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Nucleophilic activity of a linked bis{guanidine} leading to formation of a dicationic C_4N_4-heterocycle†

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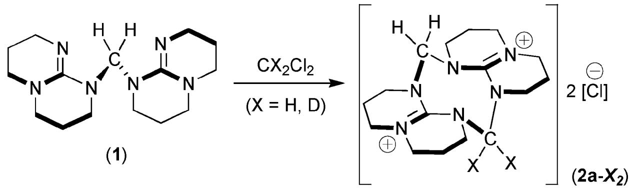
The methylene-linked bis{guanidine}, $H_2C\{hpp\}_2$ (hppH = 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine), displays nucleophilic activity towards organic halides, including the activation of dichloromethane under ambient conditions affording the cyclic dication, $[H_2C\{hpp\}_2CH_2]^{2+}[Cl]_2$.



Scheme 1

1,3,4,6,7,8-Hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (hppH) is a strong, non-nucleophilic base with a pK_a of 25.98 in MeCN.[1] Its bicyclic framework, along with that of other polycyclic guanidines and amidines, has been used as a convenient scaffold for the development of chiral organocatalysts that continue to be applied to a number of key transformations.[2] Whilst the chemistry of the related amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is also dominated by high basicity,[3] (pK_a\{MeCN\} 24.33),[1] several "unusual" reactions have been reported in which nucleophilic behaviour predominates.[4] These reactions generally proceed *via* $N_{amidine}$–element bond formation, and examples involving both activated organic,[5] and main group[6] electrophiles have been cited in the literature. Given the recent interest in hppH, DBU and related cyclic amidines as organocatalysts for ring-opening polymerization,[7] and our recent observation of the nucleophilic activity of the hpp-group at phosphorus centres,[8] we feel it timely to report a recent observation involving the nucleophilic activity of the linked bis{guanidyl} system, $H_2C\{hpp\}_2$ (**1**),[9] towards organohalides, including dichloromethane.

During studies of the coordination of **1** at neutral[9] and cationic[10] metal centres, it was noted that a CD_2Cl_2 solution of **1** deposited colourless, prismatic crystals (**2a**) upon standing at room temperature. X-Ray diffraction† indicated formation of $[H_2C\{hpp\}_2CX_2][Cl]_2$ (X = H or D), in which both of the imine *N*-atoms are incorporated in an unusual dicationic, C_4N_4-heterocycle (Scheme 1). Whilst related quaternization of amino nitrogen atoms to afford imidazolodinium dications has been reported,[11] nucleophilic activity of hpp-based systems has not been studied in detail,[12] and the activation of dichloromethane by such systems has hitherto not been reported.

Crystallographic data are unable to determine between bridging CH_2 and CD_2 groups in **2a**; however, ^{1}H NMR integral values were consistent with only one unit containing hydrogen.‡ The correct formula of the isolated crystals is therefore $[H_2C\{hpp\}_2CD_2][Cl]_2$ (**2a-D$_2$**),[13] verified by [^{2}H]-NMR spectroscopy in which inequivalent deuterium resonances at δ 5.05 and 4.13 ppm were observed. ^{13}C NMR data support this formulation; a multiplet is observed at δ 47.3 ppm comprising overlapping CH_2 and CD_2 signals, with an observable secondary isotope shift (9 ppb) to the α-methylene carbon of the guanidine. The predominant ions in the electrospray mass spectra correspond to a cation : anion ratio of 2 : 3, with exact masses (**2a-H$_2$**, 715.324; **2a-D$_2$**, 719.017) also consistent with partial deuteration in **2a-D$_2$**.

NMR studies of the *protio*-compound (**2a-H$_2$**) showed that the bridging methylene groups resonate as two AB spin-systems (4.4 : 1 ratio) indicative of an asymmetric environment for this group in solution. There is no exchange between the doublets in the major species, assigned to a rigid chair[14] conformation with *pseudo*-axial and -equatorial hydrogens. Exchange between the major and minor conformers is a relatively high energy process, only detected in solution at temperatures greater than 90 °C.

To ascertain whether the chloride counter-ions were associated with the different conformeric forms of **2a**, anion metathesis was conducted with $NaBPh_4$, affording $[H_2C\{hpp\}_2CH_2][BPh_4]_2$ (**2b**).† NMR spectroscopic analysis, however, indicated identical solution behaviour (major : minor ratio of 4.5 : 1), suggesting the adoption of different conformers is independent of the anion. These solution data contrast those for $[Me_2Si\{hpp\}_2SiMe_2][Cl]_2$ in which the silicon-methyls resonate as a singlet,[15] reflecting a more flexible ring system in the disiladiguanidinium cation, or processes that involve rupture of the Si–N bond.[16]

The molecular structure of **1**† (Fig. 1a) shows bond distances consistent with localized single- and double-bonds within the N1–C1–N2 fragment. The remaining C1–N3 bond is of an intermediate order [1.378(2) Å] which is indicative of partial delocalization throughout the core of the guanidyl moiety. In contrast, the bond lengths within the 'CN_3' core of the dication of **2a-D$_2$** indicate symmetrical bonding across N1–C1–N2, with a greater contribution to double bond character in the remaining C1–N3 bond [1.324(3) Å]. The chloride counter-ions are located above and below the C1–N3 'double' bond (Fig. 1b), with closest

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† Electronic supplementary information (ESI) available: Experimental procedures and characterizing data for all new compounds; crystallographic data (CIF) for **1**, **2a-D$_2$**, **2b**, **4b** (CCDC reference numbers 617399–617401 and 662882); ORTEP of **2b** and **4b**; optimized coordinates of stationary-points. See DOI: 10.1039/b715209d

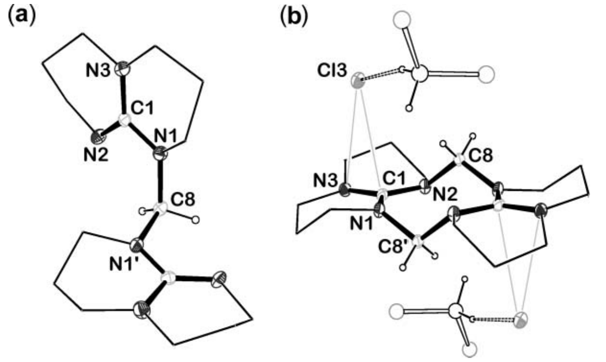


Fig. 1 Molecular structure of (a) $H_2C\{hpp\}_2$ (**1**) and (b) $[H_2C\{hpp\}_2CD_2][Cl]_2$ (**2a-D$_2$**). Selected bond lengths (Å): **1** C1–N1 1.394(2), C1–N2 1.288(2), C1–N3 1.378(2); **2a-D$_2$** C1–N1 1.343(3), C1–N2 1.358(3), C1–N3 1.324(3), N1–C8′ 1.459(3), N2–C8 1.477(3).

contacts of 3.26 Å and 3.35 Å to C1 and N3, respectively; one equivalent of dichloromethane per formula unit is also present, hydrogen-bonded to each chloride ion. The molecular structure of **2b**† reveals the same trends in C–N bond lengths.

As the conformational differences within the different forms of **2** were not immediately apparent, we have analyzed the characteristics of the dicationic component computationally, by means of geometry optimizations at a B3LYP/6-31+G** level of theory.[17] Several minima were identified in the potential hypersurface (Fig. 2); the nature of these singular points were determined through the calculation of second derivatives.

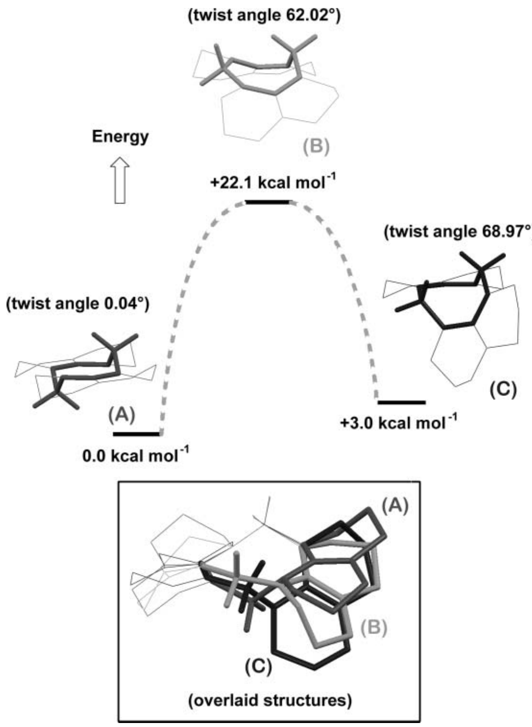
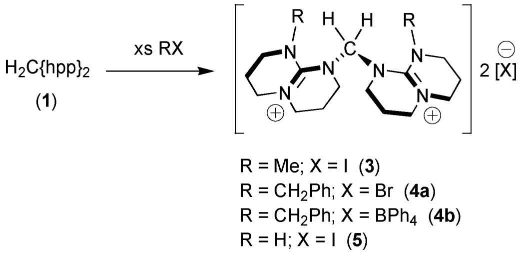


Fig. 2 Computationally determined conformations for the dication, $[H_2C\{hpp\}_2CH_2]^{2+}$, with reported free energy differences calculated at 325 K. Twist angles reported between mean CN_3 planes of each hpp-moiety.

Consistent with solid-state data, the lowest energy structure (**A**) approximates to a chair conformation with clearly defined axial and equatorial environments for the bridging methylene protons. A second minimum (**C**) was identified at only +3.0 kcal mol^{-1} higher energy, closely resembling a twist-boat conformation in which both bridging methylene groups are on the same side of the mean C_2N_4-heterocyclic plane. These conformational changes are accompanied by notable twisting of the central heterocycle and significant displacement of the annular methylene groups within the C_4N_2-guanidinyl rings, responsible for off-setting any strain induced in this structure.[18]

Our attention then focused on the 'chair-to-twist-boat' conversion, which has an energy difference large enough to allow the spectroscopic detection of both species in solution. Initial results indicated that interconversion between the different solution species was not due to cleavage of the central ring, as this process implies an energy close to 60 kcal mol^{-1}. A transition-state structure (**B**) was identified at +22.1 kcal mol^{-1} relative to the chair minimum, with a more pronounced boat-like conformation. This energy barrier reflects the high temperatures necessary to interconvert the two conformers observed in solution. Although these results preclude the influence of anion and/or solvent interactions with the cation, they clearly illustrate the presence of several stable conformers for the heterocycle.

The further reactivity of bis{guanidine} **1** was briefly explored by surveying its reaction with a series of alkyl halides (Scheme 2).† The products $[H_2C\{hppR\}_2][X]_2$, formed with excess MeI (**3** R = Me, X = I) and $PhCH_2Br$ (**4a** R = CH_2Ph, X = Br; **4b** R = CH_2Ph, X = BPh_4), are as expected. Reaction with excess 2-iodopropane (NMR scale, CD_3CN) proceeded *via* an elimination pathway (100% conversion in 15 h) with formation of propene and the iodide salt of the known protonated guanidinium, $[H_2C\{hppH\}_2]^{2+}$ (**5**).[10] The crystal structure of **4b**† confirms formation of the acyclic dication containing *N*-bonded benzyl groups at each guanidinium. The carbon–nitrogen bond lengths are comparable to those found in **2a-D$_2$**, with essentially equal N1/5–C1/9–N2/4 distances [av. 1.350 Å]; the remaining bond to the central carbon is once again shorter [av. 1.328 Å].



Scheme 2

In conclusion, the present study demonstrates the nucleophilicity of the linked bis{guanidine} **1** under ambient conditions, leading to the formation of dicationic guanidinium-containing products. Further studies on the nucleophilic behaviour of this compound will be presented in future publications.

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Notes and references

‡ **2a-H$_2$**: ^{1}H NMR (500 MHz, D$_2$O, 298 K): major isomer: δ 5.15 and 4.22 (d, $^2J_{\mathrm{HH}} = 15.6$ Hz, *exo*cyclic CH_2) ppm. Minor isomer: δ 5.31 and 4.31 (d, $^2J_{\mathrm{HH}} = 15.8$ Hz, *exo*cyclic CH_2) ppm. The remaining methylene groups of the bicyclic framework overlap in the following regions: δ 3.43 (m, 4H, hpp-CH_2), 3.29 (m, 8H, hpp-CH_2), 3.20 (m, 4H, hpp-CH_2), 1.88 (m, 8H, hpp-CH_2) ppm. ^{13}C NMR (125 MHz, D$_2$O, 298 K): δ 160.8 (*C*N$_3$), 152.0 (*C*N$_3$), 74.8 (*exo*cyclic *C*H$_2$), 68.1 (*exo*cyclic *C*H$_2$), 47.5 (hpp-*C*H$_2$), 47.4 (hpp-*C*H$_2$), 47.2 (hpp-*C*H$_2$), 21.4 (hpp-*C*H$_2$), 21.1 (hpp-*C*H$_2$) ppm. **2a-D$_2$**: [^{2}H]-NMR (76.8 MHz, D$_2$O, 298 K): 5.05 (br, CD_2), 4.13 (br, CD_2) ppm.

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14 Whilst the terms chair, boat and twist-boat are normally reserved for six-membered rings, the planar 'N–C–N' moieties within the C$_4$N$_4$ heterocycle enables reasonable parallels to be made between the two systems, and are therefore adopted in this work.

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