
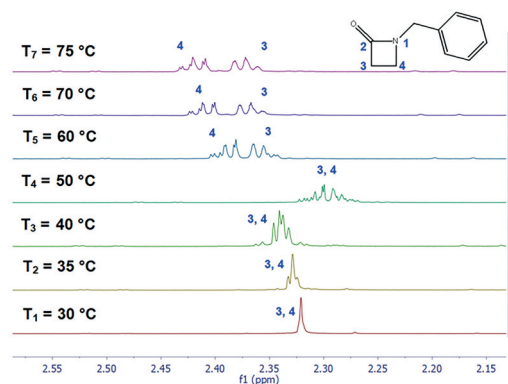


A New Approach Using Aromatic-Solvent-Induced Shifts in NMR Spectroscopy to Analyze β -Lactams with Various Substitution Patterns

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Abstract The chemical shifts of protons depend not only on the properties of the solute molecule but also on the medium in which the solute resides. A series of β -lactams with various substitution patterns were synthesized to study aromatic-solvent-induced shifts (ASISs) in chloroform and benzene by using ^1H NMR spectroscopy. The results agreed with those obtained by theoretical density functional theory calculations. The protons of the β -lactam ring are the most affected by the ASIS effect, and they tend to overlap due to the anisotropic effect of benzene.

Key words lactams, NMR spectroscopy, solvent effect

^1H NMR chemical shifts of organic molecules can vary depending on the solvent used. When a compound is dissolved in an anisotropic solvent such as benzene, the solvent causes NMR signals to shift upfield in comparison with their shifts in an isotropic solvent such as tetrachloromethane. This chemical shift in the ^1H NMR when using solvents with different magnetic properties is known as an aromatic-solvent-induced shift (ASIS) and is defined as follows: $\Delta\delta(\text{ASIS}) = \delta_{\text{AS}} - \delta_{\text{S}}$, where δ_{AS} is the position of the signal of an H atom in an aromatic solvent (e.g., C_6D_6) and δ_{S} is the value for the same signal in an isotropic solvent (e.g., CDCl_3).^{1,2} If the value of $\Delta\delta(\text{ASIS})$ is positive, this indicates a downfield shift relative to the signal position in the isotropic solvent. If the value of $\Delta\delta(\text{ASIS})$ exceeds 1.5 ppm, this can be a useful tool for resolving structural, stereochemical, and conformational problems.^{3–8}

This phenomenon has been rationalized by considering small perturbations in a solvent–solute mixture. For example, if a solute molecule has a dipole moment, as in the case of benzene, its greatest electron density will be located at

the positive end of the dipole, whereas at the peripheral edge of the molecule will be oriented toward to the negative part of the dipole.⁹ Other explanations have also been proposed for the origin of the ASIS effect, such as the induced quadrupole–quadrupole interaction model,⁶ the hydrogen-bond interaction model,¹⁰ a solvent–solute model of 1:1 complexes, and the formation of time-averaged clusters.¹¹

The anisotropy of benzene can help to disclose solute–solvent interactions that might not be detected without it. For example, ASIS has been used to differentiate axial and equatorial hydrogen atoms or methyl substituents alpha to carbonyl groups. In cyclohexanone, the ^1H NMR signal for an axial 2-methyl group is shifted 0.2–0.3 ppm upfield in benzene compared with that in tetrachloromethane, whereas the signal for an equatorial 2-methyl group is shifted 0.005–0.1 ppm downfield.³ This has been used to define the configuration at the 2-position and to measure the conformational equilibrium in 2-methylcyclohexanone.

The carbonyl-plane rule permits the location of hydrogen atoms relative to a keto group (Figure 1).^{12–14} If we imagine a plane perpendicular to the C–CO–C plane that passes through the sp^2 carbon, the value of $\Delta\delta(\text{ASIS})$ is positive for hydrogen atoms lying in front of the perpendicular plane and negative for those lying behind it. As can be seen

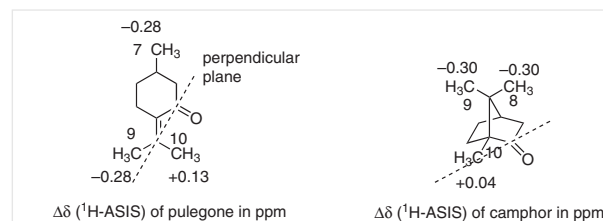


Figure 1 Examples of the carbonyl-plane rule

in Figure 1, the $\Delta\delta$ (ASIS) values for pulegone are positive for the methyl group in front of the plane perpendicular to the C–CO–C plane and negative for methyl groups lying behind this plane. A similar effect is observed for camphor.¹²

When we synthesized a series of cyclic β -dipeptides and β -lactams with various substitution patterns and examined their ¹H NMR spectra, we obtained important results on applying the ASIS methodology. We observed that ¹H chemical shifts for aliphatic protons in these compounds exhibited outstanding differences in multiplicity as well as changes in chemical shifts when we used benzene-*d*₆ (C₆D₆) and chloroform-*d*₁ (CDCl₃) as solvents.¹⁵ On the basis of these results, we decided to study the ASIS effect in β -lactams with specific substitution patterns.

For this study the samples were prepared at an equal concentration of 47 mM and $w^{1/2} = 0.5$ in CDCl₃ and C₆D₆ as solvents. The first β -lactam in the working group for which an ASIS effect was observed was β -lactam **1**. In the ¹H NMR spectrum recorded in chloroform-*d*₁ as the solvent, we observed a triplet shifted to $\delta = 3.02$ ppm, corresponding to the H-3 proton. At $\delta = 3.31$ ppm there was a second triplet corresponding to the H-4 proton. On switching to C₆D₆ as solvent, we expected a change in the chemical shifts of the

signals, but surprisingly we observed a single signal at $\delta = 2.39$ ppm corresponding to the H-3 and H-4 protons (Table 1). To establish the effect of a substituent R¹ on the N atom, we synthesized the β -lactam derivatives **2–6**.¹⁶ For compound **2**, we introduced a methyl group, whereas for derivatives **3–6**, anisotropy was introduced to determine its effect in benzene as a solvent.

On comparing chemical-shift changes in compounds **1–6**, we can see that the methyl derivative **2** shows the greatest value for the H-4 chemical shift, and its calculated ASIS effect shows a value of a $\Delta\delta_4 = -1.05$, meaning that the anisotropy of benzene shields the protons causing upfield changes. On the other hand, the introduction of anisotropy at the nitrogen atom for lactams **3–6** showed that the H-3 protons are less affected by the benzene ring, whereas the H-4 protons exhibited the same chemical shift change in the aromatic medium, so that the N–H and N–Ar systems are affected in the same way. As can be seen, the protons H-4 are the most affected by a solvent change for the methyl derivative **2**. To confirm this finding, HSQC and HMBC spectra recorded in CDCl₃ and C₆D₆ were used to confirm the assignment of H-3 and H-4 to their corresponding carbon atoms.

Table 1 ¹H NMR Chemical Shifts and ASIS Analyses for β -Lactams **1–8** in CDCl₃ and C₆D₆ (400 MHz)

β -Lactam		CDCl ₃ (multiplicity, δ ppm)	C ₆ D ₆ (multiplicity, δ ppm)	$\Delta\delta$ (ASIS) = $\delta_{AS} - \delta_S$
1	R ¹ , R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 3.02) H-4 (t, 3.31)	H-3, H-4 (s, 2.39)	$\Delta\delta_3 = -0.63$ $\Delta\delta_4 = -0.92$
2	R ¹ = CH ₃ ; R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 2.95) H-4 (t, 3.23) CH ₃ -5 (s, 2.83)	H-3 (t, 2.31) H-4 (t, 2.19) CH ₃ -5 (s, 2.21)	$\Delta\delta_3 = -0.64$ $\Delta\delta_4 = -1.05$ $\Delta\delta_5 = -0.62$
3	R ₁ = R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 2.96) H-4 (t, 3.23) H-5 (d, 3.82) H-6 (m, 5.74) H-7 (m, 5.25)	H-3, H-4 (m, 2.34) H-5 (d, 3.39) H-6 (m, 5.32) H-7 (m, 4.82)	$\Delta\delta_3 = -0.62$ $\Delta\delta_4 = -0.89$ $\Delta\delta_5 = -0.43$
4	R ¹ = Bn; R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 2.94) H-4 (t, 3.13) CH ₂ -5 (s, 4.37) Ph (m, 7.34)	H-3, H-4 (s, 2.31), H-5 (s, 4.02) Ph (m, 7.00)	$\Delta\delta_3 = -0.63$ $\Delta\delta_4 = -0.82$ $\Delta\delta_5 = -0.35$
5	R ¹ = (1-naphthyl)methyl; R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 2.86) H-4 (t, 2.99) CH ₂ -5 (s, 4.80) Ar (m, 7.37–8.12)	H-3, H-4 (m, 2.20) CH ₂ -5 (s, 4.43) Ar (m, 6.97–8.34)	$\Delta\delta_3 = -0.66$ $\Delta\delta_4 = -0.79$ $\Delta\delta_5 = -0.37$
6	R ¹ = (1-anthryl)methyl; R ² , R ³ , R ⁴ , R ⁵ = H	H-3 (t, 2.81) H-4 (t, 2.88) CH ₂ -5 (s, 5.36) Ar (m, 7.40–8.60)	H-3, H-4 (m, 2.09) CH ₂ -5 (s, 4.98) Ar (m, 7.11–8.34)	$\Delta\delta_3 = -0.72$ $\Delta\delta_4 = -0.79$ $\Delta\delta_5 = -0.38$
7	R ¹ = H; R ² , R ³ , R ⁴ , R ⁵ = CH ₃	H-5 (s, 1.11) H-6 (s, 1.22)	H-5 (s, 1.00) H-6 (br s, 0.86)	$\Delta\delta_5 = -0.11$ $\Delta\delta_6 = -0.36$
8	R ¹ = Bn; R ² , R ³ , R ⁴ , R ⁵ = CH ₃	H-5 (s, 1.21) H-6 (s, 1.11) CH ₂ -7 (m, 4.26) Ph (m, 7.13)	H-5 (s, 1.02) H-6 (s, 0.73) CH ₂ -7 (m, 4.02) Ph (m, 7.10)	$\Delta\delta_5 = -0.19$ $\Delta\delta_6 = -0.38$ $\Delta\delta_7 = -0.24$

To obtain a better idea of the ASIS effect observed for compound **2**, we conducted a titration experiment analyzed by ^1H NMR. β -lactam **2** (5.0×10^{-5} moles) was dissolved in $350 \mu\text{L}$ of CDCl_3 and a first spectrum was obtained. When aliquots of 1.13×10^{-3} moles of C_6D_6 were added up to 6.77 mmol , we observed that as the concentration of C_6D_6 increased, the signals for H-3 and H-4 approached and then overlapped one another (Figure 2).

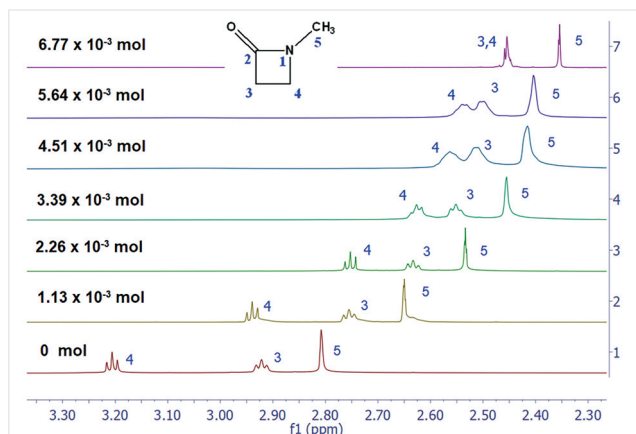


Figure 2 ^1H NMR (400 MHz) of β -lactam **2** in CDCl_3 containing increasing concentrations of C_6D_6

Surprisingly, β -lactam **4** in C_6D_6 at 25°C did not show the expected change in its chemical shift; instead, a single signal at $\delta = 2.32 \text{ ppm}$ corresponding to protons H-3 and H-4 was observed. To explain and verify this finding, we performed a variable-temperature experiment (Figure 3). The single signal became split into two multiple signals as the temperature was increased from 30 to 75°C .

In the case of amides the participation of dipole resonance forms causes the benzene atom to be located near the nitrogen atom and as far as possible from the oxygen

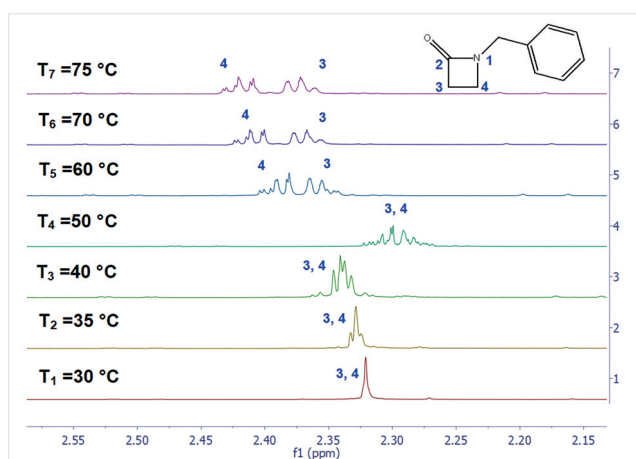


Figure 3 ^1H NMR (500 MHz) variable-temperature experiment for β -lactam **4** in C_6D_6

atom (Figure 4). The same phenomenon might also be observed in β -lactams, which would explain why the H-4 protons were more affected by a change in the solvent from CDCl_3 to C_6D_6 , causing a greater shift of the signals towards lower frequencies. This was confirmed by introducing allyl and aryl substituents into β -lactams **3–6**. In these cases, the signal from H-3 was less affected by stacking of the benzene ring with the allyl or aryl groups.

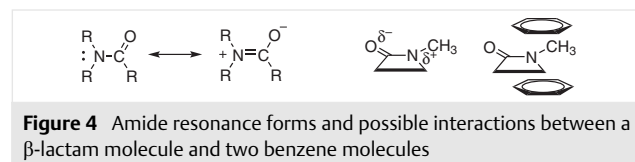


Figure 4 Amide resonance forms and possible interactions between a β -lactam molecule and two benzene molecules

To develop a structural analysis of β -lactams, we performed theoretical calculations by using density functional theory (DFT). The optimized geometry of the β -lactam **2** was placed in the middle of a stacking displaced (SD) model that represents the hypothetical structural conditions that explain the ASIS effect in β -lactams by considering a distance slightly greater than the van der Waals radius between **2** and the benzene rings (Figure 5).



Figure 5 Stacking displaced adduct of β -lactam **2** with two benzene molecules

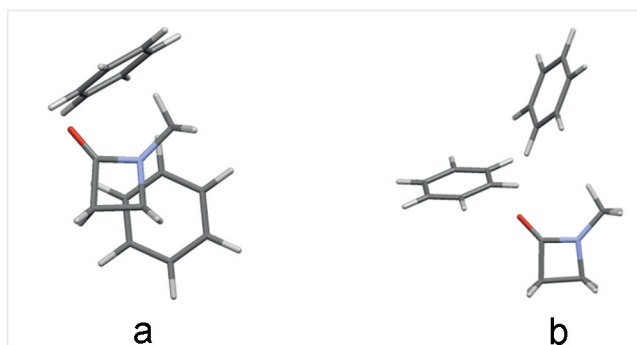
First, the shielding effect [$\Delta_{\delta\delta}(\text{ASIS})$] of the aromatic rings over H-3 and H-4 was evaluated. The best model is that which approximates the value of $\Delta_{\delta\delta}(\text{ASIS})$ nearest to zero. The analysis confirmed that the SD perspective reproduced the experimental data (SD in Table 2).

To examine whether the SD configuration corresponds to the more stable arrangement for the trimer, a geometry optimization at the same level of theory were carried out. By analyzing the optimized geometries of the adduct (OA in Table 2), it was demonstrated that the SD perspective does not correspond to a minimum and that the stacking aggregation needs to be reconsidered. By comparing the results obtained by using two different functionals, it is possible to see that the ω -B97XD functional gives a better description

Table 2 Theoretical Chemical Shifts and Analysis of the ASIS Effect for the β -Lactam **2**

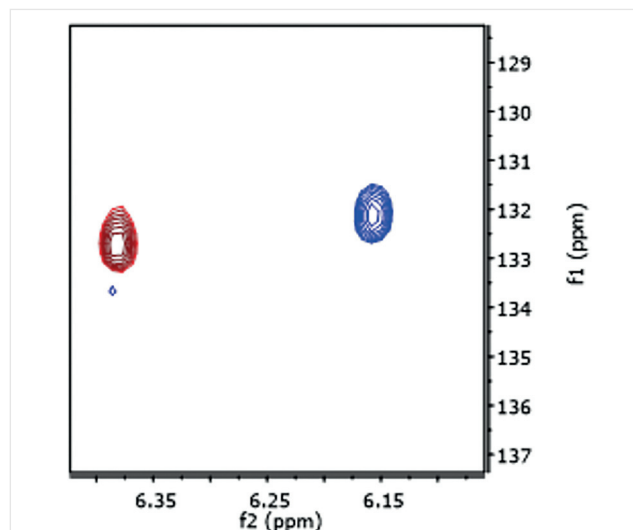
Functional	$\Delta_{\delta\delta}(\text{ASIS}) = \Delta_{\delta\delta\text{exp}}(\text{ASIS}) - \Delta_{\delta\delta\text{theo}}(\text{ASIS})$	
	Stacking displaced (SD)	Optimized geometry of the adduct (OA)
B3LYP	$\Delta_{\delta\delta}3 = 0.50$ $\Delta_{\delta\delta}4 = -0.32$ $\Delta_{\delta\delta}5 = -0.01$	$\Delta_{\delta\delta}4 = -1.69$ $\Delta_{\delta\delta}3 = -0.75$ $\Delta_{\delta\delta}5 = -0.67$
ω B97XD	$\Delta_{\delta\delta}3 = 0.61$ $\Delta_{\delta\delta}4 = -0.13$ $\Delta_{\delta\delta}5 = 0.05$	$\Delta_{\delta\delta}4 = 0.82$ $\Delta_{\delta\delta}3 = -0.15$ $\Delta_{\delta\delta}5 = -0.32$

of the change in chemical shifts (Table 2) than does the B3LYP functional. First, the optimized geometry of the trimer obtained by using the ω -B97XD functional predicts a stacking displaced configuration between the β -lactam **2** and one molecule of benzene (Figure 6a), whereas the optimization using the B3LYP functional suggest that two molecules of benzene are far from the **2** molecule (Figure 6b). Also, it is assumed that this enhancement arises from a better description of the dispersion interactions from the ω -B97XD functional.

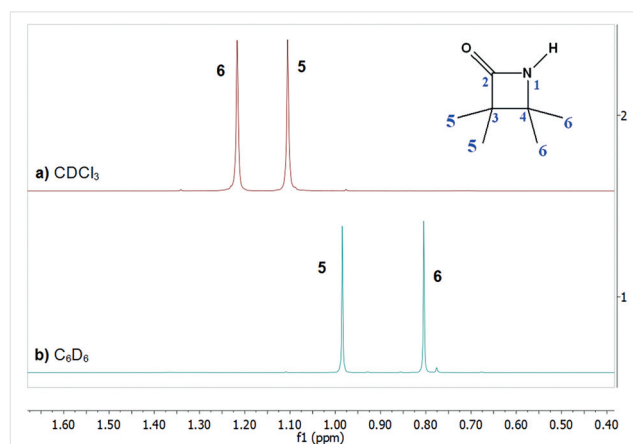
**Figure 6** Optimized geometries of β -lactam **2** with two molecules of benzene

Obviously, this study supported the idea of stacking protection from benzene rings to the β -lactam ring, but a more rigorously approximation is necessary to permit the evaluation of the bulk effect of the solvent. A likely CH- π interaction has been suggested in comparing the theoretical parameters (distances) reported for this kind of interaction, which are in the range 3.2–3.8 Å.^{17,18} In the present work, we found a range of distances between 3.18 to 4.8, which confirmed the presence of a weak CH- π interaction.

We then performed a ^{15}N HSQC experiment to examine the ASIS effect for the amide moiety in compound **1**. The solvent aromatic ring exhibited a deshielded effect over the ^{15}N and ^1H chemical shifts, confirming the presence of the interaction shown in Figure 4. This means that the lactam protons are close to the shielding effect of the benzene ring, whereas NH is deshielded (Figure 7).

**Figure 7** ^{15}N HSQC experiment for compound **1** to examine the ASIS effect on nitrogen nuclei. C_6D_6 (red) and CDCl_3 (blue). $\Delta\delta(\text{ASIS}) = 0.6$ ppm, which corresponds to a deshielding effect due to the anisotropy of benzene.

With the aim of establishing the ASIS effect for tetramethyl β -lactams, we synthesized compound **7**.¹⁹ In CDCl_3 , the ^1H NMR spectrum of **7** showed singlet signals at $\delta = 1.11$ and 1.22 ppm for CH_3 -5 and CH_3 -6, respectively (Figure 8a). It is interesting to note that in C_6D_6 , the chemical shifts of CH_3 -5 were located at low fields whereas those for CH_3 -6 were located at high fields (Figure 8b).

**Figure 8** ^1H NMR (500 MHz) spectra of β -lactam **7** in (a) CDCl_3 and (b) C_6D_6

HMBC spectra recorded in CDCl_3 and C_6D_6 were used to assign protons CH_3 -5 and CH_3 -6 unambiguously. In CDCl_3 , the shift in the signal corresponding to protons CH_3 -5 to 1.11 ppm allowed us to correctly assign the correlation with C-5, C-3, C-4, and C(O) at 175.35 ppm, whereas proton CH_3 -6 at 1.22 ppm correlated only with C-6, C-3, and C-4 (Figure 9).

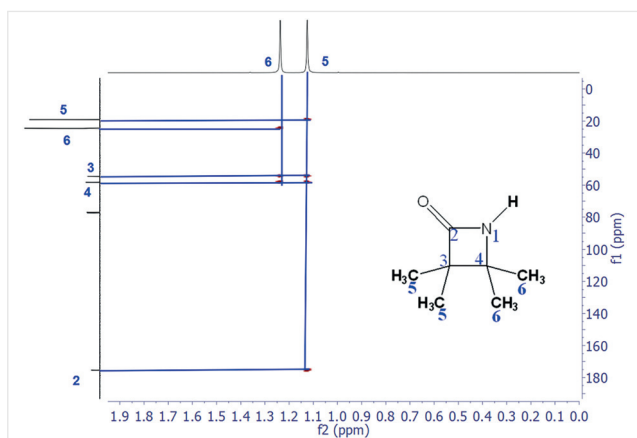


Figure 9 HMBC (500 MHz) of β -lactam **7** in CDCl_3

On the other hand, in the HMBC spectra recorded in benzene- d_6 , the signal corresponding to the CH_3 -5 proton shifted by 0.98 ppm again showed the same correlation with C-5, C-3, C4, and C(O) at 174.32 ppm, whereas proton CH_3 -6 at 0.86 ppm correlated only with C-6, C-3, and C-4 (Figure 10).

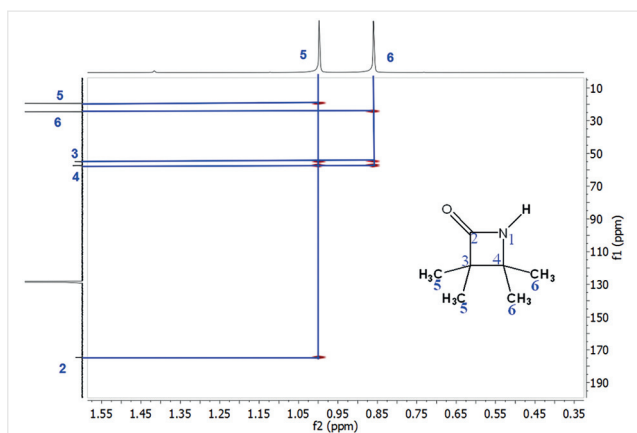


Figure 10 HMBC (500 MHz) of β -lactam **7** in C_6D_6

Finally, a titration experiment with 5.0×10^{-5} moles of β -lactam **7** in 350 μL of CDCl_3 was carried out. When 0.7 μL aliquots of C_6D_6 were added, the signals for CH_3 -5 and CH_3 -6 approached then overlapped one another (Figure 11). Surprisingly, however, at 1.4 μL (2.26×10^{-3} mol) of C_6D_6 , a single signal at $\delta = 1.1$ ppm corresponding to CH_3 -5 and CH_3 -6 was observed. At a higher concentration of C_6D_6 (3.39×10^{-3} mol; 2.1 μL), CH_3 -5 and CH_3 -6 could be differentiated once more, but at this point, their chemical shifts reversed, as in 100% C_6D_6 . Changing the solvent usually results in preferential movement of one signal more than the other, but after addition of 2.8 μL (4.51×10^{-3} mol) of C_6D_6 , the signal corresponding to CH_3 -6 appeared to split into two signals.

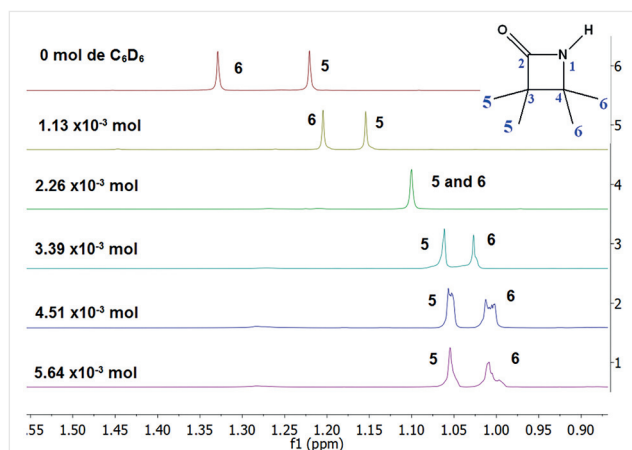


Figure 11 ^1H NMR (500 MHz) of β -lactam **7** in CDCl_3 with increasing concentrations of C_6D_6

A possible explanation of this is that C_6D_6 as a solvent allows us to differentiate CH_3 -6- α from CH_3 -6- β (Figure 12).

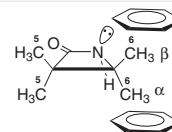


Figure 12 Possible interaction between β -lactam **7** in benzene- d_6 permitting differentiation of CH_3 -6- α and CH_3 -6- β

Crystals of 3,3,4,4-tetramethylazetidin-2-one (**7**) suitable for X-ray diffraction analysis were obtained by slow diffusion of a chloroform solution of the lactam at room temperature. Lactam **7** crystallized in an orthorhombic system with a cell volume of 751.95(2) \AA^3 and space group $P2_12_12_1$.²⁰ The minimum repetitive unit consist of one molecule of the β -lactam (Figure 13a). A structural analysis revealed the formation of a four-membered planar ring consisting of atoms C1, C2, C3, and N1. The bond distances ranged between 1.3359(18) and 1.5910(18) \AA , being shorter for C1-N1 and C3-N1, respectively. The four-membered ring is slightly bent, with a dihedral angle of 2.5° between the C2, C1, N1 plane and the C2, C3, N1 plane. The structure

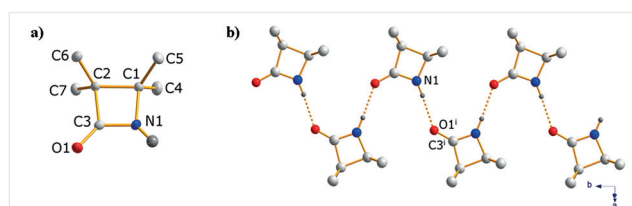


Figure 13 Solid-state structure of 3,3,4,4-tetramethylazetidin-2-one (**7**); (a) asymmetric unit and (b) 1D supramolecular tape formed through hydrogen bonding. Symmetry operators: (i) $2 - x, -0.5 + y, 1.5 - z$. Some hydrogens atoms are omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level.

forming the $C_1^1(4)$ chain pattern is typical of many $N-H\cdots O=C$ hydrogen-bonded systems ($N-H$, 0.86 Å; $H\cdots O$, 2.00 Å; $N\cdots O$, 2.857 Å; $\angle N-H\cdots O$, 175°) (Figure 13b).

Intermolecular interactions of 3,3,4,4-tetramethylazetid-2-one (**7**) were analyzed by using a Hirshfeld surface,²⁰ a powerful technique for understanding the nature of the intermolecular interactions within a crystalline structure. The surface was drawn from single-crystal X-ray structures in the CIF format by using *Crystal Explorer* software.²¹ The surface was mapped over the d_{norm} function in the range 0.6–2.6 Å; the red regions show contact points shorter than the sum of the van der Waals radii with negative d_{norm} (complementary hollows). The blue regions are contact sites longer than the sum of the van der Waals radii with d_{norm} negative equal to zero (bumps where the surfaces of two molecules touch each other). For compound **7**, red areas on the surface mapped with d_{norm} function were located on the amide moieties due to the formation of hydrogen bonds (Figure 14a).

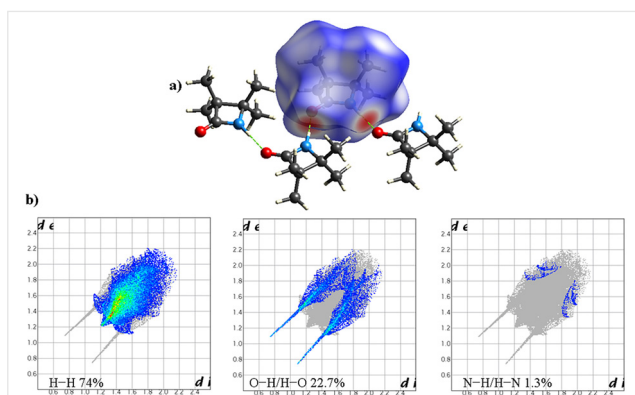


Figure 14 (a) Hirshfeld surface for 3,3,4,4-tetramethylazetid-2-one (**7**) mapped with d_{norm} . (b) Representative 2D fingerprints plots.

Decomposition of this surface to provide a molecular fingerprint (a directly accessible 2D plot that provides the full distribution of interactions) was performed by using d_i and d_e , which are defined as the distances from the surface of the Hirshfeld surface to the nearest core within or outside the surface, respectively. In the 2D fingerprint plots of **7**, H–H interactions predominate, with a percentage of 74%; these appear where $d_e \approx d_i$ near the van der Waals radius of the hydrogen atom (1.20 Å). The percentage of O–H/O–H contacts is 22.7%, and these appear as a pair of long sharp spikes characteristic of a strong hydrogen bond (Figure 14b). The minimum contributions are attributed to N–H/H–N and C–H/H–C contacts.

In conclusion, we have demonstrated an ASIS effect in eight β -lactam derivatives by using deuterated chloroform and benzene solvents. The stacking adduct of the benzene ring with the lactam ring plays a determining role in chemical-shift changes. *N*-Methyl groups exhibited the best shielded effect in H-4 lactam protons, whereas in te-

tramethylated β -lactams, the ASIS effect is lower than that in the other lactams synthesized. In β -lactams with anisotropic substituents, it was observed that protons H-3 and H-4 are already affected by the anisotropy of the substituent itself. Consequently, an intercalative interaction between the β -lactam and benzene- d_6 might overestimate these changes. From a theoretical point of view, we have demonstrated that at least one stacking interaction between the β -lactam and the molecule of benzene is necessary to produce the changes in the chemical shifts. ^{15}N HSQC results confirm the presence of a deshielded effect over the amide moiety while the protons of the ring are shielded.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1691498>.

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- N-Alkylation of β -Lactams; General Procedure**
A 10 mL flask equipped with a magnetic stirrer was charged with the appropriate β -lactam (1 mmol) in anhyd THF (5 mL). The solution was cooled to -10°C and treated with Bu_4NBr (0.1 equiv), the appropriate alkyl iodide or bromide (3 equiv), and freshly ground KOH pellets (1.6 equiv). After 2 h, the temperature was allowed to rise to -7°C and the mixture was stirred overnight. The temperature was then increased to 0°C and, when the reaction was nearly complete (TLC; 5 h), it was quenched with sat. aq NH_4Cl . The mixture was extracted with

EtOAc and the extracts were purified by chromatography [silica gel, hexane–EtOAc (1:1)]. The spectral data for the lactams were consistent with those reported in the literature.^{16,22,23}

1-Methylazetidin-2-one (2)

Yield: 23 mg (28%). FTIR (ATR): 1724.05 (C=O) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): 3.23 (t, $^3J = 4$ Hz, 2 H, CH_2N), 2.95 (t, $^3J = 4$ Hz, 2 H, $\text{CH}_2\text{C=O}$), 2.83 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): 170.4, 43.3, 39.9, 31.3.

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(19) **3,3,4,4-Tetramethylazetidin-2-one (7)**

2,3-Dimethylbut-2-ene (16.8 mmol, 2.0 mL, 1.5 equiv) in a 100 mL round-bottom flask was treated with chlorosulfonyl isocyanate (11.5 mmol, 1.0 mL) at 0–5 °C under N_2 . The mixture became solid and was then dissolved in CHCl_3 (2.4 mL) and treated with 2 M aq NaSO_3 (17.38 mL, 34.5 mmol, 3 equiv). The reaction flask was then fitted with a reflux condenser and a stirrer bar and placed in a Discover CEM microwave oven. The microwave oven was programmed by the open-vessel method to heat at 80 °C at a microwave power of 50 W. The mixture was

heated for 5 min and then allowed to cool to below 50 °C. After extraction with CH_2Cl_2 (4×3 mL), the two phases were separated and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography [silica gel, hexane–EtOAc (8:2 to 4:6)] to give white crystals; yield: 1.23 g (84%); mp 98–99 °C.

^1H NMR (400 MHz, CDCl_3): $\delta = 1.22$ (s, 6 H, $\text{CH}_3\text{--C--N}$), 1.11 (s, 6 H, $\text{CH}_3\text{--C--C=O}$). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.2$, 24.5, 54.5, 58.21, 175.4. FAB-MS: $m/z = 128$ [$\text{M} + \text{H}$] $^+$. HRMS (FAB): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_7\text{H}_{14}\text{NO}$: 128.1070; found: 128.1022.

(20) CCDC 1487449 contains the supplementary crystallographic data for compound **7**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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