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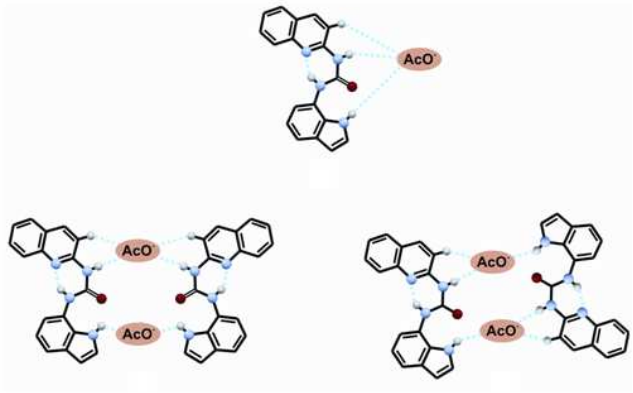

The interaction between neutral ureidic receptors and acetate is described via an accurate combination of ^{1}H-NMR and 2D ^{1}H-^{1}H NOESY NMR experiments.

Cite this: DOI: 10.1039/c0xx00000x

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COMMENT

Reply to the 'Comment on "Non-symmetric substituted ureas locked in an (*E*,*Z*) conformation: an unusual anion binding *via* supramolecular assembly" by B. Ośmiałowski and E. Kolehmainen, *New J. Chem.*, 2014, 38, DOI: 10.1039/c3nj01282d

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

We reply to the comments raised by Osmialowski and Kolehmainen in rheir discussion on conformations of ureidic receptors as set out in our article (*M. Olivari et al.*, *New J. Chem.*, 2013, **37**, 663-669). Here we appreciate the common views we share and welcome the coarity this gives, and we discuss and question some of their criticisms of the original paper and clarify our opinion in this area.

We welcome this comment[1] on our article" Non-symmetric substituted ureas locked in an (*E*,*Z*) conformation: an unusual anion binding *via* supramolecular assembly"[2] and we would like to thank the authors for their comments which highlight the fact that the debate on the conformation/geometry assumed by neutral hydrogen bond donor/acceptor molecules in the formation of non-covalent interactions is currently a hot topic.

We would like to answer Osmialowski and Kolehmainen on each of the four points they raised.[1]

1) The association constants between **L**[1] and a set of anionic guests, in particular acetate, have been calculated and reported in the original paper (Table 1)[2] and were determined by means of ^{1}H-NMR titrations in DMSO-d_6. The broadening up to the disappearance of the NH signals was not observed in DMSO-d_6 up to the addition of six equivalents of acetate (Figure 1, Figure 8 in the original paper), but it was observed in $CDCl_3$ (Figure 2, Figure 5 in the original paper); therefore, the calculation of the affinity constants was not possible in this solvent ($CDCl_3$).

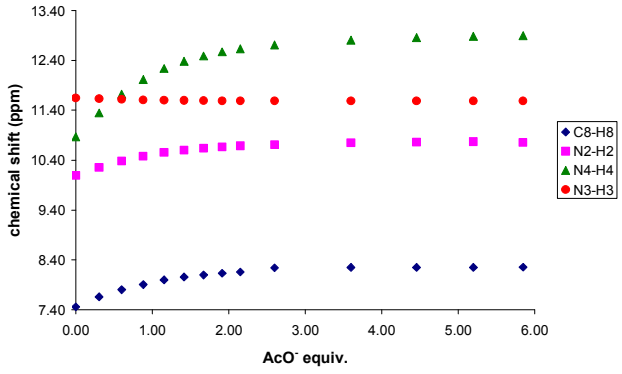

Figure 1 ^{1}H-NMR titration curves of **L**[1] (0.005 M) with tetrabutylammonium acetate (0.075 M) in DMSO-d_6. Reproduced from Ref. 2.

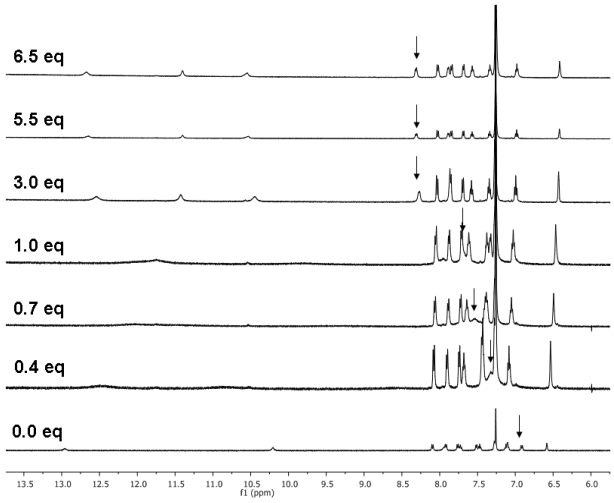

Figure 2 ^{1}H-NMR stack plot of a $CDCl_3$ solution of **L**[1] (0.005 M) upon addition of tetrabutylammonium acetate (0.075 M) in $CDCl_3$ at 298 K. The arrows indicate the C8–H8A signal. Reproduced from Ref. 2.

Changes in the aromatic CH (namely the C8-H8 in the original paper) chemical shift were also observed during the titration of **L**[1] and they were attributed by us to an interaction of the anions (acetate in particular) with the receptor, assuming an (*E*,*Z*) conformation. Osmialowski and Kolehmainen suggest that such a shift depends on the magnetic anisotropy of the C=O bond of the receptor interacting with the acetate in an "open" conformation (*cf.* Figure 1 in the Comment). Although this might be a straightforward interpretation, we wonder whether similar

changes in the chemical shift of the aromatic proton C12-H12 (in the original paper) should be observed during the titration experiments. In fact, in the conformation of **L**[1] proposed by Osmialowski and Kolehmainen in the optimised acetate adduct **L**[1]f, this proton should experience the same anisotropic effect as C8-H8 due to the interaction with the ureidic C=O, with the distance between C=O···H8 and C=O···H12 being 2.22 Å and 2.21 Å, respectively. However, the chemical shift of this signal did not change during titration with acetate. This difference strongly suggests that the changes observed for C8-H8 depends merely on the interaction with the anion and makes the conformation proposed by Osmialowski and Kolehmainen questionable at least.

2) The structures shown in figure 3 (Figure 9 in the original paper) are just pictorial two-dimensional sketches aimed only at presenting the possible acetate binding hypotheses on the basis of NMR evidence. When the third dimension is not taken into account, Coulombic repulsion between the oxygen of acetate and the C=O group of the ligand might actually be incorrectly deduced.

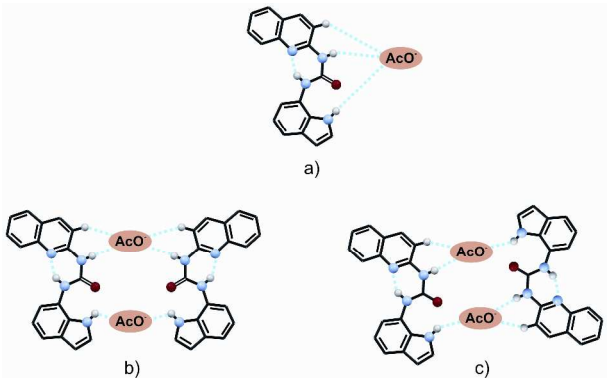

Figure 3 Proposed coordination modes of **L**[1] with acetate. Reproduced from Ref. 2.

In fact, a more realistic three-dimensional picture of the adduct of **L**[1] with acetate is presented in Figure 4 (Figure 11 of the original paper) to represent the most probable configuration that is compatible with the NMR data (NOESY, in particular), as obtained from a simulated annealing procedure. Carbonyl oxygens point far from the acetate molecules, indeed.

3) Figure 1 (Figure 8 in the original paper) shows the changes in the chemical shifts for the protons C8-H8, N2-H2, N3-H3 and N4-H4. Osmialowski and Kolehmainen suggest that changes in the conformation of the receptor **L**[1] upon acetate binding should cause a slight change in the chemical shift of H3, because this proton should pass from an intramolecular NH···N bond to an intermolecular NH···O⁻ bond. Osmialowski and Kolehmainen point out that a change of 0.1-0.2 ppm, although small, is still noticeable for the ureidic H3 proton interacting with the anion.
First of all, from our experimental data, the maximum Δppm observed for H3 was only 0.061 (for the other signals we observed Δppm (H4) = 2.031, Δppm (H8) = 0.791, Δppm (H2) = 0.677). The Δppm of 0.061 which was observed for H3 is, in our opinion, within the experimental error. Also, according to the data in the literature,[3] including those reported in Chart 6b of reference 12[4] in the Comment,[1] it cannot be interpreted as due to an interaction with acetate. In fact, Osmialowski and Kolehmainen, in reference 4, explain the slight variation that occurs in the chemical shift of H10 (less than 0.1 ppm) in their system upon interaction with benzoic acid either with this proton involved in an intramolecular NH···N hydrogen bond (as we did) or assuming no interaction with the guest. It is worth noting that we observed a significant shift in the indolic N4-H4 signal during the titration (Δppm= 2.031) despite this proton passing from an intramolecular NH···O bond with the ureidic C=O to an intermolecular NH···O⁻ bond with acetate. We wondered why, for this interaction change, which is similar to that proposed by Osmialowski and Kolehmainen for H3, we should not observe a much smaller change (0.1-0.2 ppm) in the chemical shift. Therefore, we believe that the difference in the chemical shift trend observed for H3 and H4 cannot be explained by the model proposed by Osmialowski and Kolehmainen.

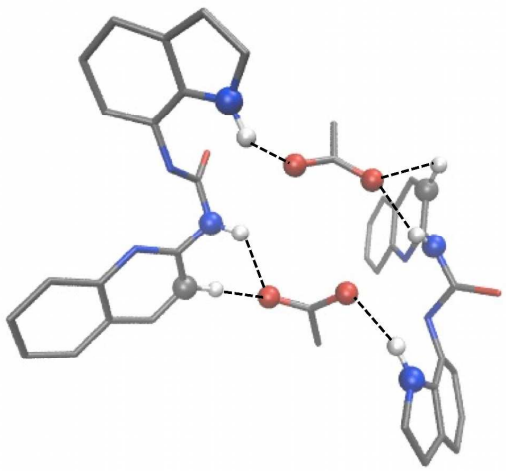

Figure 4 The most representative calculated configuration for two **L**[1] and two interacting acetate molecules in the assembly formed in DMSO-d_6. Reproduced from Ref. 2.

4) Although the quantum chemical calculations performed by Osmialowski and Kolehmainen indicate that the most stable conformers for **L**[1] in the presence of acetate is **L**[1]f, this is in contrast with our NMR experimental results (see above). In fact, NOESY NMR data cannot be fitted with the structure of the adduct in solution corresponding to **L**[1]f. In particular, a comparable cross-peak intensity was observed for the dipolar coupled protons H3-H4 and H3-H12 for **L**[1] upon interaction with acetate, whereas in the model **L**[1]f proposed by Osmialowski and Kolehmainen, the corresponding distances were 2.14 Å and 3.73 Å, respectively, and could not account for this experimental evidence. Furthermore, in the solid state, both **L**[1] and **L**[2] adopt the same (*E*,*Z*) conformation (Figure 5, Figure 1 in the original paper) in which the intramolecular hydrogen bond N3H3···N1 (for **L**[1]) or N2H2···N4 (for **L**[2]) is observed. Under our experimental conditions, the same conformation was maintained in solution for both receptors. If a change in the conformation of **L**[1] (i.e. the breaking of the N3H3···N1 intramolecular hydrogen bond) in the presence of AcO⁻ occurred (as suggested by Osmialowski and Kolehmainen), there would be no reason why this should not also occur in the case of **L**[2] in order to make both

the ureidic NHs available for interaction with acetate.

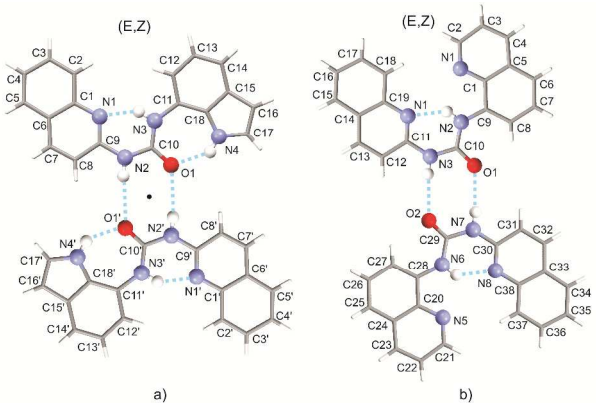

Figure 5 Ureidic dimer and relevant intra and inter-molecular interactions for $\mathbf{L^1\alpha}$ (a) as representative for the polymorphic pair ($\mathbf{L^1\alpha}$ and $\mathbf{L^1\beta}$) and $\mathbf{L^2}$(b) in the (*E,Z*) conformation. The numbering scheme is also reported. Centre of inversion is indicated as • (symmetry code: -x+5/3, -y+1/3, -z-2/3). Reproduced from Ref. 2.

The fact that this was not experimentally observed (no changes in the chemical shift of the two ureidic NHs of $\mathbf{L^2}$ were detectable in the presence of anions, (Figure 6, Figure S12 in the ESI of the original paper), corroborates our initial hypothesis that the intramolecular NH···N interaction also persists in the presence of an anionic guest for both $\mathbf{L^1}$ and $\mathbf{L^2}$.

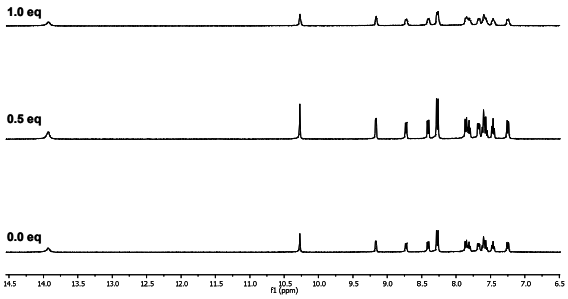

Figure 6 ^{1}H-NMR stack plot of a DMSO-d_6 solution of $\mathbf{L^2}$ (0.005 M) upon addition of tetrabutylammonium acetate (0.075 M) in DMSO-d_6 at 298 K. Reproduced from Ref. 2.

Therefore, in our opinion, the model we proposed for describing the interaction between $\mathbf{L^1}$ and acetate better accounts for all of the experimental data available.

Notes and references

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