# Azolium Cyclophanes

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**Abstract**: This review covers the synthesis, conformational analysis, mass spectrometry, and reactivity and supramolecular chemistry of azolium cyclophanes. Included is a comprehensive coverage of the structural diversity of azolium cyclophanes. Aspects of reactivity examined include anion binding, carbene formation and metal coordination chemistry and H/D exchange.

**Keywords:** Cyclophanes, azolium cyclophanes, supramolecular chemistry, imidazolium, anion binding, NHC carbenes.

## 1. INTRODUCTION

Cyclophane structures have been of great interest for many years, for reasons as diverse as the challenge of their synthesis, remarkable host-guest chemistry, and potential applicability to advanced materials [1, 2]. Numerous types of cyclophanes now exist. Over the last decade there has been a growing interest in azolium cyclophanes, particularly for their potential applications in anion recognition and, in the case of imidazolium- and benzimidazolium-based cyclophanes, as precursors to *N*-heterocyclic carbene metal complexes. This review provides a comprehensive coverage of the azolium cyclophanes reported to date.

In the context of this review, azolium cyclophanes are structures containing two or more azolium groups, with the azolium groups constituting parts of a macrocycle. The range of structures exhibited amongst azolium cyclophanes is diverse. Examples exist in which the azolium components are imidazolium, benzimidazolium, triazolium, benzotriazolium, or pyrazolium units. The diversity of the components linking the azolium units is even broader, and includes groups based on simple alkanes, benzene, phenol, pyridine, poly-aromatics, pyrrole, triazole and triazolate.

A number of the figures associated with the synthesis section of this review show cyclophane structures with dashed lines cutting across some of the bonds. These lines indicate the bonds that are formed during the step in which the cyclophane structure is assembled.

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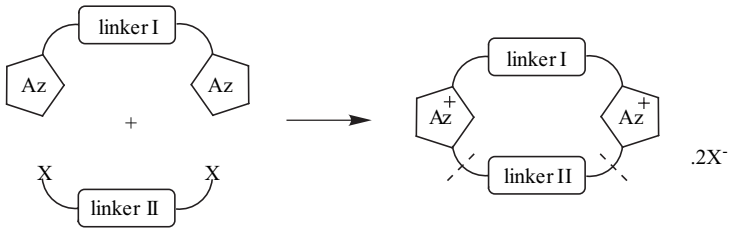
## 2. SYNTHESIS

Almost all azolium cyclophanes have been synthesized using a convergent methodology, usually a 3+1 (or pseudo 3+1) pathway involving the reaction of a *bis*-azole species with a di-functional linker (Scheme **1**). While the synthetic methodologies are generally very similar there is significant structural diversity amongst the azolium cyclophanes that have been reported to date. In most cases the counter anions (usually halides or tosylate) associated with the cationic cyclophanes are derived from the di-functional linker but in some cases anion metathesis is conducted to afford the cyclophanes as salts with alternative anions such as hexafluorophosphate. The most common linkers are based on *bis*(halomethyl)arenes, although a number of linkers are based on ditosyl- or dihaloalkanes. Tables **1**-**4** and Figs. (**1**)-(**3**) summarize the various imidazolium, benzimidazolium, benzotriazolium and pyrazolium cyclophanes that contain two azolium units and which were prepared by a 3+1 or a pseudo 3+1 synthetic pathway. The synthesis of azolium cyclophanes is not limited to structures formed by 3+1 pathways. A variety of azolium cyclophanes in which the macrocycle is relatively large have been prepared following 3+3, 4+1, 4+2, 5+1 and 5+3 pathways (Figs. (**4**)-(**6**)), but in all cases a "linear" *bis*-azole species was reacted with a di-functional linker to form the macrocycle.




**Scheme 1**. Convergent 3 + 1 pathway to azolium cyclophanes.

Various interesting aspects in the synthesis of azolium cyclophanes warrant special comment. In a number of cases it has been reported that the macrocyclization step (cyclophane formation step) is concentration and/or solvent dependent. Typical macrocycle syntheses involve the use of high dilution conditions to prevent polymerisation processes competing with ring-closure processes [49]. While this is also the case in the preparation of many azolium cyclophanes

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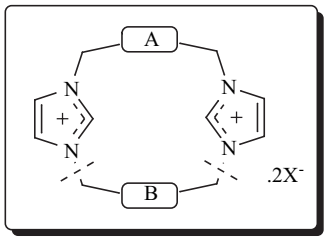
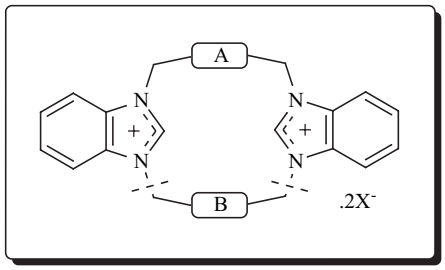
**Table 1. Imidazolium Cyclophanes Synthesized by a 3+1 Strategy**




| Cyclophane | A | B | Yield[a] | Ref. |
|---|---|---|---|---|
| **1** | $CH_2$ | $CH_2$ | | [3-5] |
| **2** | $(CH_2)_2$ | *m*-$C_6H_4$ | 87 ($Br^-$) | [6, 7] |
| **3** | $(CH_2)_2$ | *p*-$C_6H_4$ | 79 ($Br^-$) | [6] |
| **4** | *o*-$C_6H_4$ | *o*-$C_6H_4$ | 90 ($Br^-$) | [8-10] |
| **5** | *o*-$C_6H_4$ | *m*-$C_6H_4$ | 70 ($Br^-$) | [8] |
| **6** | *o*-$C_6H_4$ | 2,6-pyridinediyl | 77 ($Br^-$) | [8] |
| **7** | *o*-$C_6Me_4$ | *o*-$C_6Me_4$ | 82 ($Br^-$) | [8] |
| **8** | 1,2-$C_6H_2$-4,5-$(C_7H_{15})_2$ | 1,2-$C_6H_2$-4,5-$(C_7H_{15})_2$ | 46 ($Br^-$) | [9] |
| **9** | 1,2-$C_6H_2$-4,5-$(C_7H_{15})_2$ | 1,3-$C_6H$-2,4,6-$Me_3$ | 54 ($Br^-$) | [11] |
| **10** | 2,3-naphthalenediyl | 2,3-naphthalenediyl | 84 ($Br^-$) | [8, 9] |
| **11** | *m*-$C_6H_4$ | *m*-$C_6H_4$ | 90 ($Br^-$) | [5, 8, 10, 12-15] |
| **12** | 1,3-$C_6H_3$-5-$Bu^t$ | 1,3-$C_6H_3$-5-$Bu^t$ | | [5, 14] |
| **13** | 1,3-$C_6H$-2,4,6-$Me_3$ | 1,3-$C_6H$-2,4,6-$Me_3$ | 88 ($Br^-$) | [8] |
| **14** | 1,3-$C_6H$-2,4,6-$Me_3$ | *o*-$C_6H_4$ | 71 ($Br^-$) | [8] |
| **15** | 1,3-$C_6H$-2,4,6-$Me_3$ | 2,6-pyridine | 84 ($Br^-$) | [8] |
| **16** | 2,6-$C_6H_2OH$-4-$Bu^t$ | 2,6-$C_6H_2OH$-4-$Bu^t$ | 37 ($Br^-$) | [8] |
| **17** | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 73 ($PF_6^-$)[b] | [16] |
| **18** | 2,6-pyridinediyl | $C(OH)_2$ | 90 ($Cl^-$) | [17] |
| **19** | 2,6-pyridinediyl | 2,6-$C_6H_2OH$-4-$NO_2$ | 45 ($Br^-$) | [18] |
| **20** | 2,6-pyridinediyl | 3,5-$C_6H_3OMe$ | 57 ($Br^-$) | [18] |
| **21** | 2,6-pyridinediyl | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 56 ($Br^-$) | [19] |
| **22** | 2,6-pyridinediyl | 2,6-$C_6H_2OMe$ | 41 ($Br^-$) | [19] |
| **23** | 2,6-pyridinediyl | 2,6-pyridinediyl | 71 ($Br^-$) | [8, 18-21] |
| **24** | 2,6-pyridinediyl | 2,5-pyrroledilyl | 68 ($PF_6^-$)[b] | [22, 23] |
| **25** | 2,5-pyrroledilyl | 2,5-pyrroledilyl | 55 ($PF_6^-$)[b] | [22] |
| **26** | 2,6-pyridinediyl | 2,9-phenanthrolinediyl | 50 ($PF_6^-$)[b] | [24] |
| **27** | *p*-$C_6H_4$ | *p*-$C_6H_4$ | 90 ($Br^-$) | [8, 10, 25-28] |
| **28** | 1,4-$C_6H_2$-2,5-$Me_2$ | 1,4-$C_6H_2$-2,5-$Me_2$ | | [8, 26] |
| **29** | *p*-$C_6Me_4$ | *p*-$C_6Me_4$ | | [8, 26] |
| **30** | 1,8-anthracenediyl | 1,8-anthracenediyl | 62 ($PF_6^-$)[b] | [29] |

[a]Isolated yield (%), anion of isolated salt in parentheses. [b]Anion changed by salt metathesis.

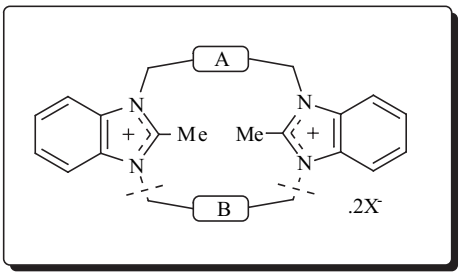
**Table 2. Benzimidazolium Cyclophanes Synthesized by a 3+1 Strategy**




| Cyclophane | A | B | Yield[a] | Ref. |
|---|---|---|---|---|
| **31** | $CH_2$ | $CH_2$ | 24 ($Br^-$) | [30, 31] |
| **32** | $(CH_2)_2$ | $(CH_2)_2$ | 11 ($Br^-$) | [30, 31] |
| **33** | $CH_2OCH_2$ | $CH_2OCH_2$ | 67 ($TsO^-$) | [19, 32, 33] |
| **34** | $(CH_2OCH_2)_2$ | $(CH_2OCH_2)_2$ | 51 ($TsO^-$) | [32] |
| **35** | $(CH_2OCH_2)_3$ | $(CH_2OCH_2)_3$ | 86 ($TsO^-$) | [32] |
| **36** | $(CH_2OCH_2)_4$ | $(CH_2OCH_2)_4$ | 75 ($TsO^-$) | [32] |
| **37** | $(CH_2OCH_2)_5$ | $(CH_2OCH_2)_5$ | 74 ($TsO^-$) | [32] |
| **38** | $CH_2OCH_2$ | $(CH_2OCH_2)_2$ | 77 ($TsO^-$) | [32] |
| **39** | $(CH_2OCH_2)_2$ | $(CH_2OCH_2)_3$ | 65 ($TsO^-$) | [32] |
| **40** | $CH_2SCH_2$ | $CH_2OCH_2$ | 75 ($TsO^-$) | [32] |
| **41** | $CH_2OCH_2$ | 2,6-$C_6H_3OMe$ | 48 ($Br^-$) | [19] |
| **42** | $CH_2OCH_2$ | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 42 ($Br^-$) | [19] |
| **43** | $CH_2OCH_2$ | 2,6-$C_6H_2OH$-4-$Bu^t$ | 86 ($Cl^-$) | [19] |
| **44** | $CH_2OCH_2$ | 2,6-pyridinediyl | 59 ($Cl^-$) | [19] |
| **45** | *o*-$C_6H_4$ | $CH_2$ | 35 ($Br^-$) | [30] |
| **46** | *o*-$C_6H_4$ | $(CH_2)_2$ | 20 ($Br^-$) | [30] |
| **47** | *o*-$C_6H_4$ | $CH_2OCH_2$ | 54 ($TsO^-$) | [32] |
| **48** | *o*-$C_6H_4$ | *o*-$C_6H_4$ | 50 ($Br^-$) | [8, 9, 30] |
| **49** | 2,3-naphthalenediyl | 2,3-naphthalenediyl | 68 ($Br^-$) | [8] |
| **50** | 2,6-$C_6H_3OMe$ | 2,6-$C_6H_2OH$-4-$Bu^t$ | 56 ($Br^-$) | [19] |
| **51** | 2,6-pyridinediyl | $(CH_2)_2$ | 27 ($Br^-$) | [7] |
| **52** | 2,6-pyridinediyl | *m*-$C_6H_4$ | 82 ($Br^-$) | [7] |
| **53** | 2,6-pyridinediyl | 2,6-pyridinediyl | 90 ($Br^-$) | [18, 19] |
| **54** | 2,6-pyridinediyl | 2,6-$C_6H_2OH$-4-$NO_2$ | 58 ($Br^-$) | [18] |
| **55** | 2,6-pyridinediyl | 3,5-$C_6H_3OMe$ | 68 ($Br^-$) | [18] |
| **56** | 2,6-pyridinediyl | 2,6-$C_6H_3OMe$ | 56 ($Br^-$) | [19] |
| **57** | 2,6-pyridinediyl | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 46 ($Br^-$) | [19] |
| **58** | 2,6-pyridinediyl | 2,6-$C_6H_2OH$-4-$Bu^t$ | 92 ($Cl^-$) | [19] |
| **59** | *p*-$C_6H_4$ | *p*-$C_6H_4$ | 90 ($Br^-$) | [25, 27, 28] |
| **60** | 1,2-$(CH_2O)_2C_6H_4$ | 1,2-$(CH_2O)_2C_6H_4$ | 60 ($TsO^-$) | [32] |

[a]Isolated yield (%), anion of isolated salt in parentheses.

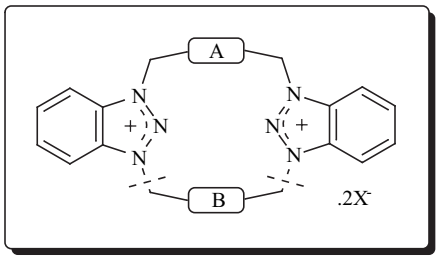
**Table 3. 2-Methylbenzimidazolium Cyclophanes Synthesized by a 3+1 Strategy**




| Cyclophane | A | B | Yield[a] | Ref. |
|---|---|---|---|---|
| **61** | $CH_2OCH_2$ | $CH_2OCH_2$ | 42 ($TsO^-$) | [19] |
| **62** | $CH_2OCH_2$ | 2,6-pyridinediyl | 48 ($Cl^-$) | [19] |
| **63** | $CH_2OCH_2$ | 2,6-$C_6H_3OMe$ | 73 ($Br^-$) | [19] |
| **64** | $CH_2OCH_2$ | 2,6-$C_6H_2OMe$-4-$Bu^t$ | 66 ($Br^-$) | [19] |
| **65** | 2,6-pyridinediyl | 2,6-$C_6H_3OMe$ | 51 ($Br^-$) | [19] |

[a]Isolated yield (%), anion of isolated salt in parentheses.

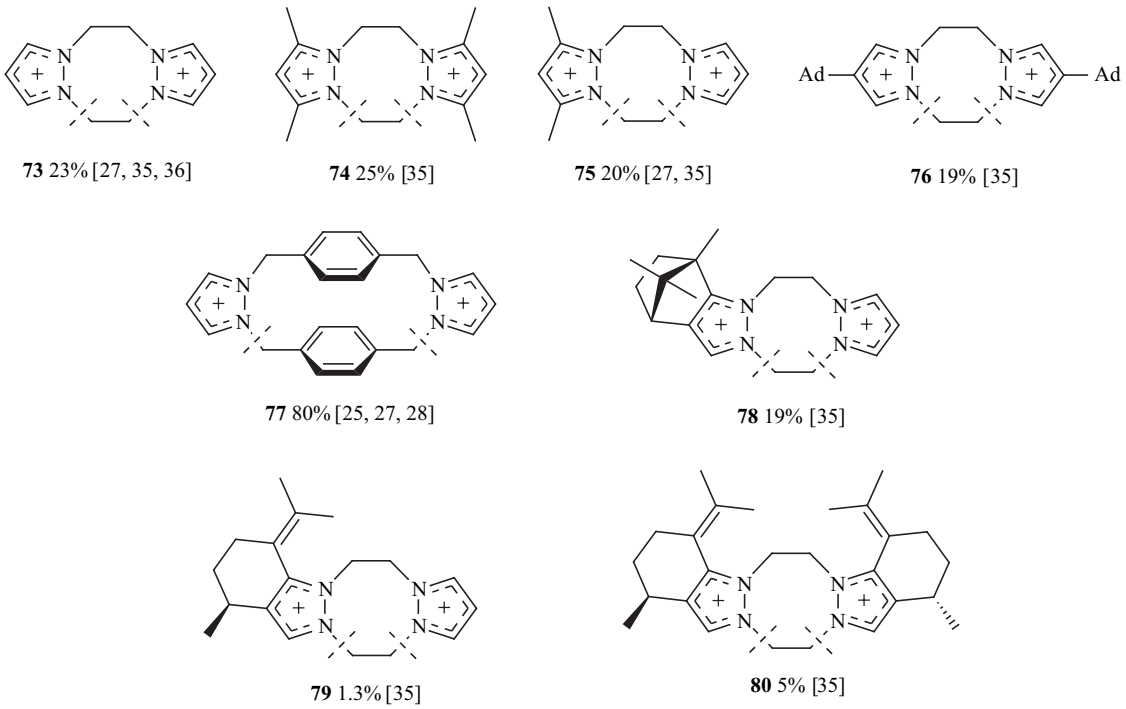
**Table 4. Benzotriazolium Cyclophanes Synthesized by a 3+1 Strategy**




| Cyclophane | A | B | Yield[a] | Ref. |
|---|---|---|---|---|
| **66** | *o*-$C_6H_4$ | *o*-$C_6H_4$ | 42 ($Br^-$) | [34] |
| **67** | *m*-$C_6H_4$ | *m*-$C_6H_4$ | 40 ($Br^-$) | [34] |
| **68** | *p*-$C_6H_4$ | *p*-$C_6H_4$ | 55 ($Br^-$) | [34] |
| **69** | 4,4'-biphenyldiyl | 4,4'-biphenyldiyl | 44 ($Br^-$) | [34] |
| **70** | 2,6-pyridinediyl | 2,6-pyridinediyl | 72 ($Br^-$) | [8, 18] |
| **71** | 2,6-pyridinediyl | 3,5-$C_6H_3OMe$ | 59 ($Br^-$) | [18] |
| **72** | 2,6-pyridinediyl | 2,6-$C_6H_2OH$-4-$NO_2$ | 52 ($Br^-$) | [18] |

[a]Isolated yield (%), anion of isolated salt in parentheses.

(reactant concentrations typically range from less than 1 mM up to 20 mM), some azolium cyclophanes have been prepared at remarkably high concentration in excellent yield. The ether-linked cyclophane **33** (Table **1**) has been prepared in 67% yield from a solution containing the reactants in *ca.* 220 mM concentration, but, as the linker was lengthened, considerably more dilute conditions were used (7 mM for **37**) (Fig. ( **7**)) [32]. Bitter and co-workers report that for the synthesis of the benzimidazolium cyclophanes **33**, **44**, **53**, **61**, and **62** *via* the ring closure reactions involving diethylene glycol ditosylate or 2,6-*bis*(chloromethyl)pyridine at concentrations of 330 mM, the cyclophanes were all isolated in reasonable yields (Fig. (**7**)) [19]. Youngs and co-workers have reported the synthesis of *bis*(methylene) pyridine- and *bis*(methylene)pyrrole-linked imidazolium cyclophanes **24** and **25** (Table **1**) from 100 mM solutions of the reactants (Fig. (**8**)) [22].



**73** 23% [27, 35, 36]

**74** 25% [35]

**75** 20% [27, 35]

**76** 19% [35]

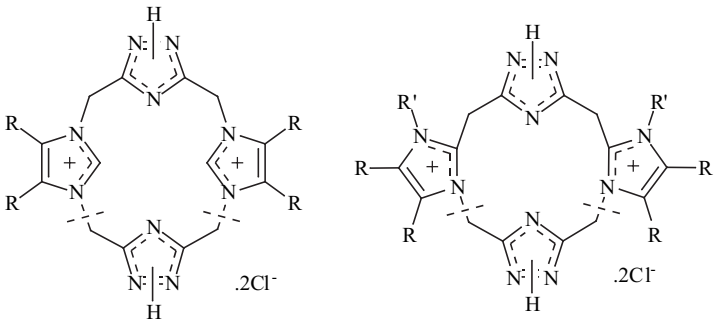
**77** 80% [25, 27, 28]

**78** 19% [35]

**79** 1.3% [35]

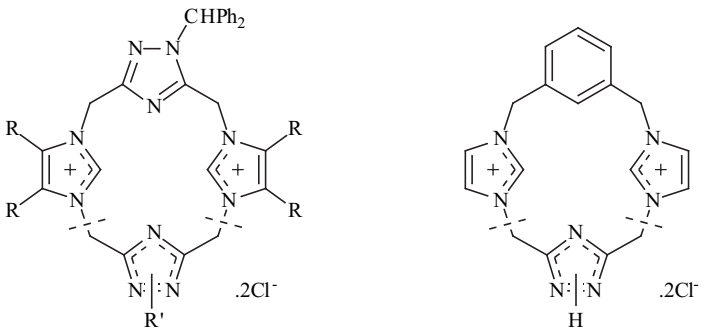
**80** 5% [35]

**Fig. (1)**. Pyrazolium cyclophanes, synthesized as dibromide salts by a 3+1 or pseudo 3+1 strategy (percentage yields indicated, reference(s) in square brackets).



**81** R = H 42% [15, 37-39]
**82** R = Me 40% [37, 39]
**83** R = Bu 51% [37, 39]

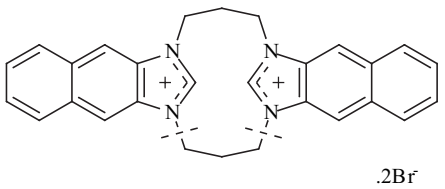
**84** R = H, R' = Me 55% [37, 39]
**85** R = H, R' = Bu 60% [37, 39]
**86** R = Me, R' = Me 30% [37, 39]



**87** R = H, R' = H 63% [38, 40]
**88** R = Me, R' = H 40% [40]
**89** R = H, R' = $CHPh_2$ [40]
(mixture of isomers)

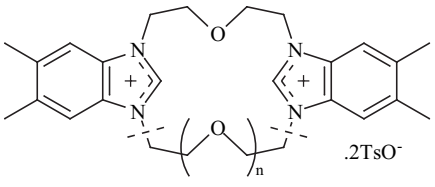
**90** 50% [15]

**Fig. (2)**. Imidazolium cyclophanes with triazole linkers, synthesized by a 3+1 strategy (percentage yields indicated, reference(s) in square brackets).



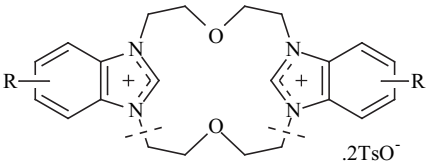
.2Br$^-$

**91** 30% [4]



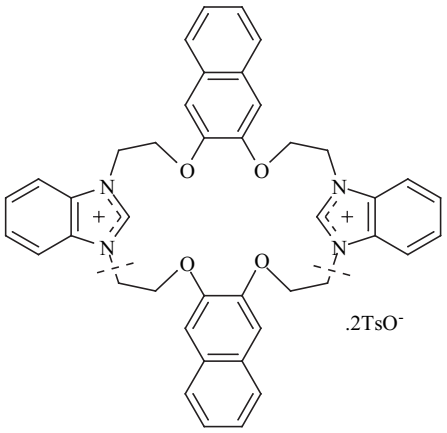
.2TsO$^-$

**92** n = 1 83% [32]
**93** n = 2 87% [32]



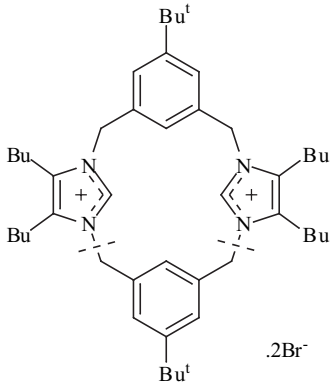
.2TsO$^-$

**94** R = Me 54% [32]
**95** R = OMe 94% [32]
**96** R = Cl 87% [32]
**97** R = $CF_3$ 54% [32]
**98** R = $NO_2$ 87% [32]



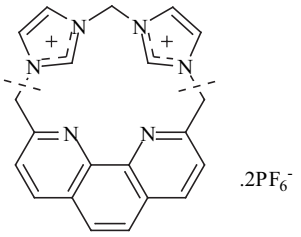
.2TsO$^-$

**99** 68% [32]



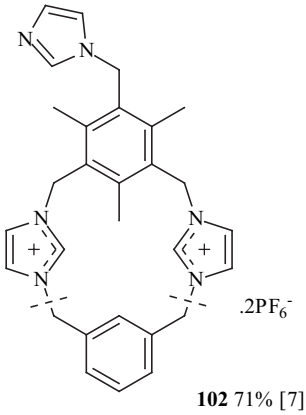
.2Br$^-$

**100** [5, 14]



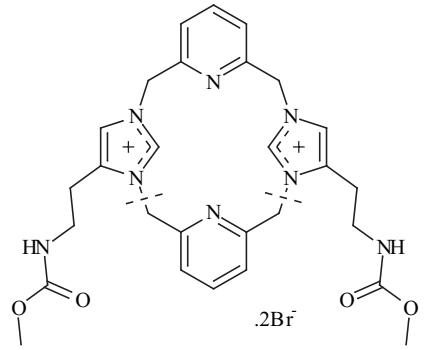
.2PF$_6^-$

**101** 17% [24]



.2PF$_6^-$

**102** 71% [7]



.2Br$^-$

**103** 70% [41]

**Fig. (3)**. Miscellaneous azolium cyclophanes formed by a 3+1 or pseudo 3+1 strategy (percentage yields indicated, reference(s) in square brackets).

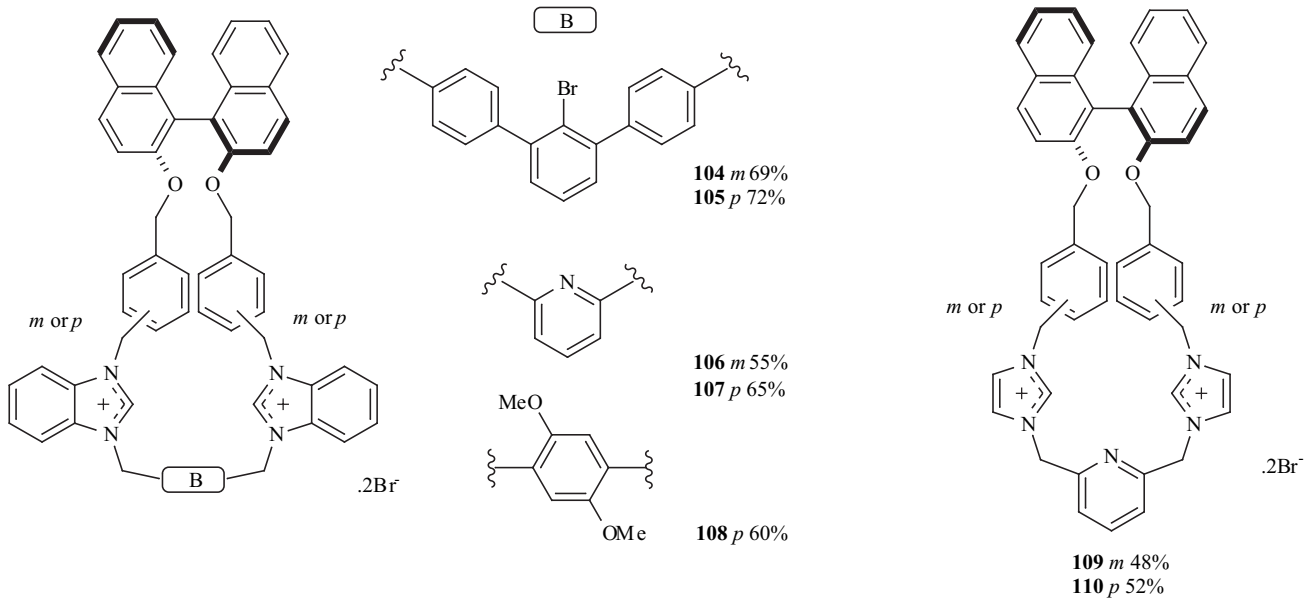
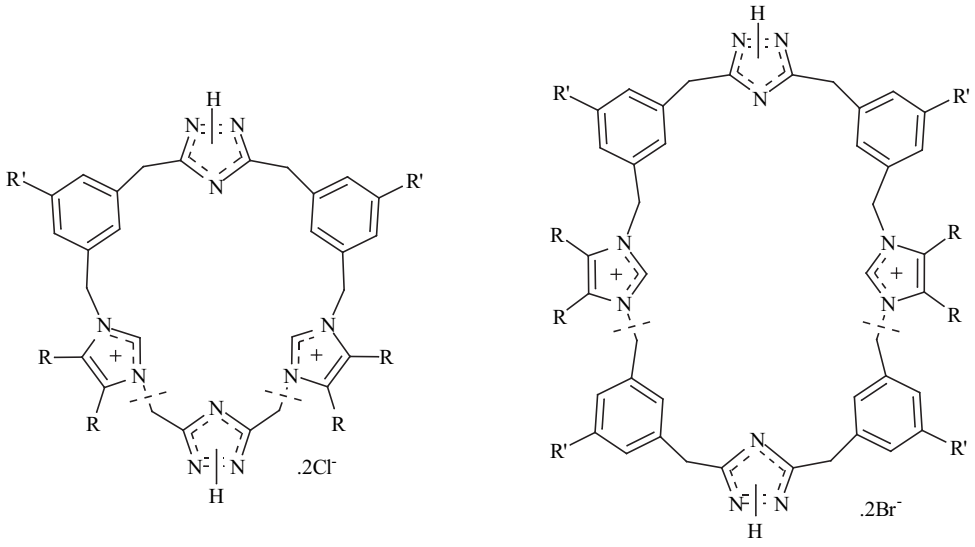



**Fig. (4)**. Large macrocycle azolium cyclophanes containing a BINOL moiety (percentage yields indicated) [42].

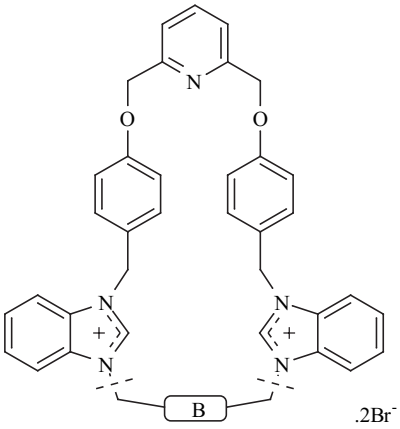


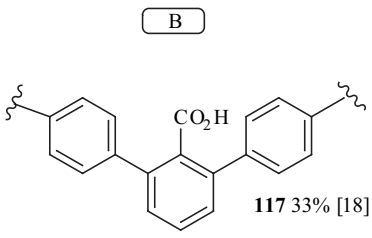

**111** R = H, R' = H 35% [43]
**112** R = H, R' = Bu$^t$ 26% [44]
**113** R = Bu, R' = Bu$^t$ 46% [44]

**114** R = H, R' = H 20% [43]
**115** R = H, R' = Bu$^t$ 52% [44]
**116** R = Bu, R' = Bu$^t$ 62% [44]

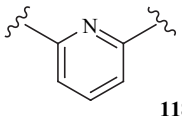
**Fig. (5)**. Large macrocycle azolium cyclophanes containing triazole linkers (percentage yields indicated, reference(s) in square brackets).

Despite the above observations, the choice of concentration in syntheses of azolium cyclophanes can be critical, especially with respect to the purity of products and the minimization of polymerisation processes. The extent to which low concentrations are required to produce a macrocyclic product is affected by the size, reactivity and structures of the precursors (the *bis*-azole and the di-functional linker). For example, Baker *et al*. found that in the preparation of the *p*-xylyl linked imidazolium cyclophanes **27**-**29**, as the number of methyl groups on the xylyl component of the *bis*-azole was increased (none in **27**, two in **28** and four in **29**) the requirement for the use of low concentrations to avoid polymeric products decreased (Fig. (**9**)) [26]. This result may be a consequence of the additional methyl groups restricting conformational freedom of the imidazole unit in the intermediate formed during the 3+1 synthesis, and thereby favouring cyclization over polymerization [26]. It should be noted that the non-methylated cyclophane **27** has been prepared by Cabildo *et al.* in high yield (90%) under conditions of relatively high concentration (50 mM, compared to ~1 mM used by Baker *et al*.) [25]. In these two syntheses of **27** the different solvents used may have been a significant factor in the relative efficiency of the macrocyclization process.

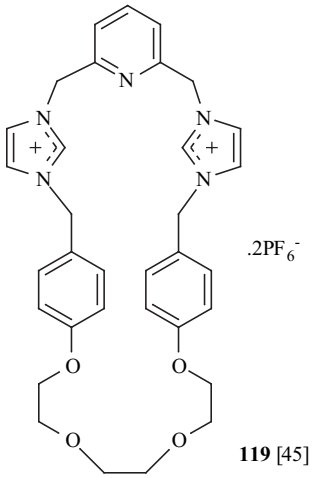


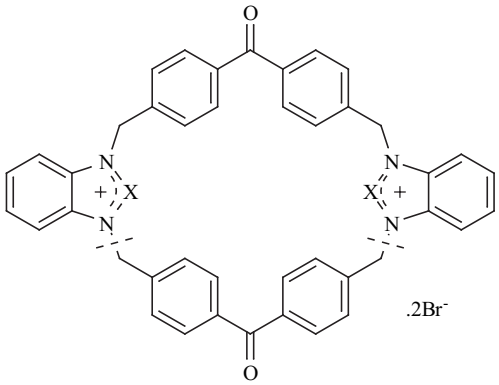

**117** 33% [18]



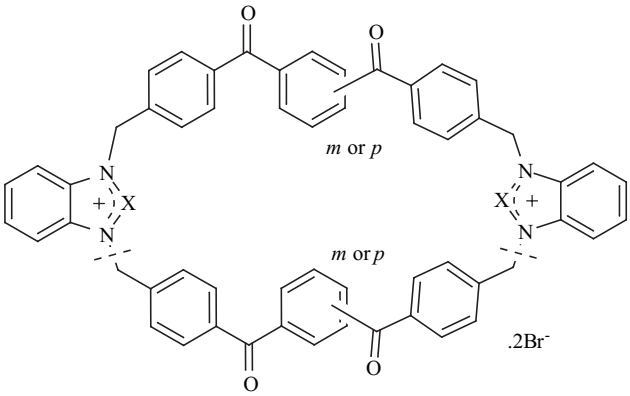
**118** 69% [18]



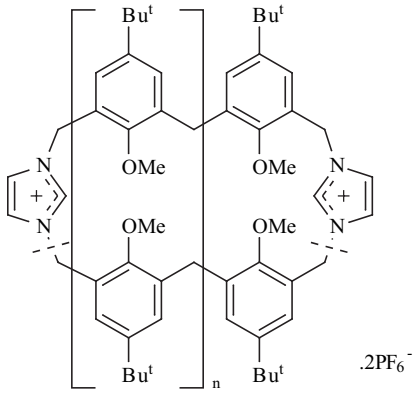

**119** [45]



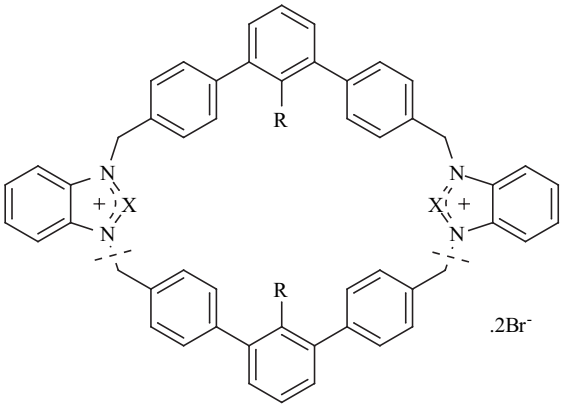

**120** X = CH 52% [46]
**121** X = N 45% [46]




**122** *m* X = CH 48% [46]
**123** *m* X = N 55% [46]
**124** *p* X = CH 54% [46]
**125** *p* X = N 54% [46]

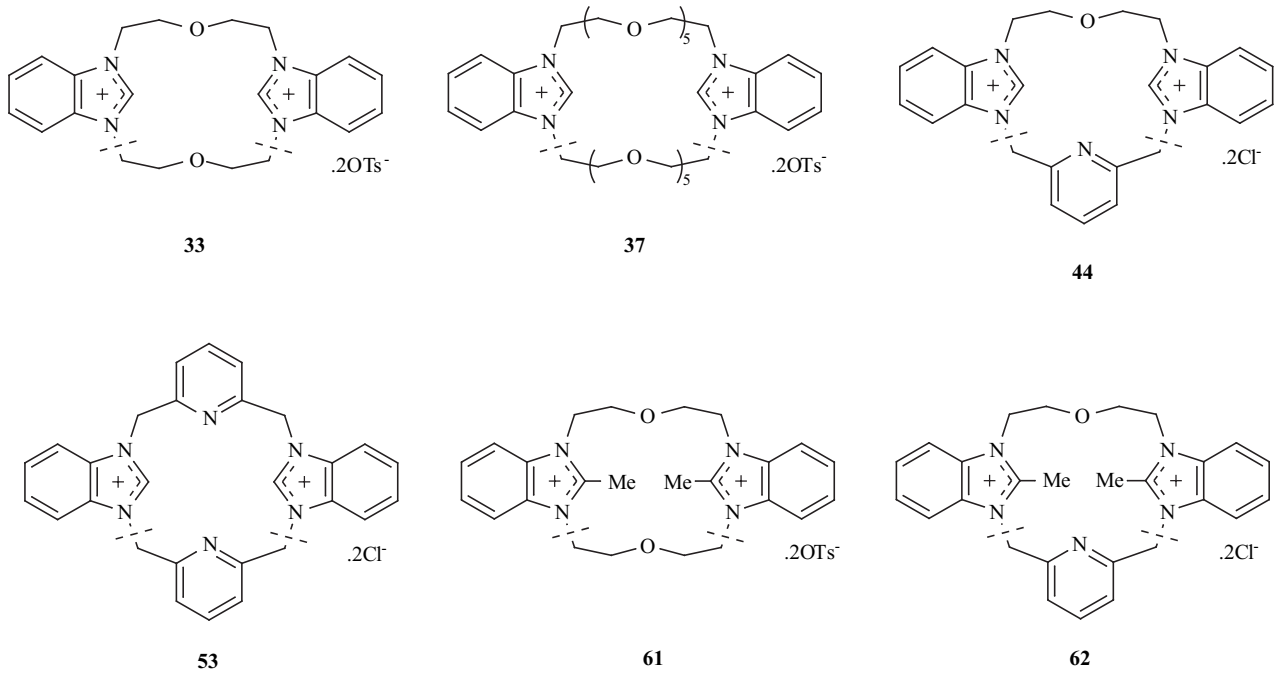



**126** n = 1 54% [16]
**127** n = 2 40% [16]




**128** X = CH, R = H 70% [47, 48]
**129** X = CH, R = Br 60% [47, 48]
**130** X = CH, R = $CO_2H$ 50% [47, 48]
**131** X = CH, R = $CO_2Me$ 45% [47, 48]
**132** X = CMe, R = H 50% [47, 48]
**133** X = CMe, R = Br 55% [47, 48]
**134** X = N, R = H 60% [34, 48]
**135** X = N, R = Br 57% [34, 48]
**136** X = N, R = $CO_2H$ 40% [34, 48]
**137** X = N, R = $CO_2Me$ 43% [34, 48]

**Fig. (6)**. Miscellaneous large macrocycle azolium cyclophanes (percentage yields indicated, reference(s) in square brackets).



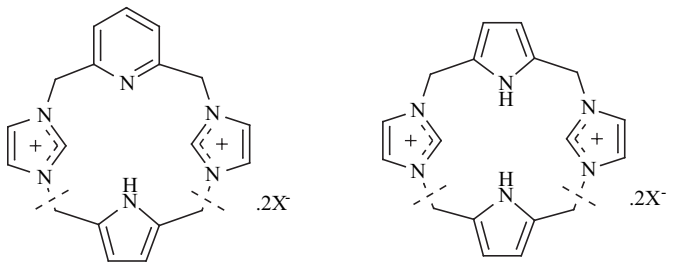

**33** **37** **44**

**53** **61** **62**

**Fig. (7)**. Some benzimidazolium cyclophanes that have been synthesized at different concentrations; **33**, **44**, **53**, **61** and **62** at high concentrations and **37** at low concentrations.

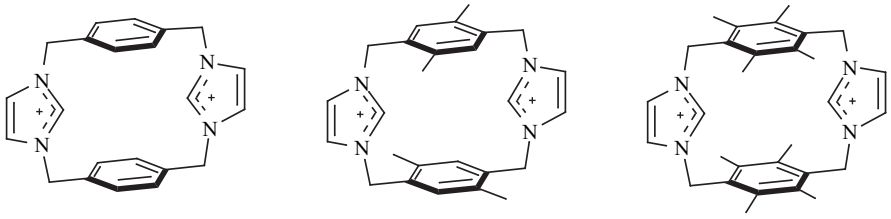
Other studies have highlighted the importance of the choice of solvent for the synthesis of azolium cyclophanes. In some cases solvents have been chosen based on boiling temperature, higher boiling solvents being used to improve reaction rates for less reactive reagents [19]. In other cases it has been reported that the use of one solvent over another has significantly improved the yields of the isolated cyclophanes [6]. While many of the reported syntheses are adequate they are presumably not optimised systems; many similar cyclophanes have been prepared at various concentrations and in different solvents. It is clear that optimisation of syntheses of azolium cyclophanes requires consideration of concentration, solvent, and reaction temperature.

For cyclophanes containing two azolium units and two different linkers (*i.e.* linker I ≠ linker II in Scheme **1**) there are two possible 3+1 synthetic routes, one involving the *bis*-azole species containing one type of linker (*i.e.* linker I) and the alternative route with the *bis*-azole species containing the other type of linker (*i.e.* linker II). Reports in the literature have shown that the yields of the cyclophanes produced by these two different routes can be different. The yield of **90** from the reaction of 1,3-*bis*(imidazol-1-ylmethyl)benzene



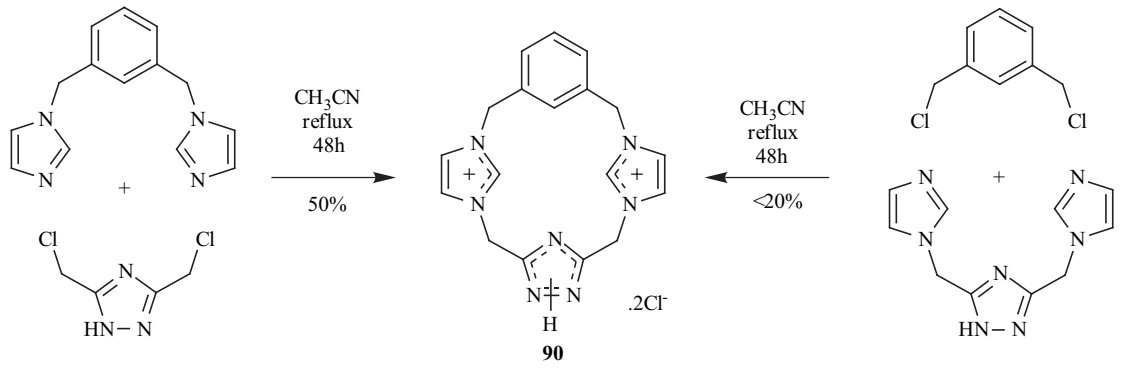

**24** **25**

**Fig. (8)**. Some pyrrole-linked imidazolium cyclophanes that have been synthesized in concentrated solutions.

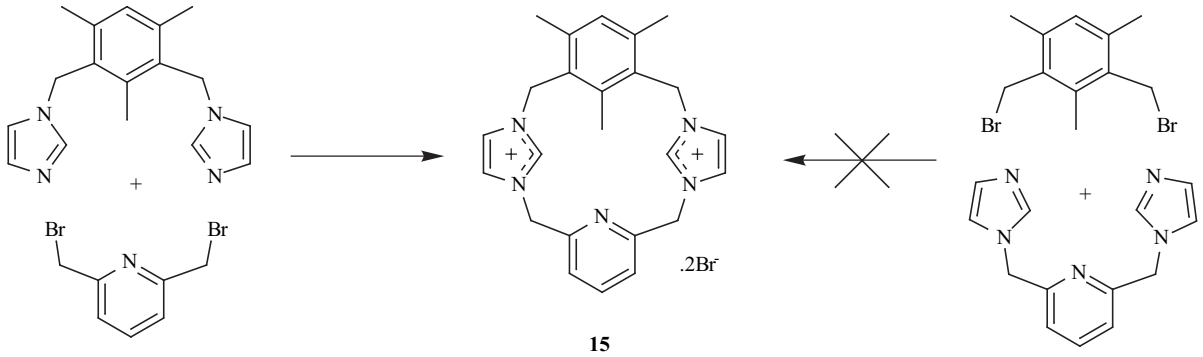


**27** **28** **29**

**Fig. (9)**. Some imidazolium paracyclophanes, the ease of synthesis of which varies with the degree of methylation.




**Scheme 2**. Alternative routes to azolium cyclophane **90**.

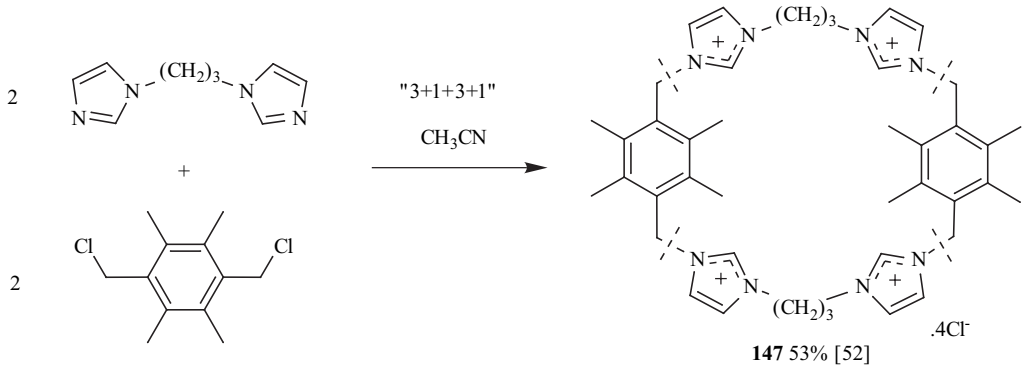



**Scheme 3**. Potential routes to azolium cyclophane **15**. Only one route was successful.

and 3,5-*bis*(chloromethyl)-1,2,4-triazole was 50%, but under identical conditions the yield from the reaction of 1,3-*bis*(chloromethyl)benzene and 3,5-*bis*(imidazol-1-ylmethyl)-1,2,4-triazole was less than 20% (Scheme **2**) [15]. In the case of **15**, the cyclophane could only be prepared if the precursors were 2,4-*bis*(imidazol-1-ylmethyl)mesitylene and 2,6-*bis*(bromomethyl)pyridine; the reaction of the alternative precursors, 2,4-*bis*(bromomethyl)mesitylene and 2,6-*bis*(imidazol-1-ylmethyl)pyridine, did not afford the cyclophane in any appreciable yield (Scheme **3**) [8]. While these examples show that the order in which the different linkers are introduced into the cyclophane can affect the final macrocyclization step, other studies have found no difference in the results obtained from alternative cyclization routes [42].

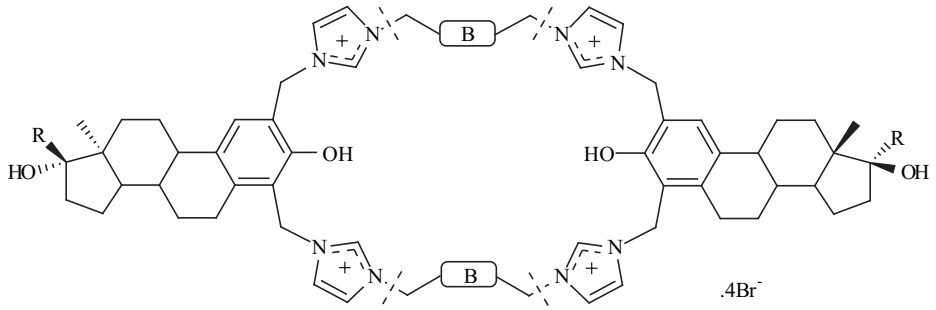
Alcalde and co-workers have studied the mechanism of the cyclization process that affords the azolium cyclophanes **11**, **81**, and **90**, particularly focusing on templating effects, and found that the rate of the ring-closing step for these cyclophanes was increased in the presence of chloride ions [12, 15]. They concluded that the chloride ion acted as a template by forming hydrogen bonds with the imidazolium/imidazole H2 protons, stabilizing the transition state and thus favouring the macrocyclization (ring-closing) step. However, the same group also reported that the yield of cyclophane **87** was not improved, but rather decreased, by the addition of chloride to the reaction mixture [40].

Rajakumar and Murali have used microwaves to decrease the reaction time in the preparation of benzimidazolium and benzotriazolium cyclophanes [48]. The cyclophanes **128**-**137** (Fig. (**6**)) were prepared in 15 minutes using the microwave method compared to 5 days using a conventional solution method, albeit in slightly reduced yields. The cyclophane precursors were supported onto solid sodium sulfate and the resulting mixture was subjected to microwave radiation.

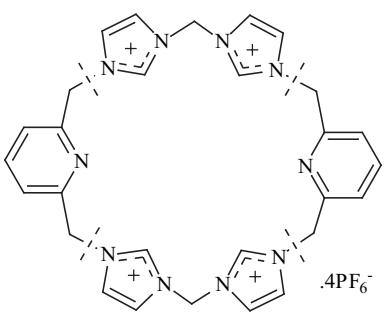



**Scheme 4**. Synthesis of **147** *via* a "3+1+3+1" method.

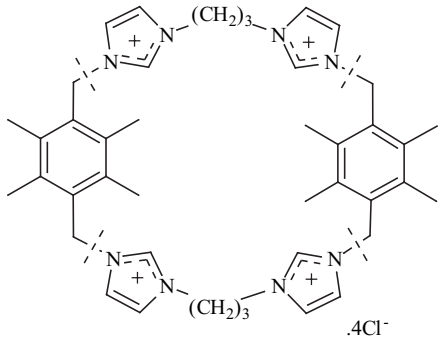
While almost all of the reported azolium cyclophanes have been synthesized by a two component A + B strategy involving the reaction of one equivalent of a *bis*-azole with one equivalent of a di-functional linker (Scheme **1**), there are a few reports of cyclophanes that have been prepared differently. The tetra-imidazolium cyclophanes **138**-**145** [50], **146** [51] and **147** [52] (Fig. (**10**)) are formed by a "3+1+3+1" method involving the one-pot reaction of two equivalents of a *bis*-azole species with two equivalents of a di-functional linker (e.g., Scheme **4**). A similar tetra-benzimidazolium cyclophane **148** was isolated as a by-product of the synthesis of the *bis*-benzimidazolium cyclophane **31** [30, 31]. It has been reported that in the synthesis of the estradiol based cyclophanes **138**-**145**, the reaction conditions, particularly concentration, solvent choice and the method of addition of the di-functional linker [*bis*(bromomethyl)arenes] are crucial for the preparation of the "3+1+3+1" product [50].



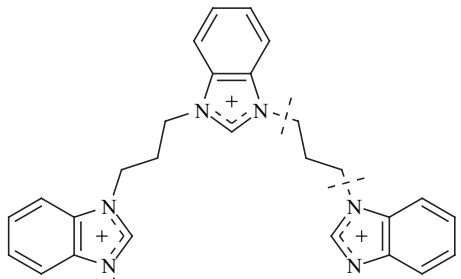

| | **138** | **139** | **140** | **141** | **142** | **143** | **144** | **145** |
|---|---|---|---|---|---|---|---|---|
| B | *p*-$C_6H_4$ | *p*-$C_6H_4$ | *m*-$C_6H_4$ | *m*-$C_6H_4$ | *o*-$C_6H_4$ | *o*-$C_6H_4$ | 2,6-pyridinediyl | 2,6-pyridinediyl |
| R | H | C≡CH | H | C≡CH | H | C≡CH | H | C≡CH |
| yield | 89 | 89 | 90 | 87 | 87 | 82 | 86 | 86 |




**146** 80% [51]

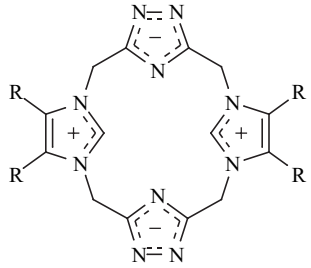



**147** 53% [52]

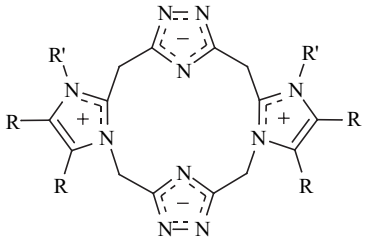



**148** [30, 31]

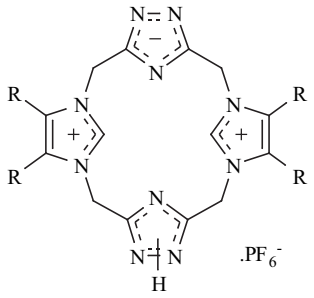
**Fig. (10)**. Tetra-azolium cyclophanes formed from a "3+1+3+1" one-pot pathway (percentage yields indicated, reference(s) in square brackets). Cyclophanes **138**-**145** are from ref. [50].



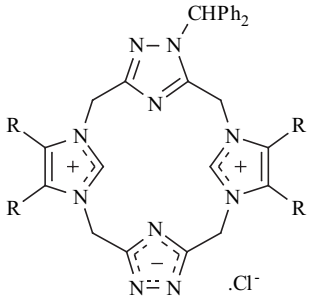
**149** R = H 97% [37-39]
**150** R = Me 98% [37, 39]
**151** R = Bu 98% [37, 39]



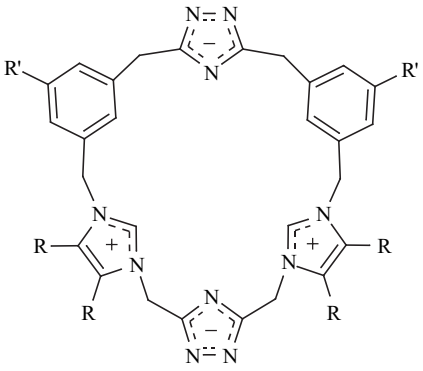
**152** R = H, R' = Me 90% [37, 39]
**153** R = H, R' = Bu 85% [37, 39]
**154** R = Me, R' = Me 75% [37, 39]



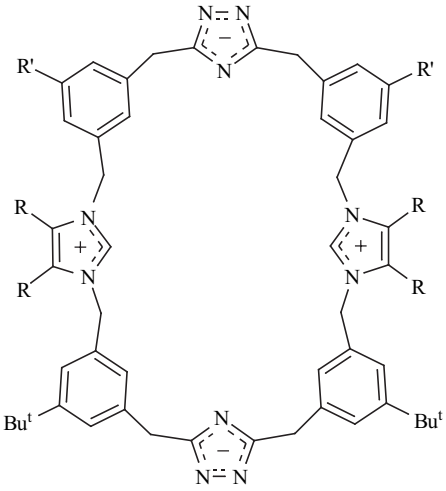
**155** R = H 87% [37, 38, 40, 53]
**156** R = Me 85% [37, 40]
**157** R = Bu 91% [37, 40, 53]



**158** R = H 90% [38, 40]
**159** R = Me 89% [40]



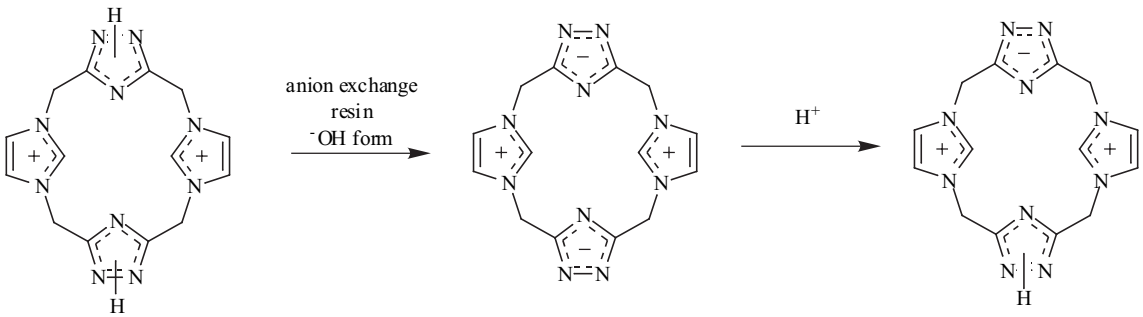
**160** R = H, R' = H 85% [43]
**161** R = H, R' = Bu$^t$ 74% [44]
**162** R = Bu, R' = Bu$^t$ 95% [44]



**163** R = H, R' = H 90% [43]
**164** R = H, R' = Bu$^t$ 90% [44]
**165** R = Bu, R' = Bu$^t$ 69% [44]

**Fig. (11)**. Imidazolium cyclophanes, with triazolate linkers, synthesized by deprotonation (and subsequent protonation in the cases of **155-157**) of the corresponding triazole linked cyclophanes (percentage yields indicated, reference(s) in square brackets).

The triazole linked *bis*-imidazolium cyclophanes **81-86** and **111-116** (Figs (**2**) and (**5**)) can be deprotonated using an anion exchange column in the hydroxide form to afford triazolate-linked imidazolium cyclophanes **149-154** and **160-165** (Fig. (**11**) and Scheme **5**) [37-40, 43, 44, 53, 54]. The interesting zwitterionic (betaine) structures **149-154** and **160-165** exhibit no net charge, but each contains two positively charged rings and two negatively charged rings. Careful protonation of **149-151** can afford the mono-triazolate, mono-triazole linked cyclophanes **155-157** (Scheme **5**). In addition to protonation, the triazolate groups of **149** and **151** can be alkylated by reaction with butyl iodide [40].



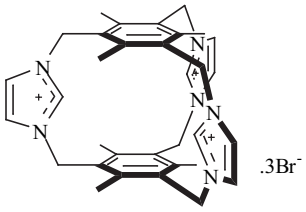

**81** **149** **155**

**Scheme 5**. Protonation/deprotonation chemistry of triazole-derived imidazolium cyclophanes.

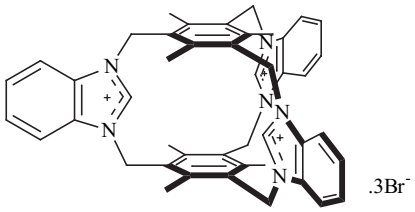
Azolium cyclophanes with bicyclic structures (triply bridged cyclophanes, Fig. (**12**)) are rare. The cyclophanes **166** and **167** represent the only examples of triply bridged cyclophanes where each azolium unit constitutes part of an separate bridge [8, 26, 55, 56]. These two cyclophanes were synthesized in high yield by the reaction of a tris-azole species [1,3,5-tris(imidazol-1-ylmethyl)mesitylene in the case of **166** and 1,3,5-tris(benzimidazol-1-ylmethyl)mesitylene in the case of **167**] with a tri-functional "capping" agent [1,3,5-tris(bromomethyl)mesitylene]. The tris-dihydroimidazolium (tris-imidazolidium) cage **168** [57] is included here due to its similarities to **166** and **167**, although it is formally not a cyclophane as it does not contain an aromatic component. In the case of **168**, the bicyclic structure existed in the precursor, which was a bicyclic polyamine that contained three -$NHCH_2CH_2NH$- fragments. Reaction of the polyamine with triethyl orthoformate afforded the tris-dihydroimidazolium cage. The tetra-imidazolium cyclophanes **169** and **170** were prepared by the reaction of a tetra-imidazole species (two *bis*-imidazole components that were linked by an alkyl chain) with two equivalents of 2,6-*bis*(bromomethyl)-4-chlorophenol, a reaction for which choice of solvent again proved important [58]. In the syntheses of cyclophanes **171** and **172**, however, a tetra-bromomethyl species (two *bis*-bromomethyl components that were linked by an alkyl chain) was reacted with two equivalents of benzimidazole or benzotriazole [34, 47]. These reactions were performed in the presence of a base so that the additional protons from the 1-H-benzimidazole or 1-H-benzotriazole were consumed. The syntheses of **171** and **172** are rare examples where the azolium cyclophanes (containing dialkylated azolium components) were constructed during a one-pot procedure starting from 1-H-azoles.

## 3. SOLID-STATE AND SOLUTION CONFORMATIONS

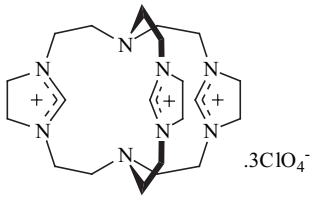
The conformations adopted by azolium cyclophanes in the solid state have been examined by X-ray crystallography. Conformations in the solid state are influenced by counter anions, solvents of crystallization, and specific intermolecular interactions (*e.g.* hydrogen bonding), as well as crystal packing effects. As an example of the influence of anions on solid state structures, conformations of the pyridinediyl linked cyclophane **23** have been reported in which the imidazolium rings are either mutually *syn* or mutually *anti,* depending whether the counter anion was $PF_6^-$ or $Cr_3O_{10}^{2-}$ [20]. In another interesting study [14], the cyclophane **11**, as its chloride salt, crystallised in a structure in which each imidazolium H2 centre was associated with a different chloride ion, and the macrocycle exhibited an unusual conformation in which the imidazolium units were mutually *anti* and the *m*-xylyl units were also mutually *anti*.



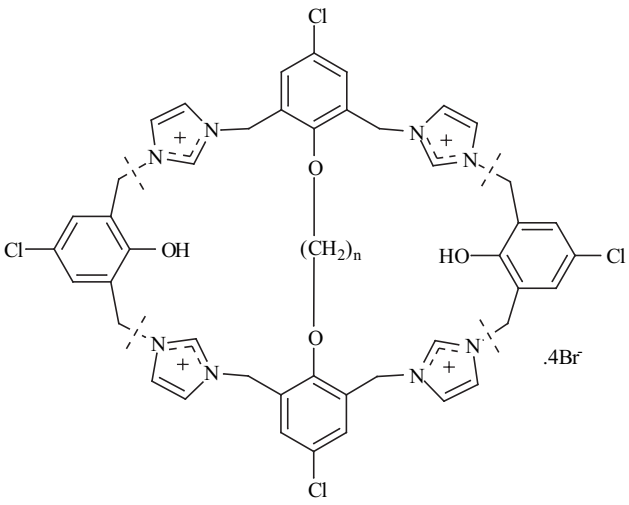

**166** 91% [8, 26, 55, 56]



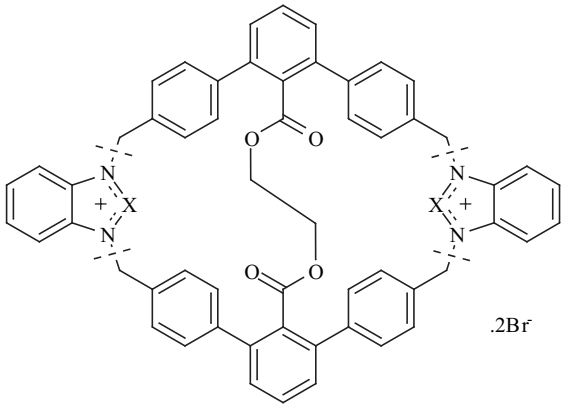

**167** 97% [56]




**168** [57]




**169** n = 4 70% [58]
**170** n = 7 69% [58]




**171** X = CH 45% [47]
**172** X = N 40% [34]

**Fig. (12)**. Azolium cyclophanes containing a bicyclic structure (triply bridged cyclophanes) (percentage yields indicated, reference(s) in square brackets).

In a related study [15], it was proposed that chloride ion played the role of a template in the synthesis of the macrocycle **11**.

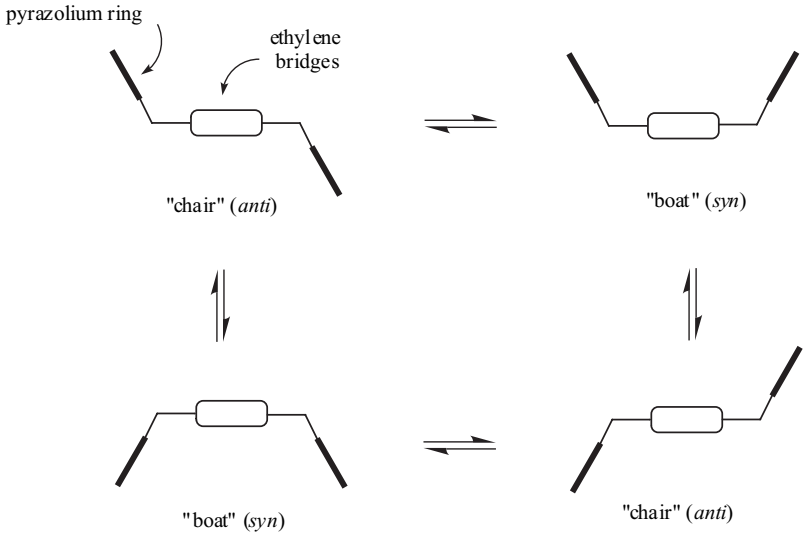
The conformations of azolium cyclophanes in solution have been probed by NMR spectroscopy. By providing information about the proximity of various protons in a structure, $^1$H NMR NOESY and ROESY experiments have provided insight into conformations of azolium cyclophanes in solution [19]. Often, however, a great deal of conformational information can be derived simply by considering NMR chemical shifts. $^1$H NMR chemical shifts can be especially informative, because magnetic anisotropies associated with various aromatic rings can cause unusual chemical shifts for signals associated with certain structures or conformations. For example, magnetic shielding by the ring currents due to the benzene rings in **166** shifts the $^1$H NMR signal due to the imidazolium H2 protons to unusually high field (δ 5.60 in dmso-$d_6$ solution, *cf.* δ 10.04 for the corresponding signal for 1,3-dibenzylimidazolium chloride) [8].

When conformations of azolium cyclophanes have been investigated in both the solid state and in solution, the structure determined by solution NMR studies sometimes matches the conformation determined by X-ray crystallography. Solution studies are usually complicated, however, by the existence of more than one conformation in solution. In some cases, the different conformations are equivalent (i.e., related by symmetry), in other conformations they are diastereotopic. Depending on the nature of the cyclophane, interconversion between the various conformations can be slow or rapid on the NMR timescale, and in favourable cases it is possible to probe the kinetics of these processes by dynamic NMR studies. The dynamic behaviour of azolium cyclophanes in solution can be strongly affected by counter anions and solvent types.

The majority of the azolium cyclophanes are non-rigid structures that nevertheless exhibit simple, sharp signals in $^1$H NMR spectra at room temperature. Perhaps as a consequence of their sharp and apparently simple $^1$H NMR spectra, the possibility of such cyclophanes adopting distinct conformations that interconvert rapidly on the NMR timescale at room temperature appears to be frequently overlooked, with many papers not reporting whether relevant variable temperature NMR studies were conducted. There have, however, been a number of in-depth studies of the solution conformations of azolium cyclophanes.

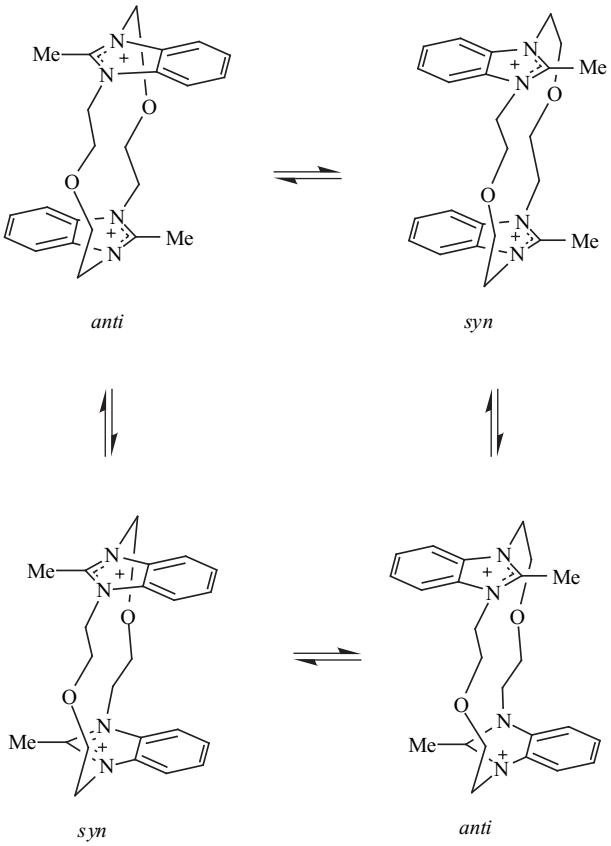
NMR studies have shown that for the ethylene linked pyrazolium cyclophanes **73** and **74**, interconversion between various conformations occurs rapidly at room temperature [35]. The $^1$H NMR spectra can be interpreted in terms of two equivalent, interconverting "chair" structures, in which the pyrazolium groups are mutually *anti*. These two chairs can interconvert by "flipping" of the pyrazolium rings, and two equivalent "boat" structures (not detected by NMR) can be envisaged as intermediates between the chairs (Scheme **6**). At low temperatures the dynamic process is frozen-out with the cyclophanes in the chair structure [35]. The chair conformation was also identified in the solid state in crystallographic studies of **73** [36]. Rate constants and energy barriers were determined for the chair ↔ chair interconversion processes for both **73** and **74** [35]. For the *p*-xylyl linked pyrazolium cyclophane **77** the interconversion processes are much slower and both the boat and chair conformations can be readily identified in the room temperature $^1$H NMR spectrum of the sample, but at higher temperatures the coalescence of some signals was observed [25]. The barrier to interconversion between chair and boat forms of **77** was estimated from the temperature for coalescence of various $^1$H NMR signals. The chair:boat ratio for **77** was determined as 54:46 by $^1$H NMR spectroscopy, but an X-ray study revealed only the chair conformation in the solid state [25].

Benzimidazolium cyclophanes with long flexible ether linkages (*e.g.* **33**) exhibit simple, sharp $^1$H NMR spectra resulting from the averaging of signals due to rapidly interconverting conformations [19]. Decreasing the length of the linker, as in **32**, can result in $^1$H NMR spectra with broad signals, as the exchange processes interconverting *syn* and *anti* conformations are slowed [30]. Introduction of a methyl group to the 2-position of each of the benzimidazolium units, as in the cyclophane **61** (Scheme **7**),




**Scheme 6**. Interconversion of conformations for pyrazolium cyclophanes **73** and **74** *via* processes involving "flip" of pyrazole rings.

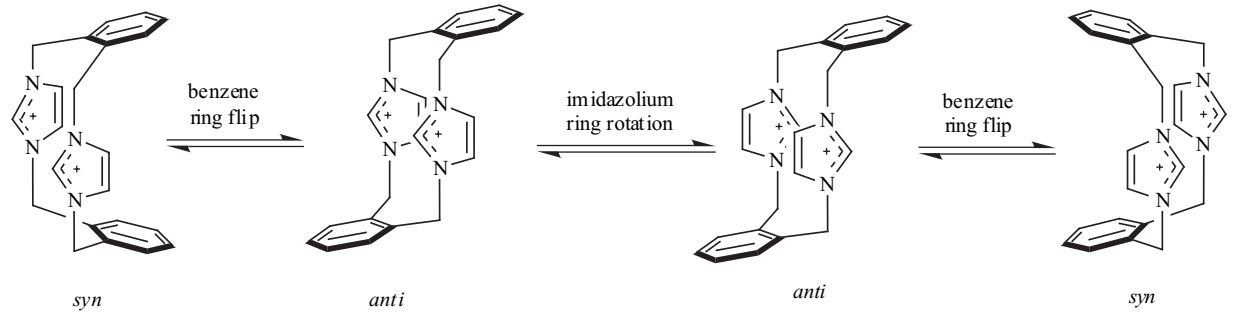
slows the exchange processes further, to the point were signals due to *anti* and *syn* conformations can be distinguished at room temperature (*anti*:*syn* ratio = 3:1) [19]. The slower interconversion of conformations for **61** compared to its non-methylated analog **33** is presumably a consequence of the size of the methyl groups, which must pass through the centre of the macrocyclic structure when a 2-methylbenzimidazolium unit undergoes a ring flip. Even for larger cyclophanes such as **132**, the introduction of 2-methylbenzimidazolium moieties significantly hinders interconversion of conformations, with *syn* and *anti* forms being identified in solution [47].




**Scheme 7**. Interconversion of the *anti* and *syn* conformers of **61** by a ring flip process.

An examination of simple *ortho*-, *meta*-, and *para*-xylyl linked imidazolium cyclophanes indicated that subtle structural features can have a significant effect on the observable dynamic behaviour [8]. The room temperature $^1$H NMR spectrum of the *o*-xylyl linked imidazolium cyclophane **4** exhibited very broad signals for the benzylic and imidazolium H4/5 protons. At low temperature, however, the exchanges processes were slow enough that sharp $^1$H NMR signals were detected for two different conformers. In both conformers, the imidazolium rings were mutually *syn*, but the benzene rings were *anti* in one conformer, *syn* in the other (Scheme **8**). Two different dynamic processes were identified: rotation of the imidazolium rings about their N-N axis, which interconverted the two different *anti* conformers, and ring flip of the benzene rings, which interconverted the *anti* and *syn* conformers. The imidazolium ring rotation process was more facile than the benzene ring flip process, and rate constants and activation energies for each process were estimated from the variable temperature NMR study. The *anti* conformation was identified in crystallographic studies of **4** [8]. Low temperature $^1$H NMR spectra of similar *ortho*-linked cyclophanes **7** and **10** displayed similar features, *syn* and *anti* conformers being frozen out at low temperature. The *syn*:*anti* ratios for **4**, **7**, and **10**, were 3.5:1, >30:1, and 4.3:1 respectively, the differences presumably reflecting different steric interactions between the imidazolium units and the linking arene units in the various cyclophanes.

Variable temperature $^1$H NMR studies of imidazolium cyclophanes containing *m*-xylyl, 2,6-pyridinediyl, and 1,3-$C_6H$-2,4,6-$Me_3$ (1,3-mesitylenediyl) linkers found that the cyclophanes with at least one mesitylene based linker (**13**, **14** and **15**) were rigid on the NMR time scale at all accessible temperatures [8]. X-ray and $^1$H NMR studies of **13** showed that the cyclophane adopts a *syn* conformation (Fig. (**13**)) reminiscent of the 1,3-alternate conformation of calix[4]arenes. In this conformation the mesitylene units form a cleft, with the imidazolium groups oriented so that their C2-H2 bonds point into this cleft. In the solid state structure, the imidazolium H2 protons were involved in hydrogen bonding with a solvent molecule (water) in the cleft [8]. The mesitylene linked cyclophane **102**, with a pendant imidazole unit, also adopts a rigid structure [7]. The cyclophanes that contained the *meta* linkages *m*-xylyl and 2,6-pyridinediyl, but without a mesitylene linker (**5**, **6**, **11** and **23**), were conformationally labile in solution at room temperature, as indicated by their sharp, simple $^1$H NMR spectra. In the case of **5**, a single conformation was "frozen out" when the sample was cooled to -78 ºC, but for the other three cyclophanes, interconversion of conformations was rapid on the NMR timescale at all accessible temperatures [8]. At low temperatures (-78 °C) $^1$H NMR spectroscopy indicates that the phenol linked cyclophane **16** exists in two




**Scheme 8**. Interconversion of the *anti* and *syn* conformers of **4** by an imidazolium ring rotation and benzene ring flip processes.

distinct *syn* conformations in solution (phenol groups mutually *syn*, Fig. (**14**)). The major conformer in solution was the same conformation that was found in the solid state by X-ray studies [8]. Although *anti* conformations were not detected by NMR at low temperatures, at higher temperatures, coalescence of $^1$H NMR signals due to the benzylic protons of **16** indicates that *anti* conformations must be involved in various exchange processes. The interconversion of *syn* and *anti* conformations of **16** requires a ring flip process in which the hydroxyl group of a phenol moiety must pass through the macrocyclic cavity. It is interesting to compare the rigid mesitylene based cyclophanes **13**, **14**, **15** and **102** with the conformationally labile phenol linked cyclophane **16**. In the case of the mesitylene linked cyclophanes the rigidity arises in part because interconversion processes involving ring flip would require the central methyl group on the mesitylene ring to pass though the macrocyclic cavity, and presumably this process is restricted because of steric interactions. The greater lability of the phenol cyclophane **16** suggests that the hydroxyl group does not give rise to the same level of steric interaction as the methyl group. Not surprisingly, replacement of the OH group in cyclophanes such as **16** by the bulkier $OCH_3$ group, as in **17**, **21**, **22**, **41**, **42**, **50**, **56**, and **57**, significantly slows exchange processes, with multiple conformers sometimes identified in room temperature $^1$H NMR spectra [16, 19].

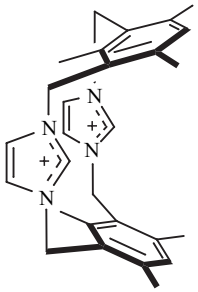


**Fig. (13).** Solution and solid-state conformation adopted by **13**.

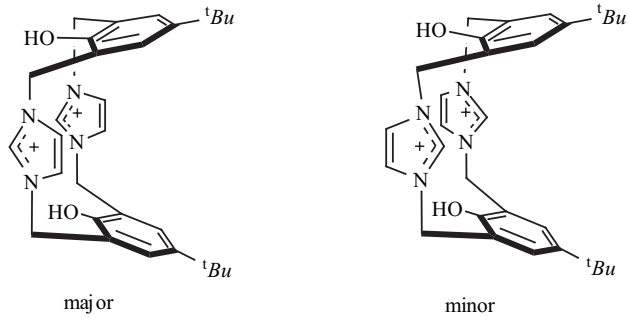



**Fig. (14).** Two *syn* conformers of **16**.

## 4. MASS SPECTROMETRY

Mass spectrometry is a common technique in the characterization of azolium cyclophanes and in most cases is used routinely. However there are a number of in-depth studies specifically focused on mass spectrometry of azolium cyclophanes. The most common ionisation techniques are fast atom bombardment (FAB) and electrospray ionisation (ESI). In the case of cyclophane salts of the type Cyc.2X (where $Cyc^{2+}$ represents a dicationic cyclophane and $X^-$ the associated counter anions, *e.g.* $Cl^-$, $Br^-$, $PF_6^-$) common ions in the mass spectrum are $[Cyc]^{2+}$, $[Cyc\text{-}H]^+$ and $[Cyc+X]^+$.

An ESI-MS study [5] of the cyclophane salt **11**.2Cl, and its isotopomer deuterium-labelled at the imidazolium-H2 positions, showed that the $[Cyc\text{-}H]^+$ ion was formed by loss of a proton from an imidazolium-H2 site. This result is not surprising, given that the imidazolium-H2 positions are the most acidic sites in **11**, and the formation of imidazol-2-ylidenes by removal of the imidazolium-H2 protons from imidazolium ions is well known [59, 60]. When ESI mass spectra were recorded for **11**.2Cl at low cone voltages the main ion was $[Cyc]^{2+}$ whereas at higher voltages the base peak corresponded to $[Cyc\text{-}H]^+$ [5].

The triazole-based cyclophanes **81**, **155**, and **149** make up a series in which the cyclophane units differ in the extent of protonation of triazole nitrogens: **149** is a neutral, zwitterionic structure while **81** and **155** are protonated forms, so that **81** = (**155** + $H^+$) = (**149** + $2H^+$). In ESI mass spectra recorded for **149**, **155**.$PF_6$, and **81**.$2CF_3CO_2$ using a cone voltage of 50 V, the base peak corresponded to the doubly protonated cyclophane **81** in each case, with the importance of the singly protonated cyclophane **155** increasing when the cone voltage was increased to 100 V [40, 53]. Analogous results were found for the series **83**, **157**, and **151** [53] and for the larger triazole and triazolate linked cyclophanes in Figs. (**5**) and (**11**) [44]. When the 1H-triazole linkers are replaced by 1-alkyl-triazoles the behaviour in ESI-MS more closely resembles that of the *m*-xylyl linked cyclophane **11** described above, signals associated with $[Cyc]^{2+}$, $[Cyc\text{-}H]^+$ and $[Cyc+X]^+$ being observed [40].

In a FAB-MS study of the pyrazolium cyclophanes **73**-**76** and **78** the effect of the matrix (*m*-nitrobenzyl alcohol *vs* glycerol) was examined [35]. Common ions that were observed included $[Cyc]^{2+}$, $[Cyc\text{-}H]^+$, $[Cyc+X]^+$ as well as $[Cyc+H]^+$, this last ion being the result of a reduction (hydride addition) reaction. In the oxidising environment of *m*-nitrobenzyl alcohol the reduction process is minor but in glycerol the process is significant. Similar results were seen in a FAB-MS study (using *m*-nitrobenzyl alcohol and glycerol) of the *p*-xylyl linked imidazolium, benzimidazolium and pyrazolium cyclophanes **27**, **59** and **77** [28]. Additional ions that were identified when the matrix was *m*-nitrobenzyl alcohol include products arising from the oxidation of the azolium ring.

Fragmentation pathways of **27**, **59**, **73**, **74** and **77** have been examined by ESI-MS/MS studies [27].

## 5. REACTIVITY AND SUPRAMOLECULAR CHEMISTRY

### 5.1 Anion Binding

The subject of anion-binding by imidazolium-based receptors, including some imidazolium cyclophanes, has recently been reviewed [61]. Their ease of synthesis and positively charged fragments have made imidazolium cyclophanes interesting subjects for anion binding studies. The imidazolium protons, particularly the H2 protons, can form strong hydrogen-bonds and such bonding is the target of many anion-binding studies. Alcalde and co-workers have

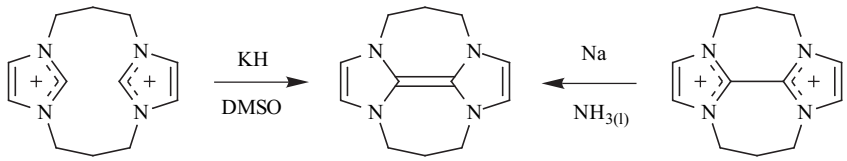
identified the occurrence of H2···anion interactions in solution and the solid state for *m*-xylyl linked imidazolium cyclophanes **11** and **12** [14]. In solution H2···anion interactions can be identified using $^1$H NMR studies, since deshielding effects of hydrogen-bonded anions can have a significant effect on the chemical shift of the signal due to the H2 proton. The *m*-mesitylene linked imidazolium cyclophane **102**, bearing an additional imidazole moiety, binds chloride in acetonitrile solutions more strongly than bromide (by a factor of 2), fluoride (by a factor of 5) and iodide (by a factor of 2000) [7]. It was postulated that the stronger binding of chloride was a result of the cyclophane structure. The anthracene linked imidazolium cyclophane **30** binds $H_2PO_4^-$ more strongly than it binds fluoride (by a factor of 4), chloride (by a factor of >600) and bromide (by a factor of >1000) [29]. The studies suggest the cyclophane forms a strong 1:1 complex with $H_2PO_4^-$, each imidazolium H2 proton forming a hydrogen bond with one of the negatively charged oxygen atoms of the $H_2PO_4^-$ anion. The cyclophane can act as a fluorescent sensor for $H_2PO_4^-$ as the binding of the anion quenches the fluorescence of the cyclophane. The tetra-imidazolium cyclophane **146** was found to bind fluoride considerably more strongly than the other halides [51]. Solution studies suggested a 1:1 complex being favoured for fluoride but a 1:2 (cyclophane:halide) complex predominating for the other halides. Crystallographic studies showed that in the case of **146**.$F(PF_6)_3$ the fluoride was located inside the macrocycle with hydrogen bonding involving all four imidazolium protons, whereas in the case of **146**.$(Cl)_2(PF_6)_2$ each chloride ion was bound to only two imidazolium H2 protons.

### 5.2 Carbene Formation and Organometallic Chemistry

*N*-Heterocyclic carbenes (NHCs) are class of compounds that have received enormous attention over the last decade, especially since Arduengo and co-workers isolated the first example of a stable NHC in 1991 [59, 60]. The most common NHCs are imidazol-2-ylidenes, derived from imidazolium salts through deprotonation. The diverse range of available imidazolium cyclophanes has allowed the exploration of the corresponding NHCs, with some interesting results.

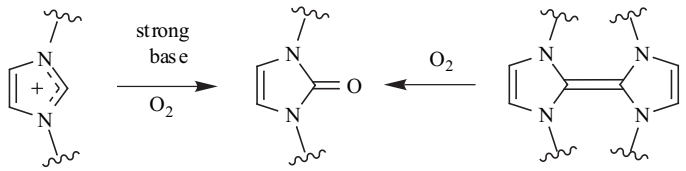
Some NHCs dimerise to form tetraaminoethylene species and it is thought that these dimeric species may be in equilibrium with the NHC form. The electron-rich dimers readily react with oxygen and can react with metal sources to form *bis*(NHC)-metal complexes. Treatment of the trimethylene-linked imidazolium cyclophane **1** with strong base afforded the carbene dimer **173** (Scheme 9) [3]. Solution and solid-state studies indicated that the carbene dimer structure, not a *bis*-carbene, was prevalent. The same carbene dimer **173** can also be formed by reduction of the corresponding trimethylene-linked biimidazolium salt (Scheme **9**). Interestingly, reduction of the analogous tetramethylene-linked biimidazolium salt affords a *bis*-carbene, not a carbene dimer species [3]. Thummel and co-workers have conducted similar studies on alkyl-linked benzimidazolium cyclophanes **31** and **32** and the alkyl linked naphthimidazolium cyclophane **91** [4, 30, 31]. Treatment of **31** with strong base, under an inert atmosphere, afforded the benzimidazole analogue of the carbene dimer **173**, with no *bis*-carbene detected. Deprotonation of the two benzimidazolium units of **31** followed by an intramolecular "dimerisation" of the resulting *bis*-carbene would lead to the benzimidazole analogue of carbene dimer **173**. However, Shi and Thummel [30] postulated that deprotonation of just one benzimidazolium group, reaction of the resulting carbene with the remaining benzimidazolium cation (held in close proximity to the carbene), and subsequent loss of a proton, would be a more likely route to the carbene dimer. Reaction of oxygen with the benzimidazole or naphthimidazole carbene dimers derived from **31**, **32**, or **91**, or the treatment of the azolium cyclophanes **31**, **32**, **48**, **91** and **148** with strong base in the presence of oxygen, affords ureaphanes, *i.e.*, the azolyl unit is converted into a urea (Scheme **10**) [4, 30, 31]. Thioureaphanes can be formed similarly from an imidazolium cyclophane by reaction with a strong base and then sulfur (instead of oxygen) [16].

One area of organometallic chemistry that is of considerable recent interest is that of metal complexes of NHCs. A number of studies have examined the use of imidazolium cyclophanes as precursors to *bis*(NHC)-metal complexes in which the NHCs are part of a cyclophane framework. The complexes are of particular interest because of their potential in cross-coupling catalysis [9, 13] or as

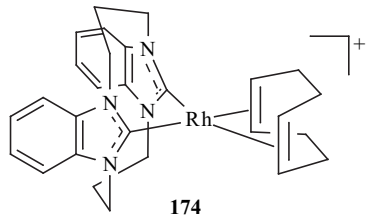



**1** **173**

**Scheme 9**. Formation of carbene dimers.



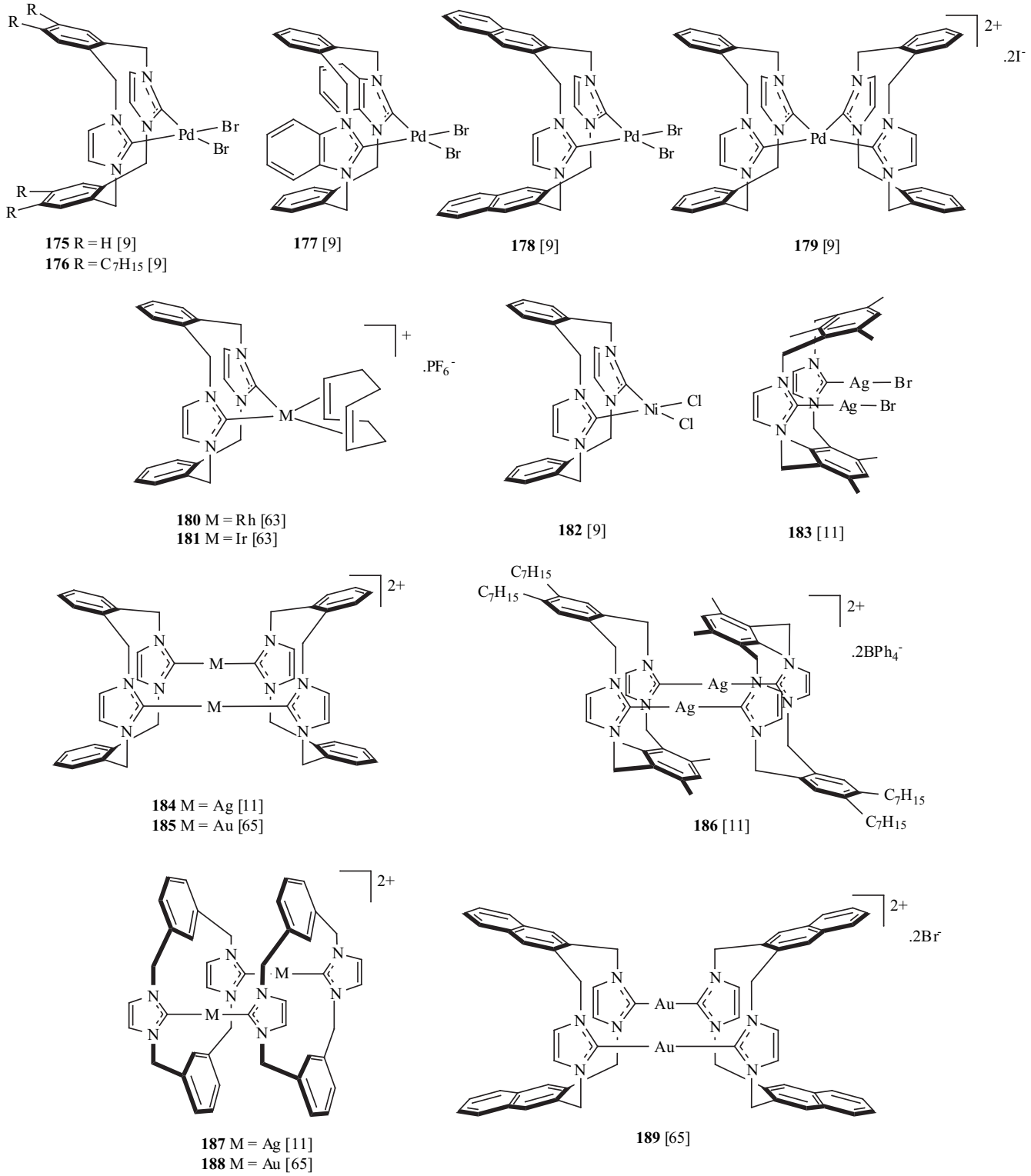

**Scheme 10.** Urea formation from imidazolium salts or carbene dimers.



**174**

**Fig. (15).** Rhodium complex synthesized from a carbene dimer.

antimicrobial [17] or antimitochondrial antitumour [62] agents. In most cases the cyclophane complexes have been prepared by the treatment of an imidazolium or benzimidazolium cyclophane with a base in the presence of a metal source. Usually a metal complex containing a basic ligand, for example palladium(II) acetate or silver(I) oxide, is used as a source of both metal ions and base in these reactions. For the NHC complex **174** (Fig. (**15**)), a benzimidazolyl-2-ylidene dimer, rather than an azolium



**175** R = H [9]
**176** R = $C_7H_{15}$ [9]

**177** [9]

**178** [9]

**179** [9]

**180** M = Rh [63]
**181** M = Ir [63]

**182** [9]

**183** [11]

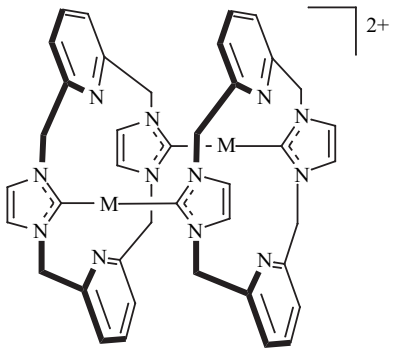
**184** M = Ag [11]
**185** M = Au [65]

**186** [11]

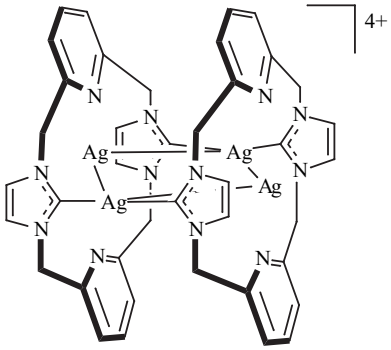
**187** M = Ag [11]
**188** M = Au [65]

**189** [65]

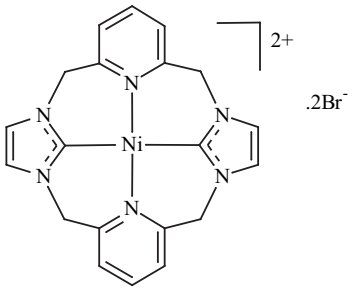
**Fig. (16).** NHC-metal complexes derived from imidazolium and benzimidazolium cyclophanes (reference(s) in square brackets).



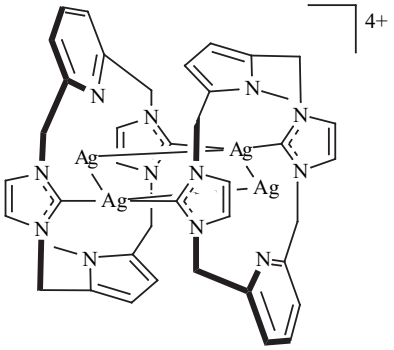
**190** M = Ag [20]
**191** M = Au [65]



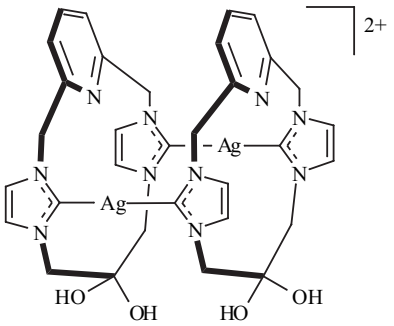
**192** [64]



**193** [21]



**194** [23]



**195** [17]

**Fig. (17).** NHC-metal complexes derived from pyridinediyl-linked imidazolium cyclophanes (reference(s) in square brackets).

cyclophane, was the precursor of the NHC ligand [31], but there have been no reports of the synthesis of cyclophane *bis*(NHC)-metal complexes in which an azolium cyclophane was first converted into free *bis*(carbene) prior to the addition of the metal source. A variety of cationic and neutral, mononuclear and dinuclear NHC-metal complexes of palladium(II) [9, 13], rhodium(I) [63], iridium(I) [63], nickel(II) [9, 21], silver(I) [11, 17, 20, 23, 64], and gold(I) [65], derived from imidazolium or benzimidazolium cyclophanes, have been prepared (*e.g.*, Figs. (**16**) and (**17**)).

### 5.3 H/D Exchange

Hydrogen-deuterium exchange is well known for imidazole and imidazolium species, occurring at H2 and H4/5 positions on the ring [66-69]. Despite its common occurrence there have been only a few H/D exchange studies involving azolium cyclophanes, all of them involving imidazolium systems. In many cases H/D exchange is facile, particularly at H2 of imidazolium species, and can readily occur when an imidazolium cyclophane is dissolved in a deuterated protic solvent such as $CD_3OD$ or $D_2O$. Consequently, in the $^1H$ NMR spectra of imidazolium cyclophanes it is common that signals for H2 protons of imidazolium groups are absent or of less than the expected intensity. One study [8] in particular has shown that the rate of H/D exchange reactions of imidazolium cyclophanes can vary substantially with the structure of the cyclophane, and, interestingly, that H/D exchange is not limited to the imidazolium sites (see Fig. (**18**)). Generally, for imidazolium cyclophanes in $D_2O$ solution, H/D exchange occurs most readily at the imidazolium H2 positions (often at room temperature) and more slowly at the imidazolium H4/H5 positions. The H/D exchange reactions are catalysed by base, and to achieve complete exchange at the imidazolium H4/5 positions it is convenient to both heat the sample and add a small amount of base. In many cases more forcing conditions can promote H/D exchange at other sites in the imidazolium cyclophanes. For example, H/D exchange at *N*-benzylic sites was achieved for **4**, **11**, **23**, and **27** (Fig. (**18**)) when $D_2O$ solutions of the cyclophanes and two equivalents of NaOH were heated at 100 ºC for several days. Under similar conditions, H/D exchange at the *N*-benzylic sites was not observed for the cyclophanes containing additional methyl groups on the phenylene linkers (**13**, **29** and **166**, Fig. (**18**)). Under these same conditions, however, complete H/D exchange occurred at the $CH_3$ sites in **166**, despite these $CH_3$ groups being somewhat removed from the imidazolium units. An *o*-xylylene intermediate has been proposed [8] to account for this remarkable exchange reaction. No H/D exchange was observed for the protons on the phenylene or pyridinediyl linkers in the imidazolium cyclophanes.

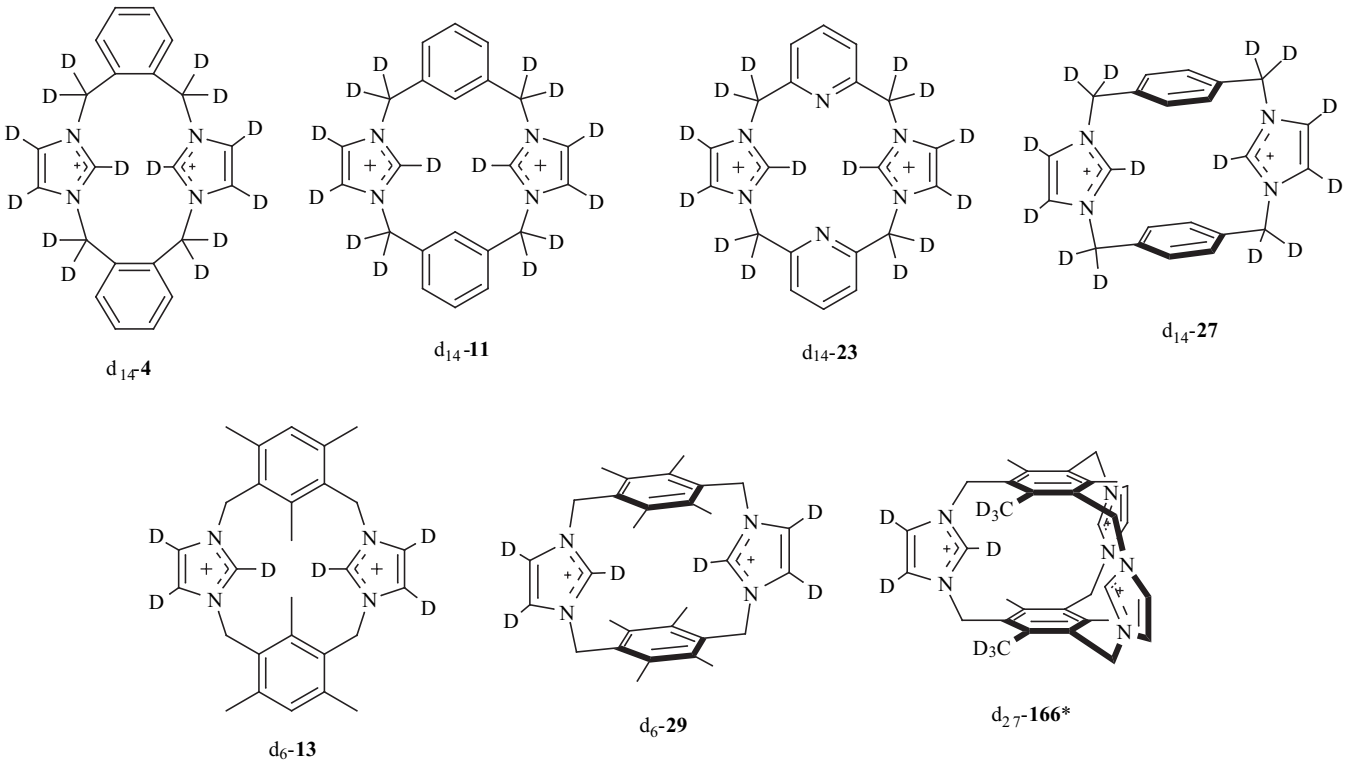
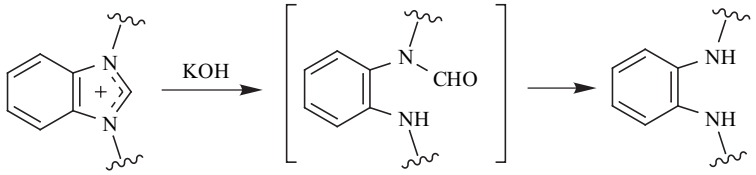


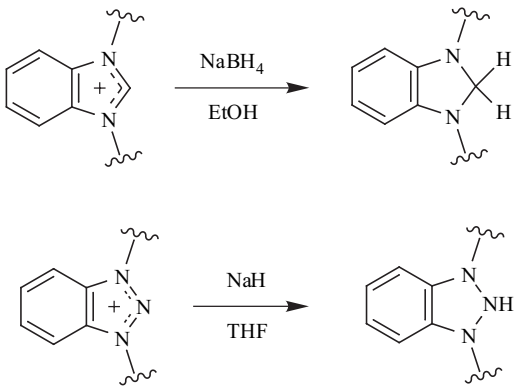

**Fig. (18)**. H/D Exchange products formed after heating (100 ºC) solutions of the imidazolium cyclophanes in $D_2O$ with NaOH for >24h. *For clarity, only one third of the deuterium atoms are displayed in the case of $d_{27}$-**165**.

### 5.4 Miscellaneous Reactions

Benzimidazolium cyclophanes can undergo hydrolysis and reduction reactions [32, 33]. In strongly basic solutions at elevated temperatures, benzimidazolium species are converted to diamines, *via* formamide intermediates (general reaction shown in Scheme **11**). This method has been used to prepare a series of dibenzotetraaza crown ethers from benzimidazolium cyclophanes such as **33**-**39** [32]. Reduction of various benzimidazolium cyclophanes such as **33**-**35** with $NaBH_4$ in ethanol afforded a series of benzimidazolidine species (general reaction shown in Scheme **12**) [32, 33]. Similarly, treatment of benzotriazolium cyclophanes **134** and **136** with NaH afforded 2H-benzotriazole linked cyclophanes (general reaction shown in Scheme **12**) [70].




**Scheme 11.** Hydrolysis of benzimidazolium species.




**Scheme 12.** Reduction of benzimidazolium and benzotriazolium species.

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## CONCLUSIONS

The volume of recent work on azolium cyclophanes is testament to the fascination chemists have with this interesting class of compounds. Synthesis of azolium cyclophanes is clearly affected by factors such as choice of precursors, concentration, and solvent, but few studies to date have addressed these issues in any depth. Despite some detailed NMR and X-ray studies, there is also still much to learn about solution and solid state behavior of azolium cyclophanes, and their supramolecular chemistry. The chemistry of azolium cyclophanes will continue to develop in two areas in particular: anion binding and formation of NHC complexes. The ease with which azolium cyclophanes can be synthesized and the interesting variety of structures that is accessible means that the future for azolium cyclophanes is bright.

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