Formation of Intrabridgehead Hydrogen-bonded Ions from Medium-ring Bicyclic Diamines

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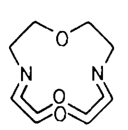
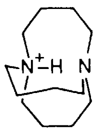
Of twenty medium-ring bicyclic diamines examined, twelve may be converted into inside-protonated ions; seven of these go by conventional, but slow, proton transfer mechanisms, three by redox-promoted rearrangements, and two by both mechanisms.

Inside protonation of macrocyclic diamines was first reported by Simmons and Park.[1] Lehn and co-workers prepared proton cryptates, a particularly interesting case being the protonation of [1.1.1] cryptand (**1**);[2] detailed kinetic studies of this[3] and other cases[4] have been reported. In these macrocyclic examples more than one proton can be inserted and there is no strong N^+–H : N bond in the monoprotonated ion. We have reported[5] the formation of inside-protonated 1,6-diazabicyclo[4.4.4]-tetradecane, *in*[4.4.4]H^+ (**2**) with a strong intrabridgehead hydrogen bond.[6] To our astonishment, we found by using deuteriated acid that the NH proton did not come from the solvent but from a CH_2 group α to nitrogen [reaction (b)]. We have recently made[7–9] an extensive set of medium-ring bicyclic diamines and report here a preliminary survey of their conversion into inside-protonated ions; our results are summarised in Table 1.

The inside protonation of the [6.4.2.]-, [5.5.2]-, [6.4.3]-, [5.5.3]-, and [6.5.3]-diamines is complete within 0.5 h at 35 °C in $CDCl_3$ containing one equivalent of CF_3CO_2H. In no case is the reaction complete in the time of mixing, *i.e.* these protonations are slow by conventional standards. Inside-protonated ions are readily recognised by the N^+–H : N absorption in the region δ 10—18,[10] which is always in slow exchange on the n.m.r. time scale with other NH and OH protons. Inside-protonated ions were isolated as ClO_4^- or BF_4^- salts, and their structures confirmed by normal methods, and by the fact that the NH proton did not exchange rapidly (or at all) when a salt was dissolved in D_2O (an exception is *in* [5.5.2]H^+ where exchange of H for D occurs quite rapidly, but is not instantaneous). The [5.4.2]diamine also inside-protonates under similar conditions but only if more than one equivalent of CF_3CO_2H is added to a $CDCl_3$ solution. While we have no specific explanation for this case, inside-protonation may be a reaction of the free diamine or [3] of its outside-protonated ion (certain to be formed in these conditions). Access to one or both inside-pyramidalised nitrogen lone pairs is presumably crucial for these reactions, and models suggest that this becomes more difficult as one progresses from the diaminoethane, to the diaminopropane, to the diaminobutane derivatives. Indeed we find that while the [5.4.2]diamine inside protonates readily by a classical mechanism, neither the [5.4.3]- nor the [5.4.4]-diamine do so. The [5.5.4]diamine does protonate inside by classical proton transfer, but in this case reaction is very slow, taking several days in neat CF_3CO_2H. As reported earlier,[8] the [6.3.3]diamine does give some inside-deuteriated ion when refluxed in CF_3CO_2D, but this classical process is only poorly competitive with the redox-promoted insertion of a C–H proton. These diamines are obviously close to one limit for classical inside protonation, a kinetic one. This limit need not coincide with the thermodynamic one, where the inside-protonated ion is less stable than the outside isomer. The [6.3.2]diamine is near this limit; on standing in $CDCl_3$, *out*[6.3.2]$H^+ClO_4^-$ (δ_{NH} 8.3) isomerises partially to its *in*-isomer (δ_{NH} 12.8); the final *out*:*in* ratio is 3:1. The remaining diaminoethane derivatives, [3.3.2], [4.3.2], [5.3.2], and [4.4.2] do not yield detectable concentrations of inside-protonated ions.



(1)

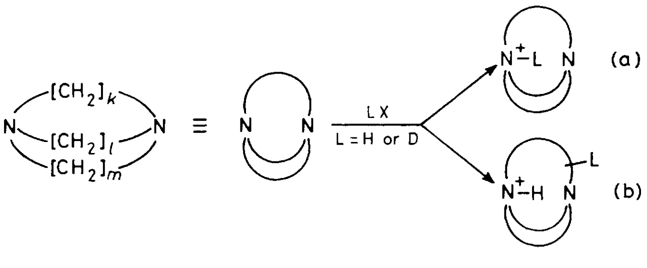


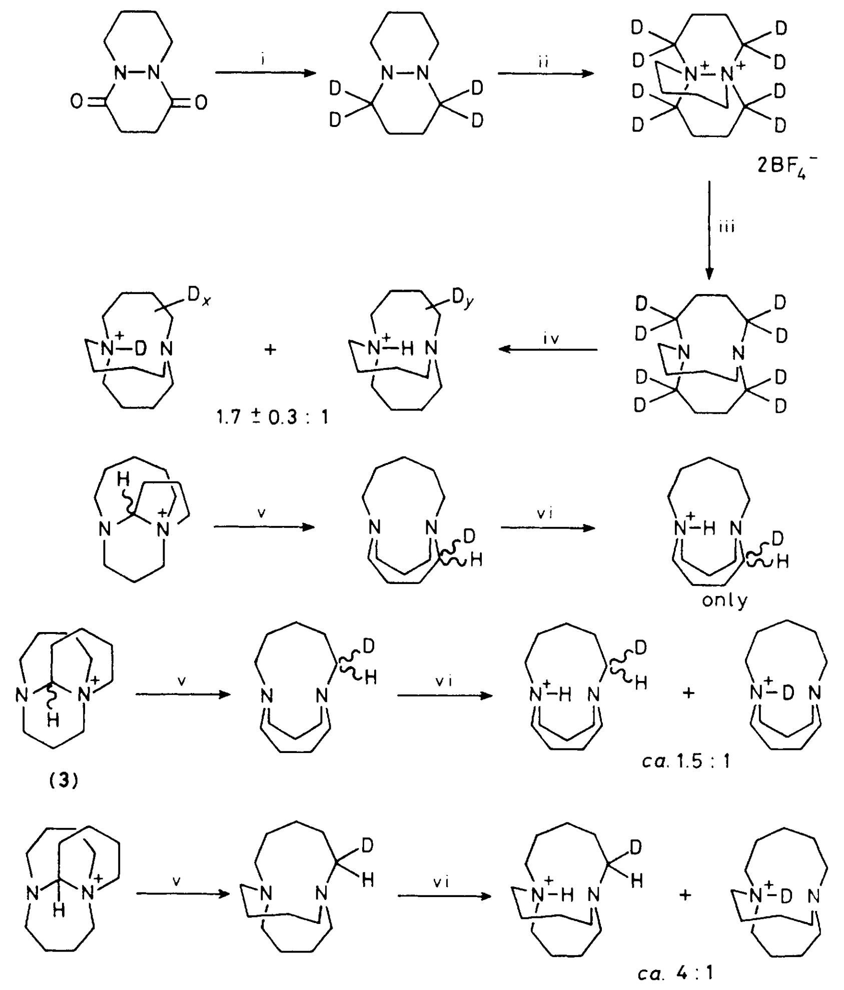
(2)

Table 1. Known medium-ring (1,k + 2)diazabicyclo[$k.l.m.$]alkanes and their conversion into inside-protonated ions. Diamines which form inside protonated-ions are shown in boldface.

$k + l + m + 2$	$H_2N[CH_2]_2NH_2$ Derivatives [$k.l.m.$]	$H_2N[CH_2]_3NH_2$ Derivatives [$k.l.m.$]	$H_2N[CH_2]_4NH_2$ Derivatives [$k.l.m.$]
10	3.3.2		
11	4.3.2	3.3.3	
12	5.3.2	4.3.3	
	4.4.2		
13	**6.3.2**(a)	5.3.3	
	5.4.2(a)	4.4.3	
14	**6.4.2**(a)	**6.3.3**(a)(b)	**4.4.4**(b)
	5.5.2(a)	**5.4.3**(b)	
15		**6.4.3**(a)	**5.4.4**(b)
		5.5.3(a)	
16		**6.5.3**(a)	**5.5.4**(a)(b)

For those diamines which inside-protonate very slowly or not at all by conventional means, we have tried to induce formation of the inside-protonated ion by redox-promoted rearrangement using the optimal conditions (60% aqueous H_2SO_4 containing $K_2S_2O_8$)[5] for preparation of *in*[4.4.4]H^+. This procedure is successful for the [6.3.3]-, [5.4.3]-, [5.4.4]-, and [5.5.4]-diamines, but fails in other cases where the diamine either remains solidly outside,outside diprotonated, or becomes oxidised to complex products. In order to prepare inside-deuteriated ions for spectroscopic studies,[10] we have prepared the C-deuteriated diamines shown in Scheme 1 and subjected them to reaction with H_2SO_4–$K_2S_2O_8$. The almost statistical product ratio from the [$^2H_8$]-[4.4.4]diamine implies a small kinetic isotope effect, k_H/k_D = 1.1 ± 0.2. This in turn suggests that the rate-limiting step precedes the N- to -C hydrogen transfer (believed[5,11] to occur in an aminium cation radical species); a conformational change to place one α-CH inside the cage is one possibility. Hoffmann–Loeffler type hydrogen atom transfers to stabilised (secondary and tertiary) aminium radicals have large kinetic isotope effects.[12]





Scheme 1. i, LiAlD$_4$ in tetrahydrofuran; ii, (BrCD$_2$CH$_2$)$_2$, 2 equiv. in PrCN; iii, Na–NH$_3$ (ref. 7); iv, 85% aq. H$_2$SO$_4$, K$_2$S$_2$O$_8$, 90 °C (ref. 5); v, LiAlD$_4$ in dimethoxyethane (ref. 9); vi, 60% aq. H$_2$SO$_4$, K$_2$S$_2$O$_8$, 25 °C (ref. 5).

As shown in Scheme 1, the redox-promoted rearrangement of the [5.4.3]diamine is regiospecific, only an α-CD in the five-carbon bridge being rearranged into the cavity. This result is confirmed by reaction of the non-deuteriated diamine in D$_2$SO$_4$–D$_2$O, when an α-CD appears in the five-carbon bridge of the product. So far we have been unable to separate the 3 : 1 mixture of diastereoisomeric salts (**3**) and thus test the stereochemistry of the rearrangement. As reported earlier,[8] the [6.3.3]diamine in D$_2$SO$_4$–D$_2$O gives rise to deuteriation at α-carbons in both the six- and the three-carbon bridges in the inside-protonated product.

What are the limits for stability of inside-protonated ions? While we may have reached them for the diaminoethane derivatives, we suggest that all the diaminopropane ions in Table 1, even *in* [3.3.3]H$^+$, might be kinetically persistent once formed and *in*[5.3.3]H$^+$ and *in*[4.4.3]H$^+$ may well be thermodynamically preferred to their outside-protonated isomers.

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