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# Conformational regulation of substituted azepanes through selective monofluorination†

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**Substituted azepanes are common bioactive epitopes with flexible ring structures. The conformational effects of monofluorination in model azepane rings were investigated by $^1$H NMR spectroscopy and computational modelling. A single fluorine atom, installed diastereoselectively, was found to bias the azepane ring to one major conformation for one diastereomer.**

Ligand–receptor interactions frequently require conformational changes in both entities.[1] Such a conformational "induced-fit" confers specificity in molecular recognition that selects for a particular reaction or binding outcome.[2] Understanding conformational synergy is critical to the rational discovery of chemical function in structure-based drug design or molecular assembly; however, the details of conformational dynamics in most ligand–receptor interactions are not well understood.[3,4]

Recent examples illustrate the principle of entropy control, where conformational tuning of ligands or receptors regulates binding specificity and affinity.[5–9] Methods for controlled conformational manipulation of ligands are needed for the rational design and discovery of bioactive epitopes,[3] and one such method is selective fluorination. The C–F bond is known to present profound conformational effects,[10] and has been shown to moderate binding specificity and affinity in a variety of ligand–receptor systems including protease inhibition, GABA receptor ligands, antivirals, insect pheromones, and antimalarials.[11]

In this context of entropy control, conformational tuning of substituted azepanes represents a challenging case study due to the flexibility of such ring systems. Substituted azepanes are common moieties in bioactive natural products, DNA binders, helix inducers, and iminosugar mimics as glycosidase inhibitors.[12] Their conformational regulation is key to the potency and specificity of their bioactivity, suggesting that the introduction of fluorine into these systems may offer attractive benefits through entropy control. Previous work has elucidated the conformational effects of incorporating fluorine atoms into four-,[13] five-,[14] six-[15] and eight-[13]membered nitrogen heterocycles, but the effect of fluorine substitution in highly flexible, heterocyclic seven-membered ring systems is unknown. In order to address this knowledge gap we recently reported methods for the stereospecific fluorination of substituted azepanes,[16a] and here we report the conformational effects of monofluorination in model azepanes **1–3** (Fig. 1). Azepane **1** bears two substituents, a C-3 azido group and a C-4 benzyloxy group, while azepanes **2** and **3** also feature a diastereospecific fluorine substitution at the C-6 position.

In azepane **1**, multiple factors exist to give rise to its complex conformational properties. For example, the mutually *trans* benzyloxy and azido groups might be expected to prefer a

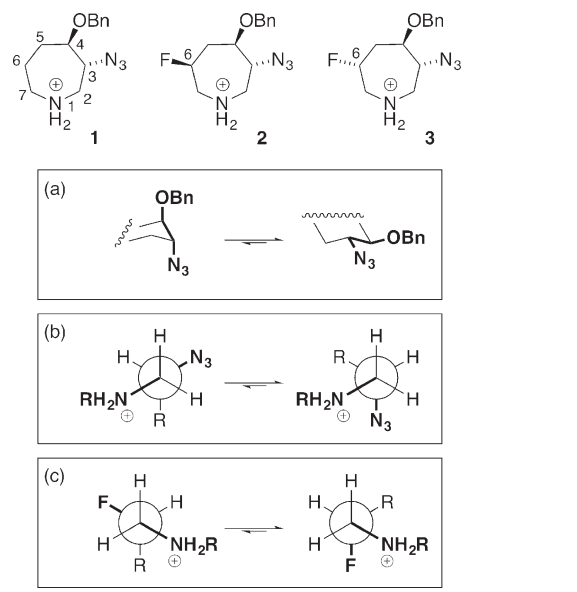


**Fig. 1** The conformations of azepanes **1–3** are expected to be influenced by: (a) a diequatorial preference of the benzyloxy/azido groups; (b) the azido *gauche* effect; and (c) the fluorine *gauche* effect (*e.g.* azepane **3**).

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diequatorial over a diaxial position in a twisted chair azepane conformation (Fig. 1a), but this would compete with the additional preference of the azido group to align *gauche* to the ring nitrogen[17] (Fig. 1b). Further, the presence of three contiguous unsubstituted methylene groups would be expected to amplify the conformational disorder in the system. In each of the fluorinated targets **2** and **3**, the expected preference of the C–F bond to align *gauche* to the ring nitrogen (Fig. 1c) would be an additional influence on the azepane conformation.[18] Comparison of the diastereoisomers **2** and **3** would allow us to explore whether an appropriately oriented C–F bond can successfully reduce or eliminate the conformational disorder inherent in substituted azepanes. A related question would be whether the C–F bond acts in synergy or in competition with the other conformational influences in the molecule. By exploring these questions, we anticipated that the general principles for entropy control in substituted azepanes might be extrapolated.

Azepane **1** was prepared from a key Boc-protected tetrahydroazepine intermediate,[19] which also gave rise to the fluorinated compounds **2** and **3** as described previously.[16a] The final Boc-deprotection in trifluoroacetic acid afforded targets **1–3** as the trifluoroacetate salt in quantitative yield in each case. The NMR spectra of **1–3** were recorded in $CDCl_3$ which gave well resolved signals, and all resonances were unambiguously assigned using appropriate two-dimensional experiments (COSY, NOESY, HSQC, and HMBC) and by accurate simulation of the spectra *in silico*.[19]

The coupling constants extracted from the $^1$H NMR spectrum of **1** confirm that this molecule exhibits extensive conformational disorder at room temperature (Fig. 2a).[20] A single set of resonances is observed, but most of the three-bond proton–proton coupling constants are intermediate in magnitude (5–6 Hz), suggesting that significant conformational averaging is occurring on the NMR timescale. Notably, this includes H-3 and H-4 next to the benzyloxy and azido substituents, which experience a coupling of 5.4 Hz (Fig. 2a); this intermediate value agrees with our hypothesis that the benzyloxy/azido diequatorial preference and the azido *gauche* effect would compete with each other, leading to conformational disorder. The western portion of the molecule also exhibits extensive conformational mobility, as is clearly demonstrated by the intermediate magnitude of the proton–proton coupling constants, and by the appearance of the methylene hydrogens, H-7a and H-7b, as an apparent triplet ($J$ = 5.9 Hz) rather than two doublet of doublets. A computational analysis[19] identified seven clusters of distinctly different azepane ring conformations within 3 kcal mol$^{-1}$ of the global minimum (Fig. 2a, overlay image of the possible conformers of **1**). Overall, azepane **1** is found to be a highly flexible and disordered molecule, and as such, is an excellent but challenging starting point for the production of conformationally biased fluorinated analogues.

For the 6*S*-fluorinated azepane **2**, an initial qualitative *J*-based analysis suggested that this molecule still exhibits considerable conformational disorder at room temperature

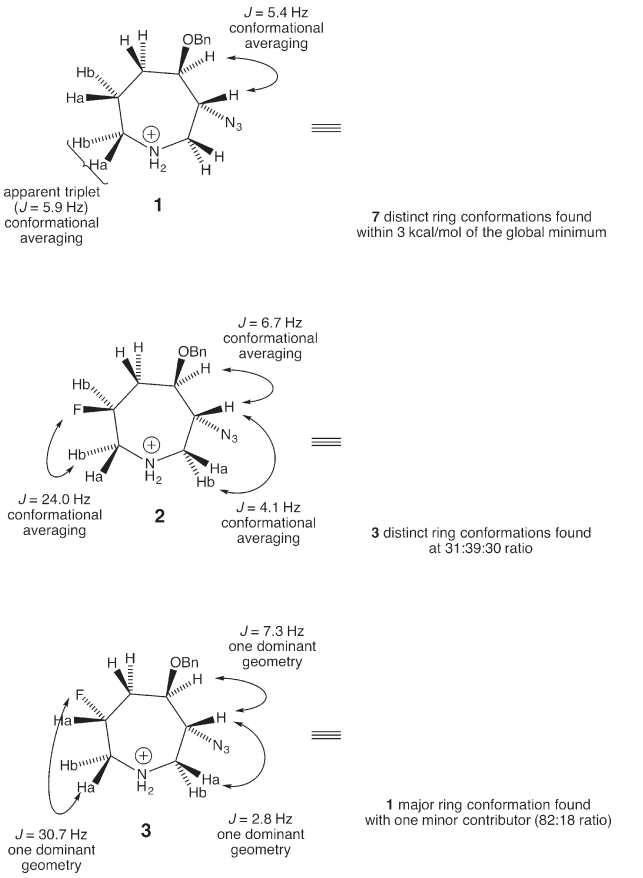


**Fig. 2** A combined NMR/computational analysis reveals that azepanes **1** and **2** exhibit considerable conformational disorder, while azepane **3** has one dominant geometry. The low-energy geometries of **1–3** are displayed in the overlay images on the right; these overlays are anchored by three ring atoms (C-7, $N^+$, and C-2), and the benzyloxy and azido side chains are omitted for clarity. The major conformer of **3** is black. See the ESI† for full details of all low-energy geometries of **1–3**.

(Fig. 2b). As described above, three conformational effects were expected to be in operation: the diequatorial preference of the benzyloxy/azido groups; the azido *gauche* effect; and the fluorine *gauche* effect (Fig. 1). It seems that each of these preferences is only partially satisfied in azepane **2**. This is demonstrated by, respectively, a key $J_{H3H4}$ value of 6.7 Hz; a key $J_{H2bH3}$ value of 4.1 Hz; and a key $J_{FH7b}$ value of 24.0 Hz (Fig. 2b), all of which are intermediate in magnitude[20] and hence suggestive of conformational averaging.

Computational analysis of **2** identified several azepane ring geometries that may possibly contribute to the observed NMR characteristics.[19] In order to identify the major geometries, the energy of each geometry candidate was subjected to DFT calculations at several different levels of theory, but it was not possible to reliably rank the geometries because of the uncertainties inherent to the calculations and the side chain rotations that tended to obscure the native preferences of the azepane ring itself.[19] Given the limited reliability of the computational methods alone, it was therefore necessary to perform *J*-based conformational analysis to assist in ranking the candidate geometries. Spin–spin coupling constants were

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calculated for each geometry using the program Gaussian09,[19] and the calculated $J$ values were compared with the experimental values. As expected, no individual geometry of **2** matched the experimental $J$ values perfectly, but a reasonably good agreement between calculated and experimental $J$ values was obtained when three candidate geometries were selected and a weighted average was created in the ratio of 39 : 31 : 30 (Fig. 2b, overlay image of the probable major geometries of **2**). This population ratio corresponds to relative energies of 0.00, 0.12 and 0.13 kcal mol$^{-1}$, which are too close to one another to have been reliably predicted by energy calculations alone. The three lowest-energy geometries thus identified all satisfy two of the three conformational preferences described in Fig. 1. Overall, introducing a single fluorine atom into azepane **2** does not reduce the conformational disorder enough to achieve one dominant ring geometry in solution.

Our attention was next turned to azepane **3** (Fig. 2c), in which the diastereospecific fluorination gives the *R* configuration at C-6. A qualitative $J$-based analysis[20] of the $^1$H NMR spectrum of **3** reveals that, in contrast to azepanes **1** and **2**, a single geometry of **3** seems to strongly dominate in solution. The benzyloxy/azido diequatorial preference is reasonably clearly satisfied, as demonstrated by a $J_{H3H4}$ value of 7.3 Hz; the azido *gauche* effect is reasonably clearly satisfied, as demonstrated by a $J_{H2aH3}$ value of 2.8 Hz; and the fluorine *gauche* effect is clearly satisfied, as demonstrated by a key $J_{FH7a}$ value of 30.7 Hz (Fig. 2).

In order to acquire theoretical confirmation of the predicted ring geometry of **3**, a computational sequence was performed similar to that already described for **2**. A ring geometry of **3** consistent with the above description was readily identified amongst the low-energy candidates from a conformational analysis followed by DFT optimisation (Fig. 2c), and the calculated coupling constants for this geometry matched the experimental values reasonably well.[19] In addition, a second closely related conformer of **3** was identified which, when included as the minor component of an 82 : 18 weighted average mixture, provided a still closer match with the experimental $J$ values. This population ratio corresponds to relative energies of 0.00 and 0.77 kcal mol$^{-1}$. The two low-energy geometries of **3** thus identified (Fig. 2c) differ only in a slight twist about the C3–C4 dihedral angle, with the lowest-energy geometry better satisfying the benzyloxy/azido diequatorial preference, and the next higher-energy geometry better satisfying the azido *gauche* effect.[19] Overall, introducing the fluorine atom into azepane **3**, with the *R* configuration at C-6, is found to greatly reduce the conformational disorder relative to the non-fluorinated parent structure **1**, to the extent that a single geometry strongly dominates in solution.

In conclusion, this study has demonstrated that a single C–F bond, installed diastereospecifically, can significantly regulate the conformations of substituted azepane derivatives.[21] The extent of conformational biasing is found to depend on both the fluorine stereochemistry and that of the other groups present: if the fluorine acts in synergy with the other groups (*i.e.* azepane **3**) a single ring conformation can be reinforced, whereas if the fluorine acts in competition with existing groups (*i.e.* azepane **2**), such a loss of synergy results in reduced conformational bias.[22] This finding has wider significance for future efforts to optimise host–guest interactions involving flexible heterocyclic ligands.

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19 See ESI.†
20 Three-bond H–H and H–F coupling constants obey Karplus relationships with the corresponding H–C–C–H and H–C–C–F dihedral angles: "typical" $^{3}J_{HH}$ values are 1–3 Hz for *gauche* alignments and 6–9 Hz for *anti* alignments; see: (*a*) A. M. Ihrig and S. L. Smith, *J. Am. Chem. Soc.*, 1970, **92**, 759–763. "Typical" $^{3}J_{HF}$ values are 5–15 Hz for *gauche* alignments and 25–35 Hz for *anti* alignments; see: (*b*) C. Thibaudeau, J. Plavec and J. Chattopadhyaya, *J. Org. Chem.*, 1998, **63**, 4967–4984. For an example of conformational analysis by NMR and DFT methods, see: (*c*) P. Tähtinen, A. Bagno, K. D. Klika and K. Pihlaja, *J. Am. Chem. Soc.*, 2003, **125**, 4609–4618.
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