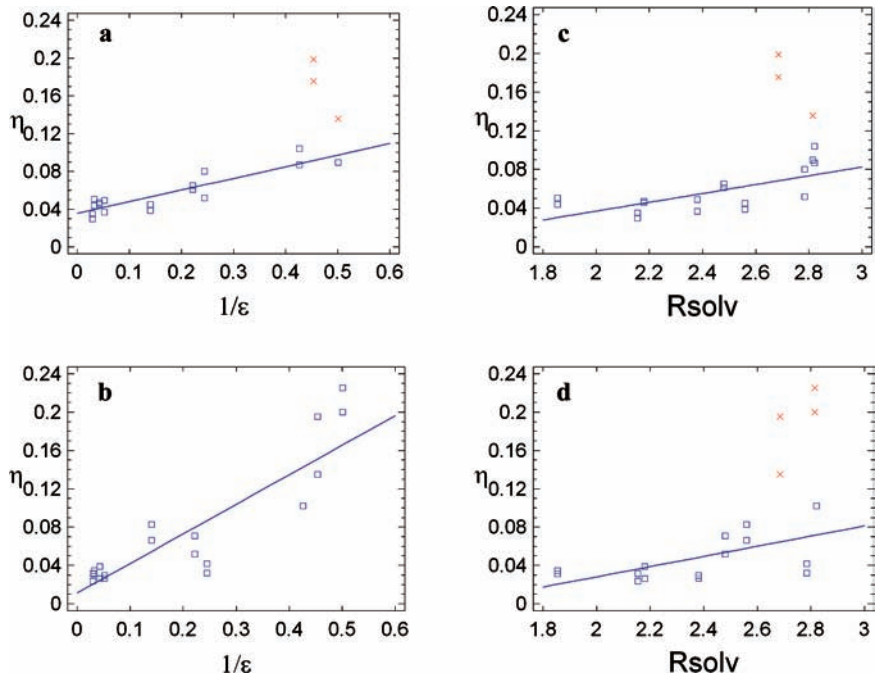

Figure 8. Relationship between the amount of ibuprofen loaded in the silica, η, and the inverse of dielectric constant for SBA-15 (a) and for MCM-48 (b), and between η and R_{solv} for SBA-15 (c) and for MCM-48 (d).

importance, which would be very convenient for studying the loading of drugs with molecules larger than that of ibuprofen.

The Roles of the Dielectric Constant and the Molecular Size of the Solvent. The parameters used in the PCM solvation model to calculate the free solvation energy depend on the characteristics of both the solute and the solvent. Since the solute is always the same, in our study, the only parameters that change from one case to another, producing the variation of ΔG_{solv}, are simply the dielectric constant ε and the characteristic radius R_{solv} of the solvent.

In Figure 2 it can be appreciated that, although there are some exceptions, there is effectively a very clear relationship between the dielectric constant ε of each solvent and the value $\Delta G_{solution}$ calculated when ibuprofen is dissolved in that solvent. A relationship could therefore be expected to exist between the dielectric constant ε of the solvents and the ibuprofen loading. Since, in turn, the quantity of ibuprofen loaded is greater the smaller the quantity of the drug that remains in solution, it can be expected that an inverse relationship exists between the quantity of ibuprofen loaded in the silica from the kth solvent (η_k)

$$\eta_k = \left(\frac{g_{IBU}}{g_{silica}}\right) = 10^{-2}\alpha_k = \frac{\%C}{75.69 - \%C} \qquad (13)$$

and the dielectric constant. In Figure 8 a graphical representation of $y = \eta_k$ against $x = 1/\varepsilon_k$ can be seen for SBA-15 (Figure 8a) and for MCM-48 (Figure 8b). Fitting linear relationships, we obtain, for SBA-15

$$\eta = (0.035 \pm 0.003) + (0.12 \pm 0.02) \cdot \varepsilon^{-1} \qquad (14)$$

and for MCM-48

$$\eta = (0.01 \pm 0.01) + (0.31 \pm 0.04) \cdot \varepsilon^{-1} \qquad (15)$$

According to Statgraphics,[34] the p-value of the ANOVA table is less than 0.01 for both cases, and therefore both relationships are statistically significant with a level of confidence of 99%.

The relationship between the loading capacity of ibuprofen on silica and the inverse of the dielectric constant allows us to understand the relationship existing between this capacity and the polarity of the solvent, which was noted by Charnay et al.[10] The relationship between the polarity and the dielectric constant is well-known. As can be seen in the first columns of Table 9, the dielectric constant and the dipole moment of the solvents utilized increase at the same time: solvents that load less ibuprofen in the molecular sieve (because they have a higher dielectric constant) are those that have a higher dipole moment. Similarly, the relationship between loading capacity and dielectric constant, and its explanation via an equilibrium (dissolved $\rightleftarrows$ adsorbed), provides an initial explanation of why ibuprofen is released when the loaded silica is introduced into

TABLE 9: Relationship between R_{solv} and the Diameter of the Solvent Molecule, and between R_{solv} and the Volume of the Solvent Molecule, Calculated with Hartree−Fock and the 6-31G Basis Set[a]

solvent	dielectric constant (37 °C)	dipole moment (D)	R_{solv} (b)	diameter (b)	volume (b^3)
cyclo-C_6H_{12}	1.997	0.0	2.815	13.94	890.2
CCl_4	2.204	0.0	2.685	12.47	829.2
$CH_3C_6H_5$	2.345	0.375	2.820	15.59	845.7
$C_2H_5OC_2H_5$	4.091	1.150	2.785	17.08	857.0
$CHCl_3$	4.506	1.040	2.480	12.51	733.0
C_4H_8O	7.130	1.750	2.560	12.65	688.5
CH_3COCH_3	19.234	2.88	2.380	12.57	568.6
C_2H_5OH	23.544	1.69	2.180	12.19	470.4
CH_3OH	30.939	1.70	1.855	9.91	359.3
CH_3CN	33.591	3.925	2.155	11.13	422.0

[a] Experimental data taken from ref 30.

body fluid. This latter consists, mainly, of water whose dielectric constant is high and whose R_{solv} is low, such that if the ibuprofen is sufficiently concentrated on the silica, it will tend to be released. However, this reasoning can only be a partial explanation, since there are many others factors that could influence the release of the ibuprofen, apart from the displacement of the equilibrium. These would include, in particular, the kinetic factors, which we have been able to ignore in our study by making the measurements of quantity of ibuprofen adsorbed after 3 days of contact between the silica and the solution.

When a correlation is sought between η_k and the radius of the solvent measured by the parameter R_{solv} from the PCM, a relationship is obtained, but rather less clear than that obtained for the dielectric constant ε. The relationship between η_k and R_{solv} when SBA-15 is employed can be seen in Figure 8c, and in Figure 8d when MCM-48 is employed. The linear fits obtained are, for SBA-15

$$\eta = (-0.06 \pm 0.03) + (0.05 \pm 0.01) \cdot R_{solv} \quad (16)$$

and for MCM-48

$$\eta = (-0.08 \pm 0.04) + (0.05 \pm 0.02) \cdot R_{solv} \quad (17)$$

The p-value of the ANOVA table becomes less than 0.01 again in both cases, indicating that the relationships between η and R_{solv} are also statistically significant with a level of confidence of 99%.

Although the explanation of the relationships $\eta = f(\varepsilon^{-1})$ or $\eta = f(R_{solv})$ that we have found may be basically statistical, it could be that such relationships turn out to be more useful than the relationship between η and ΔG_{solv} that was studied in the preceding section. Evidently, the dielectric constant is an experimental value available from the bibliography for all the usual solvents, and this value can be used directly without having to resort to any complementary calculation.

With reference to the relationship between the loading capacity and the radius of the solvent, it should be taken into account that the R_{solv} datum is not as accessible as the dielectric constant, since it is an internal parameter of the PCM that has only been calculated for some solvents. However, the purely intuitive relationship between R_{solv} and the size of the molecule of solvent is easy to demonstrate, as can be seen in Table 9 or in Figure 9, in which the value of R_{solv} employed by the PCM for the solvents dealt with in this study is compared with two estimations of their molecular size. The first is a molecular "diameter" calculated by summing the larger of the internuclear distances R_{AB} and the van der Waals radii of the atoms A and B. The second is the cubic root of the molecular volume calculated with the GAUSSIAN program and its option "Density = Volume". With this option the volume that corresponds to the interior of an area of electronic isodensity of 0.001 electrons/b^3 is determined by means of a Montecarlo integration. The relationship between R_{solv} and $V^{1/3}$ is clearly more reliable than the relationship between R_{solv} and the diameter, and although it requires an ab initio calculation, this refers to the volume of the solvent molecule (which is usually small). In addition, the results depend very little on the quality of the basis set, and so the simplest methods can be employed.

Evidently, eqs 14−15 are useful for predicting the loading of ibuprofen on the gel from different solvents, and they present some advantages with regard to the relationship as expressed in eq 10 since no quantum chemistry calculation is required. However, eq 10 should be more accurate, and it has the advantage of allowing a variety of enhancements to be made. For example, another factor that could be introduced is the effect of the solvent on the molecular geometry of the ibuprofen dissolved (this factor has been taken as invariable in the present work). Moreover, the standard PCM can be replaced by other methods that may be found more suitable. Currently we are beginning work to develop both these hypotheses.

Conclusions

Using the PCM solvation model, it is possible to give a semiquantitative interpretation with respect to the quantity of ibuprofen loaded on a surfactant-templated silica as a function of the nature of the solvent.

The dielectric constant is the most relevant of the parameters that define the action of the solvent in the PCM, for the loading of the ibuprofen on the silica; this explains and improves the empirical relationship that exists between the loading capacity and the polarity of the solvent, pointed out by Charnay et al.

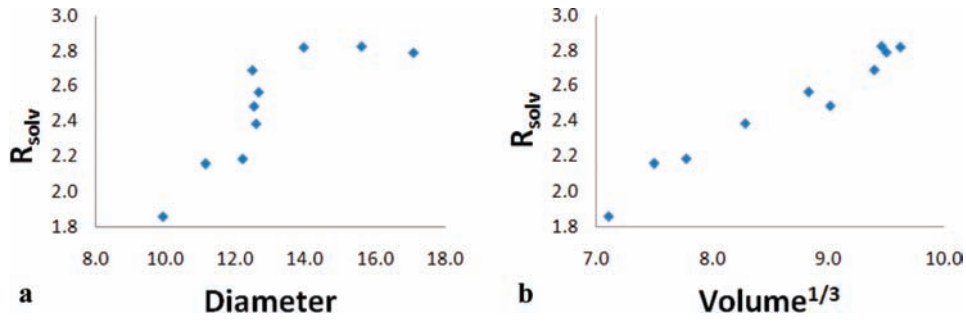

Figure 9. Relationship between (a) R_{solv} and the diameter of the solvent molecule and between (b) R_{solv} and the cubic root of the volume of the solvent molecule (HF/6-31G). Values in au.

The influence of the size of the basis set on the result of this type of calculation is not very significant. This may facilitate the application of this methodology for studying the loading on these sieves of molecules larger than ibuprofen.

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