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THE SYNTHESIS AND PROPERTIES OF ORGANIZED POLYAZA CAVITY-SHAPED MOLECULES

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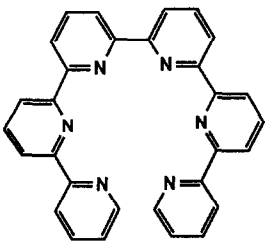
1. INTRODUCTION

Synthetic organic chemists have been increasingly directing their attention to the preparation of "unnatural products." In the past such molecules were considered to be primarily of theoretical interest and the careful study of their properties fell mainly within the realm of physical organic chemistry.[1] During the last two decades more conscious effort has been devoted to the synthesis and study of molecules which can interact with other species in a well defined manner. Attention was focussed on this area in 1987 with the award of the Nobel Prize to Lehn, Cram, and Pedersen for their pioneering work on crown ether chemistry.[2]

The favorable interaction of an organic system with an inorganic or organic substrate does not mandate the existence of a "hole" or require the host to be cyclic. Although cycles possess a certain appeal both from a synthetic and symmetry point of view, their inherent "closed"

structure in some ways can be a detriment to efficient function. A case in point would be sexipyridine (1) vs. cyclosexipyridine (2). The former has recently been shown by Constable and coworkers to complex two Cd(II) centers by wrapping them in a helical double stranded array.[3] The latter, on the other hand, is so far limited to the inclusion of alkali metals with modest selectivity.[4]



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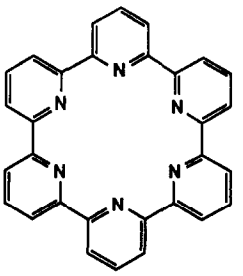

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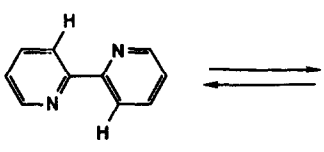
This review will attempt to present the design methodology which has been employed by ourselves and others to create cavity-shaped environments possessing useful and interesting properties. In particular, the judicious use of bridging to control conformation has been exploited. The emphasis will be on the properties of such systems from an "organic" point of view but, of necessity, their metal coordination chemistry cannot be overlooked and will also be discussed when it is relevant.

2. BRIDGED 2,2'-BIPYRIDINES

The prototype biaryl molecule is 1,1'-biphenyl. Primary interest in this molecule derives from relatively free rotation about the 1,1'-bond and the effect of such rotation on stereochemical and electronic properties.[5] From a reactivity point of view biphenyl is less interesting due to its lack of functionality.

An important diaza-analog of biphenyl is 2,2'-bipyridine (bpy). This molecule can exist in two planar conformations: *anti* and *syn* . In the solid state the *anti* form is favored due to avoidance of unfavorable 3,3'-hydrogen and N,N'-lone pair interactions found in the *syn* form. It is the *syn* form, however, which leads to the most important property of this molecule, its ability to function as a bidentate chelator. At the outset, our goal was to introduce a 3,3'-bridge onto 2,2'-bipyridine to force it into a *syn* conformation while at the same time affording the ability to control the relative coplanarity of the two aromatic rings.



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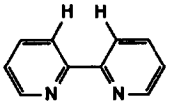

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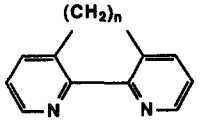


4 a n = 1
b n = 2
c n = 3
d n = 4

Examination of a simple framework molecular model quickly reveals the relationship between 3,3'-bridge length and the dihedral angle between the pyridine rings. Such models do not, however, take into account the flattening effect of conjugation between the two rings which is better estimated by MMX type calculations (see Table 1). It is important to note that rotation about the 2,2'-bond interconverts conformational enantiomers A and B so that if the barrier to inversion is sufficiently high, optical activity would result.

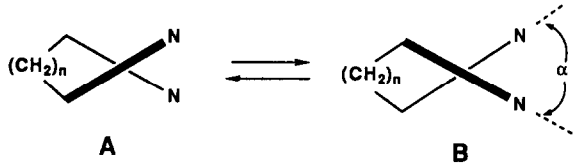


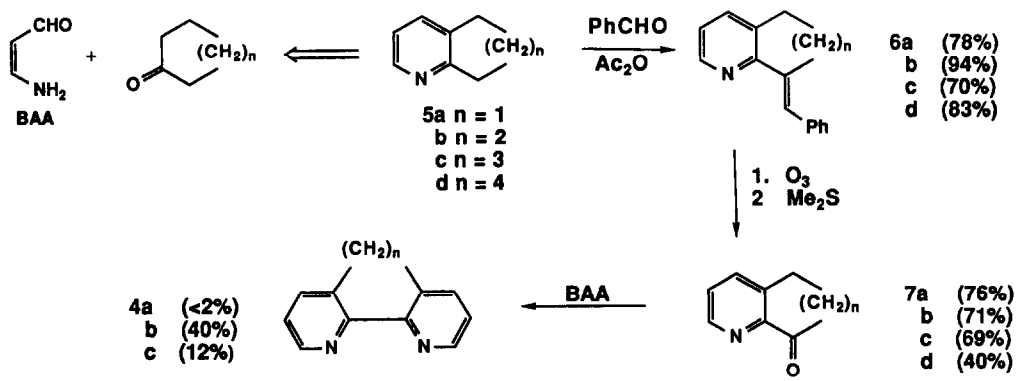
Table 1 Dihedral Angles of Bridged Bipyridines (4)

n	Molec Model	MMX[6]
1	0°	0°
2	20	18
3	55	45
4	80	58

An effective synthetic approach to such bridged systems begins with the central ring intact and involves building up the two pyridine nuclei. We have employed this same general approach in the preparation of a wide variety of small ring annelated aromatic molecules wherein one profits from the driving force of aromatization in the final step.[7]

Pyridine rings can be conveniently prepared via the Friedländer reaction in which a ß-amino-α,ß-unsaturated carbonyl compound may react with a ketone to undergo two condensations: imine formation and a crossed aldol reaction.[8] The exact sequence of these steps is not well established and there is considerable evidence for the formation of rearranged products.[9]

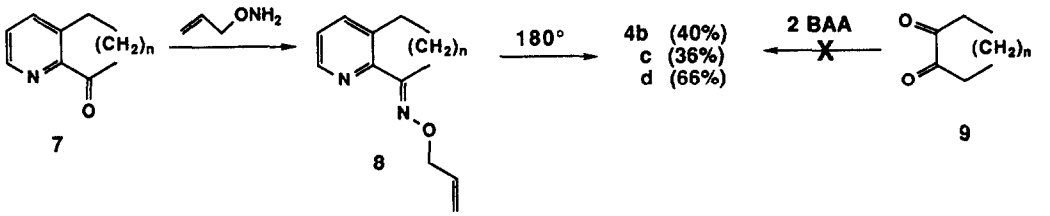
The preparation of unsubstituted 2,3-cycloalkenopyridines **5** would involve the condensation of ß-aminoacrolein (BAA) with a cyclic ketone.[10] The BAA can be obtained by the partial hydrogenation of isoxazole[11] but is a poor synthon due to its propensity for self-



condensation and reactions utilizing BAA typically proceed in low yield. The same cycloalkenopyridines **5** can be obtained in much better yields by a gas phase reaction involving acrolein, ammonia, and the cyclic ketone.[12] This reaction involves an alumino-silicate catalyst and is run at 250-550°C making it inconvenient as a laboratory procedure. Happily, a variety of 2,3-cycloalkenopyridines are now commercially available.

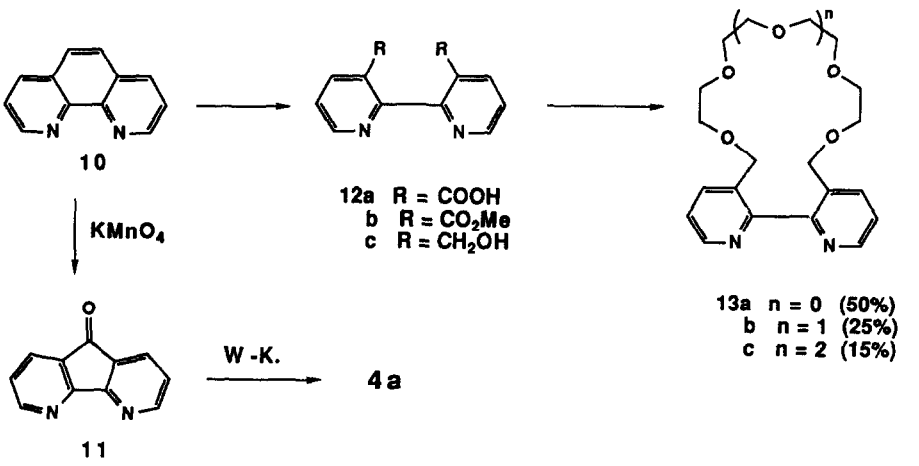
A general, two step procedure has been developed for the introduction of an oxo group at the α-position of these compounds. Treatment of 2,3-cycloalkenopyridines with benzaldehyde in acetic anhydride effects a crossed aldol condensation providing the α-benzylidine derivative **6**. The N-acetyl intermediate involved in this process specifically directs the reaction to the α-position. Ozonolysis of this species followed by reduction of the resultant ozonide with methyl sulfide provides the α-keto derivatives **7**.[13]

Treatment of **7** with BAA affords the bridged bipyridines **4** in relatively poor yields,[14] again due to the problems associated with the BAA. An alternative approach has been developed which utilizes a pyridine synthesis based on an azatriene cyclization.[15] The pyridyl ketones **7** may be converted to their O-allyloximes by treatment with O-allylhydroxylamine The same species may also be prepared by O-alkylation of the corresponding simple oxime. Generally, the former route works best. Pyrolysis of **8** in a sealed tube at 180° gives the bridged bipyridines in considerably improved yields.[14] A seemingly direct route to the bridged bipyridines **4** would be the 2:1 condensation of BAA with cyclic 1,2-diketones **9** but no useful product was ever detected under these conditions.

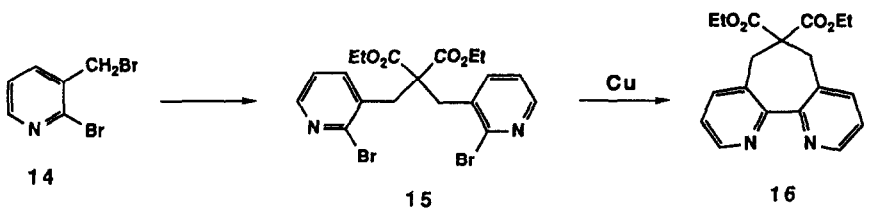


Neither the Friedländer nor the pyrolysis method works well for the preparation of **4a** which is best prepared starting from 1,10-phenanthroline (**10**). Careful oxidation of **10** with potassium permanganate gives 4,5-diazafluorenone (**11**) which can be reduced under Wolff-Kishner conditions to **4a**.[16] It is interesting to note that **4b** is usually formed as a red oil which can be purified only with considerable difficulty. One might guess the problem to be oxidation of this species to 1,10-phenanthroline but, using a variety of catalysts, this reaction does not appear to occur readily.

Aside from building up the pyridine nuclei, two other routes to 3,3'-bridged bipyridines have been reported by Rebek and coworkers. One route involves constructing the 3,3'-bridge starting from 2,2'-binicotinic acid (**12a**) which can also be derived from oxidation of 1,10-phenanthroline. The diacid can be esterified and then reduced to the diol **12c**. Etherification with polyethylene glycol ditosylates provides the 2,2'-bipyridyl crown ethers **13a-c**.[17] Other anhydride and imide type derivatives of **12a** are also readily accessible.

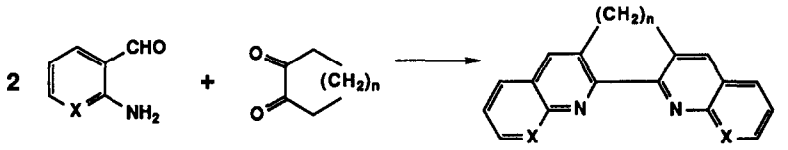


In an interesting corollary to this approach, the Rebek group prepared the substituted malonic ester **15** from 2-bromo-3-bromomethylpyridine (**14**) in 54% yield and then carried out an intramolecular Ulmann coupling in 77% yield to provide the 3,3'-trimethylene bridged diester **16**.[18] This material could, in turn, be converted to the monoacid and bromide by standard methods.



The problems associated with the use of BAA in Friedlander condensations can be mostly overcome by the annulation of an aromatic ring to the aminoaldehyde. Although 2-aminobenzaldehyde (**17a**) is no longer commercially available due to its propensity for polymerization, it can be readily prepared by the ferrous sulfate reduction of 2-nitrobenzaldehyde[19] and can be stored for a month or more at 0°C. The pyridine analog, 2-aminonicotinaldehyde (**17b**), can be prepared in two steps from nicotinamide.[20] Both of these species condense in a 2:1 fashion with cyclic 1,2-diketones to provide the 3,3'-bridged 2,2'-biquinolines (**18a-d**)[21] and 2,2'-bi[1,8]naphthyridines (**19b-e**)[13] in reasonable yields. The reaction of **17b** with 1,2-cyclopentanedione did not give the expected monomethylene bridged material.

Interestingly, these reactions prefer formation of the 2:1 product so that use of only one equivalent of the aminoaldehyde results in mostly the formation of **18** or **19** along with unreacted diketone.[22] Presumably the intermediate mono-condensed species is more reactive than the starting diketone **9** due to the activating influence of the aromatic ring conjugated



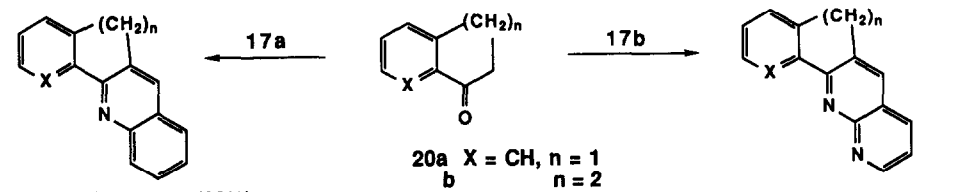
17a X = CH
b X = N

9

18a X = CH, n = 1 (47%)
b n = 2 (72%)
c n = 3 (36%)
d n = 4 (70%)
19b X = N, n = 2 (47%)
c n = 3 (67%)
d n = 4 (82%)
e n = 8 (70%)

with the remaining carbonyl group. In the case of 1,2-cyclooctanedione, some mono-condensation can be obtained due to the diminished interaction between the two carbonyl groups.

Condensation of **17a,b** with benzocycloalkanones **20** or pyridyl ketones **7** provides the 3,3'-bridged 2-phenyl- and 2-(2'-pyridyl)-quinolines **21** and **22** and [1,8]naphthyridines **23** and **24**.[13,23] From both a steric and electronic point of view, these molecules represent intermediates between the symmetrical species **4**, **18**, and **19**.

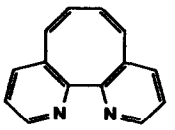


21a X = CH, n = 1 (60%)
b n = 2 (74%)
c n = 3 (85%)
22a X = N, n = 1 (50%)
b n = 2 (80%)
c n = 3 (74%)
d n = 4 (62%)

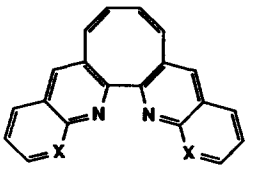
20a X = CH, n = 1
b n = 2
c n = 3
7a-d X = N

23a X = CH, n = 1 (80%)
b n = 2 (90%)
c n = 3 (93%)
24a X = N, n = 1 (41%)
b n = 2 (96%)
c n = 3 (33%)
d n = 4 (78%)

Wong and coworkers have recently reported conversion of **4d** to the corresponding cyclooctatetraene **25** via a two step procedure.[24a,c] Allylic bromination with NBS followed by bis-dehydrobromination using KOH in ethanol provided **25** in 70% yield. The 2,2'-biquinoline and 2,2'-bi[1,8]naphthyridine analogues **26a,b** were also prepared by a similar route.[24b,c] An x-ray structure of **26a** shows the COT ring to be quite non-planar with an N_1-C_2-$C_{2'}$-$N_{1'}$ dihedral angle of 62.8°. When **25** was heated with $Mo(CO)_6$ a tetracarbonyl molybdenum complex was formed. With $Cu(ClO_4)_2$, **26a** formed the complex $Cu(\mathbf{26a})_2ClO_4$ in which the copper(II) has apparantly been reduced to copper(I). Neither complex shows complete flattening of the ligand system. For the copper complex the dihedral angle between the quinoline rings is reduced to about 38°.[24b]



25



26a X = CH
b X = N

It is worthwhile to note that the benzocycloalkanones **20** can be converted to O-allyloximes which upon pyrolysis provide the 3,2'-bridged derivatives of 2-phenylpyridine **27**. These compounds react with palladium(II) hexafluoro-2,4-pentanedionate to afford the cyclopalladated species **28** in good yields. The kinetics of this process have been studied but the rates of formation of **28** were not different enough to elucidate the mechanism of the C-Pd bond forming process.[25]

27 a n = 1
b n = 2
c n = 3
d n = 4

28b n = 2 (95%)
c n = 3 (93%)
d n = 4 (83%)

As was pointed out earlier in this section, the most important property of 3,3'-bridged bipyridines is the relationship between bridge length and conformation of the molecule. This relationship is best analyzed by careful consideration of the ^1H NMR spectra of these systems. As expected, all the monomethylene bridged biaryls show a sharp singlet for their bridge protons. These molecules are essentially flat and rigid. At room temperature in $CDCl_3$ solution, the dimethylene bridged systems also show a sharp singlet for their bridge protons while the trimethylene bridges appear as a downfield triplet and an upfield quintet. For two and three carbon bridges, conformational inversion between enantiomers A and B (Table 1) is rapid on the NMR time scale. Cooling these samples to about -70°C does not appreciably alter the spectrum. Previous workers have noted the same characteristics for the analogous bridged biphenyls.[26]

Without exception, the tetramethylene-bridged systems behave differently. At room temperature, the symmetrical molecules **4d**, **18d**, and **19d** all exhibit four distinct resonances in the aliphatic region of their NMR spectra. Figure 1 illustrates this situation for **18d**. Examination of a molecular model shows that, in its most favorable conformation, one of the benzylic protons is held over the shielding region of the opposite pyridine ring while the

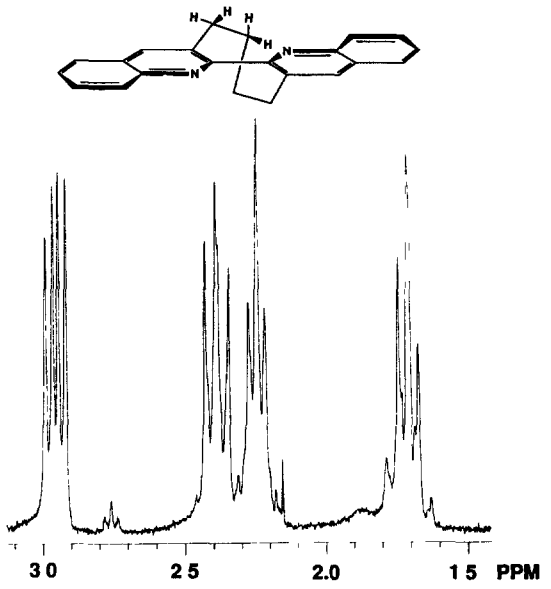


Figure 1. Upfield region of the 300 MHz ^{1}H NMR spectrum of 3,3'-tetramethylene-2,2'- biquinoline (**18d**) at 25°C in $CDCl_3$.

other benzylic proton is deshielded by the adjacent pyridine ring. One of the two non-benzylic methylene protons also experiences considerable shielding due to the closer pyridine ring.

One would expect these NMR spectra to exhibit coalescence of the geminal proton resonances with increasing temperature. Heating a sample of **4d** evidenced almost no change while samples of **18d** and **19d** showed slight broadening upon heating to 135°C in *o*-xylene-d_{10}.[27] Calculation of an approximate ΔG value for the conformational inversion process is complicated by the fact that the coalescing protons are coupled to one another as well as the adjacent methylene protons. Nevertheless, a ΔG value of greater than 17.5 Kcal/mole could be estimated for **19d**.[27]

We speculated that the tetramethylene bridged bipyridine **4d** might be resolved in a classical manner through the formation of a diastereomeric salt. Such salts were readily prepared from either *d*-tartaric acid or *d*-mandelic acid and subsequently purified by multiple recrystallizations. When the purified salts were converted back to the free bipyridine base, no optical rotation could be detected. It appears that although conformational inversion at room temperature is slow on the NMR time scale, on the real world time scale it is sufficiently rapid to prevent resolution of **4d** [28]

Treatment of the bridged biquinolines **18** with *m*-chloroperbenzoic acid converted them to either mono- or di-N-oxides depending on the stoichiometry of the reaction and congestion within the molecular cavity. The di-N-oxide of the trimethylene bridged derivative **29** is particularly interesting for two reasons. First, the incorporation of two N-oxide groups in the "pocket" of the molecule increases the 2,2'-rotational barrier sufficiently to cause the molecule to become conformationally rigid by NMR (see Figure 2). Thus the geminal benzylic protons become magnetically non-equivalent and the triplet observed at 2.7 ppm for **18c** splits into two doublets of triplets centered at 2 80 and 2.47 ppm with a geminal coupling constant of 13.8 Hz.[21]

Another intriguing feature of **29** would be its potential to behave as a thermal source of singlet oxygen. This phenomenon was first examined, without success, by Werkert and Woodward for the di-N-oxide of 2,2'-bipyridine where the cisoid conformation required for concerted loss of $^1O_2$ is unfavorable.[29] The biquinoline di-N-oxide **29**, on the other hand, has this cisoid geometry enforced by the bridge. A toluene solution of **29** and 1,3-diphenyliso-

benzofuran, an efficient singlet oxygen trap, was heated under nitrogen to 160°C for 12 hours. Only unreacted materials were obtained with no evidence for the formation of $^1O_2$ or **18c** [21] If this reaction had succeeded, it would be unique in that the two halves of the resulting oxygen molecule were initially not bound to one another.

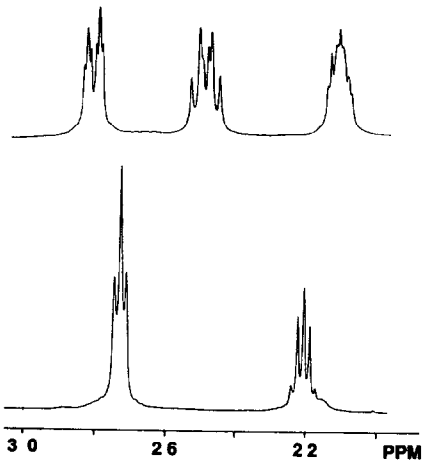
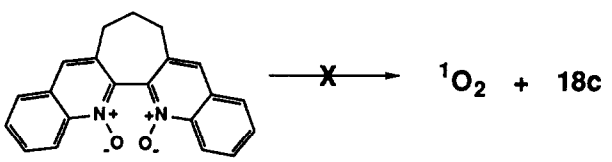


Figure 2 Upfield region of the 400 MHz ^1H NMR spectrum of di-N-oxide **28b** (top) compared with its parent biquinoline **18c** (bottom) at 25°C in $CDCl_3$. Reprinted with permission from ref 21 Copyright (1985) American Chemical Society

For bridged derivatives of biphenyl, ultraviolet spectroscopy has been used extensively to evaluate the relationship between coplanarity of the two aromatic rings and the degree of conjugative interaction between them.[30] Absorption maxima are found to shift toward shorter wavelength (higher energy) as the two rings become less coplanar. For all the series of bridged azabiaryls discussed thus far we observe the same dependency. It is further noted that the more planar, rigid systems generally show more fine structure in their long wavelength π-π^* absorption bands due to better Franck-Condon overlap between the ground and excited state of the molecule.



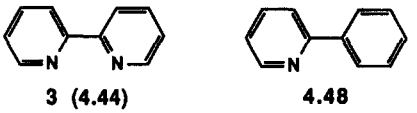
29

The cavity shaped molecules which we have been examining have a "bay region" containing 2-4 sp^2 nitrogens In the sense that the nitrogen lone pairs may function as Lewis bases, one would expect that certain cooperativity effects might be in evidence. In an early study on bridged derivatives of 2,2'-biimidazole, Deady has examined the effect of dihedral angle on lone-pair cooperativity.[31] Two primary effects are found. The electronic effect of a 2-substituted aryl group will generally be deactivating especially when this aryl group is coplanar with the pyridine ring. The steric bulk of a 2-substituent can also interfere with the reactivity of the pyridine lone pair electrons.

We have measured the basicities of some of the systems under discussion by monitoring their protonation by 0.1 N $HClO_4$/HOAc in acetic anhydride. Table 2 examines four simple systems where a higher pK value implies increased base strength.[14] Both 2,2'-bipyridine and

2-phenylpyridine are less basic than pyridine (pK_a = 5.17).[32] When 2-phenylpyridine is forced coplanar as in 9-azafluorene, the basicity decreases by 0.93 pK units, while the analogous change in 2,2'-bipyridine causes only a 0.44 diminishment in basicity. The implication is that lone pair cooperativity augments the basicity of **4a** vs. **27a**. The steric impact of removing the 6'-CH interaction in **27a**, however, cannot be ignored.

Table 2. pK Values of some substituted pyridines.

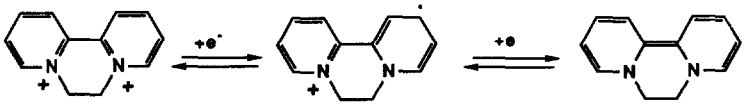


3 (4.44) 4.48

4a (4.0) 27a (3.55)

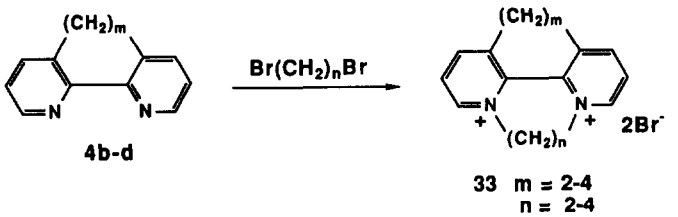
The pK values for the remaining bridged bipyridines are **4b** (5.70), **4c** (4.75), **4d** (4.70).[14] From these values we can conclude that cooperativity is important for **4b** but that the remaining two systems behave essentially as 2-aryl substituted pyridines.

It is well known that 2,2'-bipyridine can be bridged between its two nitrogens by bis-alkylation with 1,n-dihaloalkanes. The resulting diquaternary salts are important electron transfer agents in biological and other photocatalytic systems.[33] Hence the molecule **30**, known by the trivial name of "diquat", undergoes two reversible reductions to afford the radical cation **31** and the fully reduced species **32**. We reasoned that the incorporation of an N,N'-bridge onto our 3,3'-bridged bipyridines **4** should influence the barrier for conformational inversion and thereby allow us to mediate the potential required for the two reduction steps.



30 31 32

The N,N'-dialkylation did not work well for **4a** but occurred in 63-98% yields for **4b-d** to afford a series of nine bis-annelated bipyridinium salts **33** having all possible combinations of 2-4 carbon bridges.[34] The conformations of these systems can again be analyzed by NMR and we find that the system with m = 2, n = 3 is now conformationally rigid at room temperature.



4b-d

33 m = 2-4
n = 2-4

We have measured the reduction potentials for this series of diquaternary salts in acetonitrile and found that both the potential and the reversibility of the process were influenced by bridge length. Figure 3 shows three representative cyclic voltammograms in which both steps are reversible, only the first step is reversible, or both steps are irreversible Irreversibility implies that the species formed upon reduction undergoes some other process faster than it can be oxidized back to the reduction precursor. Typical processes that might interfere with reoxidation include a conformational change, a subsequent chemical reaction of the reduced species, or adsorption of this species onto the electrode surface. We are currently examining the spectral properties of the bis-annelated analogs of **31** and **32** to better understand these processes.[35]

A principal concern in our studies of bridged bipyridines was the effect of conformation on the chelating properties of these molecules as well as the reverse effect of chelation on ligand conformation. For this purpose we chose to examine ruthenium(II) complexes because of the relative ease with which they could be prepared, purified, and analyzed. Furthermore, such complexes command widespread interest due to their intriguing photochemical and electrochemical properties.[36] The reaction of three equivalents of bridged ligand L with ruthenium trichloride trihydrate in aqueous ethanol and precipitation as the hexafluorophosphate salt gave RuL_3^{2+} complexes while the same reaction using a 1·1 mixture of ligand L with $Ru(bpy)_2Cl_2$ gave the corresponding mixed ligand complex $Ru(bpy)_2L^{2+}$.[37,38] The results of these complexation reactions are summarized in Table 3.

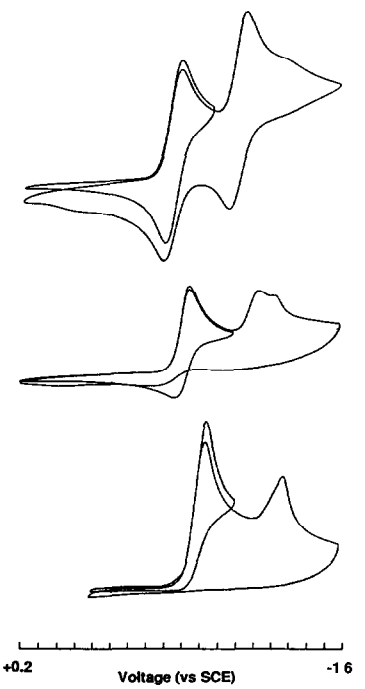


Figure 3 Cyclic voltammograms of diquaternary salts 33 m = 3, n = 4 (top), m = 4, n = 3 (middle); and m = 4, n = 4 (bottom) in acetonitrile containing 0.1 M TBAP at 25°C with a sweep width of 200 mV/sec. Reprinted with permission from ref 34 Copyright (1988) American Chemical Society

Table 3. Ruthenium(II) Complexes of Bridged Azabiaryls.

RuL_3^{2+}

L =	**4a**	61%[a]	L =	**18a**	16%	L =	**19a**	-
	4b	36		**18b**	40		**19b**	90%[b]
	4c	58		**18c**	-		**19c**	43
	4d	62		**18d**	-		**19d**	-

$Ru(bpy)_2L^{2+}$

L =	**4a**	63%[a]	L =	**18a**	96%	L =	**19a**	-
	4b	59		**18b**	81		**19b**	82%
	4c	67		**18c**	56		**19c**	80
	4d	53		**18d**	50		**19d**	89

(a) Reference 16a (b) Reference 39

The complex $Ru(\mathbf{4b})_3^{2+}$ shows a sharp singlet in its NMR spectrum for the bridge protons indicating that even in the bound state conformational inversion of the ligand is facile. On the other hand, the trimethylene-bridged analog shows a pattern which clearly reveals that the ligand is conformationally rigid. Preliminary structural data on $Ru(\mathbf{4d})_3^{2+}$ indicate that this ligand is also rigid and moreover all three bound ligands have the same absolute configuration. Conformational inversion at the metal center would require all three non-planar ligands to invert their conformations simultaneously explaining the unusually high barrier to this process in the bound state.

We were surprised to find that even the highly distorted 3,3'-tetramethylene bridged bipyridine (**4d**) formed a tris-complex in reasonable yield.[38] An x-ray structure of $Ru(bpy)_2\mathbf{4d}(PF_6)_2$ shows that the N-C-C-N dihedral angle of the bound **4d** is 30.4°. The clear implication is that octahedral coordination can accomodate considerably distorted ligands and coplanarity of the two halves of bipyridine is not mandatory.

On the other hand, congestion in the vicinity of the metal atom can very much influence coordination. One can consider 2,2'-biquinoline as a dibenzo-fused derivative of 2,2'-bipyridine. Although tris-complexes could be prepared from **18a,b**, they could not be formed from the two higher homologs, **18c,d** where congestion around the metal would be severe. This problem can be somewhat alleviated when the the C_8-H bond is replaced by a nitrogen as in **19c** which does form a tris-complex.[37] It is noteworthy that the ^1H NMR spectrum of $Ru(\mathbf{18b})_3^{2+}$ shows an AB quartet for the dimethylene bridge indicating that the barrier to conformational inversion of the ligand has been significantly increased presumably due to congestion. Monomethylene bridging has the effect of pulling the two chelating nitro-

gens apart and reducing their metal binding ability. In this regard only **19a** was found to be reluctant to coordinate.

An interesting situation is found in the case of the mixed ligand complex $Ru(bpy)_2$**4d**$^{2+}$ and is illustrated in Figure 4.[38] The complex possesses two chiral centers: one on the metal atom and one on the tetramethylene bridged ligand, giving rise to the potential existence of two pairs of diastereomers, Δ,*d*; Λ,*l* and Δ,*l*; Λ,*d* Careful purification of the complex led to a nearly quantitative recovery of crystals which were analyzed by single-crystal x-ray diffraction and found to have the former configuration. Inspection of molecular models of $Ru(bpy)_3$ and the *d* and *l* forms of **4d** indicates that significant steric interaction with H_6 on the two bpy ligands is avoided when coordination occurs in the fashion Δ,*d*, Λ,*l*. Although coordination appears to be diastereoselective, it probably occurs in a stepwise fashion so that the selectivity is thermodynamic rather than kinetic in origin

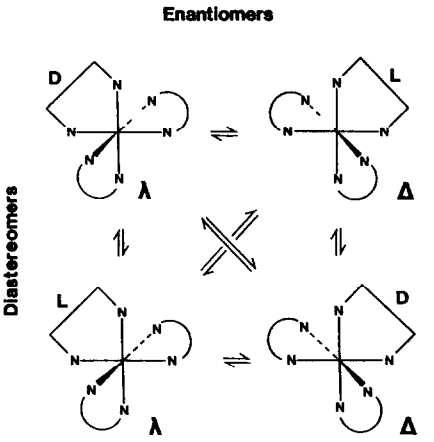
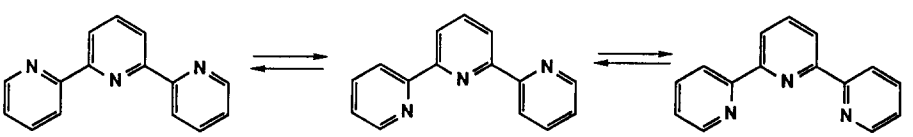


Figure 4 Stereoisomers of $Ru(bpy)_2$(**4d**)$^{2+}$. Nitrogens connected by a curved line represent 2,2'-bipyridine and nitrogens connected by right-angled lines represent **4d** Reprinted with permission from ref 38 Copyright (1987) American Chemical Society

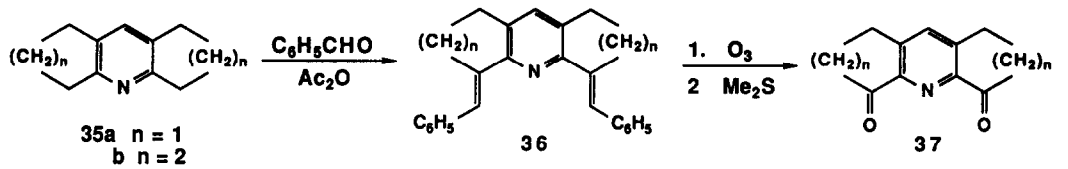
3. BRIDGED 2,2':6',2"-TERPYRIDINES

The systems examined thus far have contained two covalently bound aromatic nuclei linked by a single polymethylene bridge. If the concept of bridging is extended to the next higher homolog of 2,2'-bipyridine, we could then consider doubly bridged derivatives of 2,2':6',2"-terpyridine (**34**, tpy).[40] There are three planar conformations of this molecule: anti-anti, syn-anti, and syn-syn It is the latter conformation which is capable of functioning as a tridentate chelator and it is this conformation which is enforced by the 3,3':5',3"-bridging in **38**



34 anti-anti syn-anti syn-syn

One synthetic approach to the doubly bridged tpy systems closely parrallels that employed in making the bpy analogues [41] Thus we start with 2,3:5,6-biscycloalkenopyridines **35** which can be made either by Friedlander or enamine methodology.[11a] We are fortunate in that 1,2,3,4,5,6,7,8-octahydroacridine (**35b**) is commercially available and therefore this material

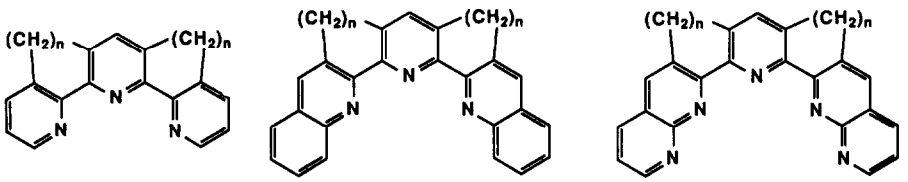


35a n = 1
b n = 2
c n = 3
d n = 4

36

37

provided the starting point for much of our work. Condensation of **35** with benzaldehyde in acetic anhydride leads to the corresponding dibenzylidene derivatives **36**. It is noteworthy that the more planar systems **35a,b** gave **36** in good yields after only a few hours of reaction and in relatively pure form. The less planar systems **35c,d** required much longer reaction times and more careful purification. Ozonolysis of **36** and *in situ* methyl sulfide reduction of the resulting bis-ozonide gave the diketones **37**. Purification of these diketones requires careful removal of benzaldehyde and dimethyl sulfoxide followed by chromatography on alumina.



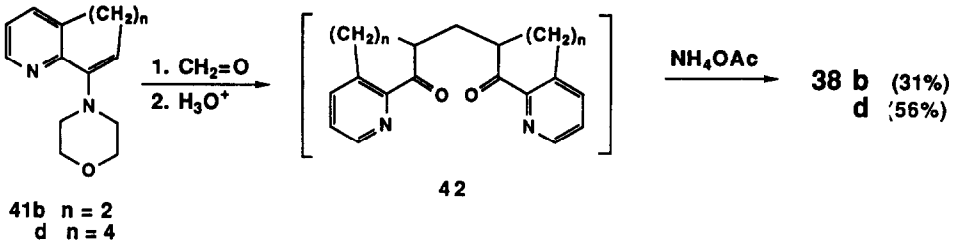
38b n = 2
c n = 3
d n = 4

39b n = 2 (87%)
c n = 3 (76%)
d n = 4 (77%)

40b n = 2 (70%)
c n = 3 (58%)
d n = 4 (64%)

When these diketones are treated with BAA a double Friedländer condensation can be effected to yield **38b-d** in yields of 3%, 21%, and 2% respectively. None of **38a** (n = 1) could be obtained. These yields being unacceptable, an alternate synthesis was developed starting from the morpholine enamines **41** of the pyridyl ketones **7**. These species could be condensed with formaldehyde in dioxane to afford the 1,5-diketones **42** after hydrolysis. These diketones can exist as a pair of diastereomers making purification somewhat tedious and, in fact, unnecessary Direct treatment of the crude **42** with ammonium acetate provides the terpyridines **38b,d** in improved yields This process involves a final dehydrogenation to aromatize the system which Bell and coworkers have reported can be accelerated by the addition of cupric acetate.[42]

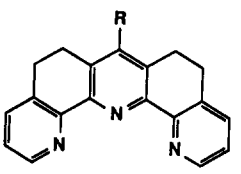
The diketones **37** can also be condensed with the *ortho*-aminoaldehydes **17a,b** to provide the the quinoline and [1,8]naphthyridine analogs **39** and **40** in reasonable yields. Reactions with **37a** once again proved unsuccessful.



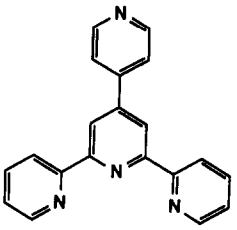
41b n = 2
d n = 4

42

The enamine synthesis of terpyridines is general and can be applied to aldehydes other than formaldehyde although best results are obtained with aromatic aldehydes.[43] Thus the enamine **41b** can be condensed with RCHO to provide 4'-R-substituted terpyridines **43** after reaction of the intermediate 1,5-diketone with ammonium acetate. Table 4 gives a representative list of aldehydes which undergo this reaction and the yields of their terpyridine products. The morpholine enamine of 2-acetylpyridine is quite labile but if it is employed with 4-pyridinecarboxaldehyde in this same manner the unbridged species **44** can be obtained in 20% yield.



43

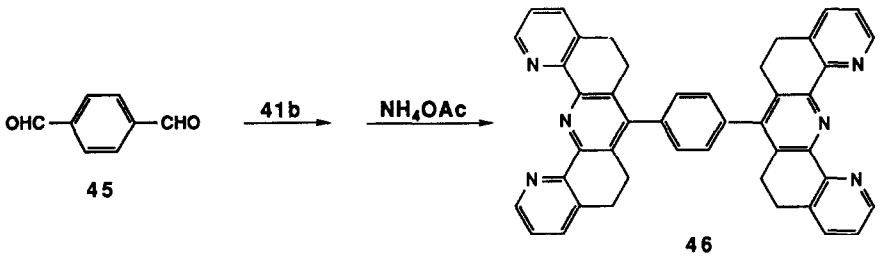


44

Table 4. 4'-Substituted Terpyridines 43 from Aromatic Aldehydes.

Aldehyde	Terpyridine	
Benzaldehyde	**43a**	(20%)
p-Tolualdehyde	**43b**	(39%)
p-Chlorobenzaldehyde	**43c**	(35%)
p-Nitrobenzaldehyde	**43d**	(19%)
4-(N,N-dimethylamino)benzaldehyde	**43e**	(35%)
3-Pyridinecarboxaldehyde	**43f**	(53%)
4-Pyridinecarboxaldehyde	**43g**	(36%)
Ferrocenecarboxaldehyde	**43h**	(26%)

A double-barrelled version of this enamine reaction can be accomplished if *p*-terephthalaldehyde (**45**) is treated with four equivalents of **41b**. The resulting bis-terpyridine **46** can be obtained in 22% yield.[43] We have accomplished the same reaction with the *meta*-isomer of **45** but have so far been unsuccessful with the *ortho*-isomer. Other aromatic dialdehydes are currently under investigation.



If bridged biaryl molecules may be considered to have one chiral center by virtue of twisting about the 2,2'-bond, then doubly bridged terpyridines such as **38**, **39**, and **40** might be considered to have two such centers controlled by twisting about the 2,2'- and 6',2"-bonds. Thus terpyridines with two bridges of two or more carbons can potentially exist as a pair of diastereomers, one of which will be a *d,l* form having C_2 symmetry and capable of optical activity and the other being a *meso* form having C_s symmetry and possessing a mirror plane Figure 5 illustrates this situation for **39d**.

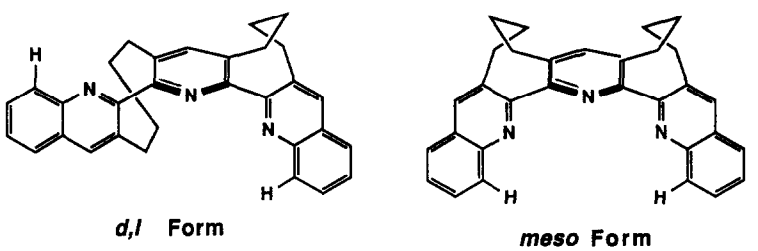


Figure 5 Diastereomers of 3,3' 5,3"-bis(tetramethylene)-2,6-di(2'-quinolyl)pyridine (**39d**)

The existence of such diastereomers may be probed by ^{13}C NMR. For the dimethylene- and trimethylene-bridged systems **39b** and **39c** we observe two and three lines respectively for the methylene carbons indicating that conformational inversion between the *d,l* and *meso* forms is sufficiently rapid to preclude diastereomeric differentiation. For **39d** however, we observe eight lines in the aliphatic region indicating the existence of a mixture of diastereomers. This situation can be further probed by consideration of the ^1H NMR wherein H_8 of the quinoline rings normally appears as a downfield doublet. For **39d** we observe two

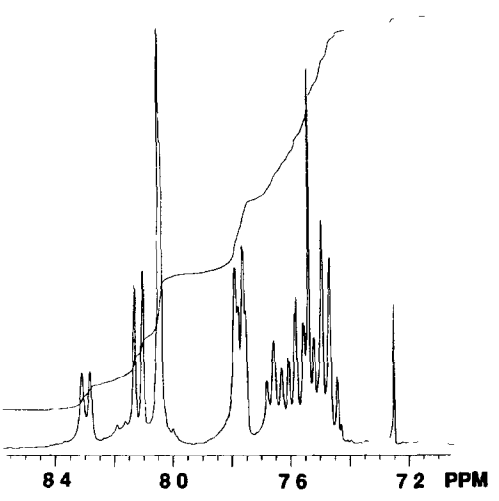


Figure 6 Downfield region of the 300 MHz ^1H NMR spectrum of **39d** at 25°C in $CDCl_3$

doublets at 8.30 and 8.12 ppm in a 60:40 ratio, integrating for a total of two protons. The most downfield resonance is assigned to the H_8-proton of the *meso* form where the cavity shape of the molecule should have a deshielding effect while the H_8-proton of the *d,l* form should be relatively unaffected (see Figure 6).[41]

Treatment of the bridged terpyridines with ruthenium trichloride trihydrate in aqueous ethanol and precipitation of the product with ammonium hexafluorophosphate resulted in the formation of complexes of the type $RuL_2(PF_6)_2$.[44] All the tpy ligands were found to complex in this manner and the results are summarized in Table 5.

Table 5. Ruthenium(II) Complexes of Bridged Azatriaryls.

$RuL_2[PF_6]_2$

L = **38b** (91%)	L = **39b** (15%)	L = **40b** (70%)
L = **38c** (66%)	L = **39c** (26%)	L = **40c** (89%)
L = **38d** (85%)	L = **39d** (35%)	L = **40d** (20%)

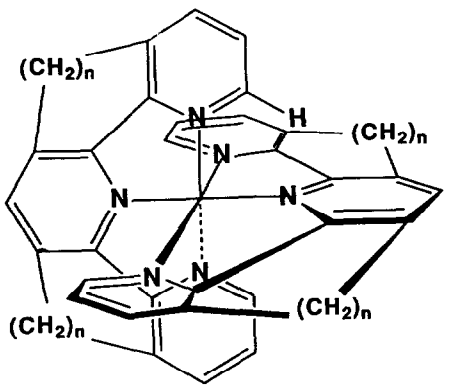


Figure 7 Octahedral coordination geometry of a bridged bis-(2,2' 6 2"-terpyridine) metal complex

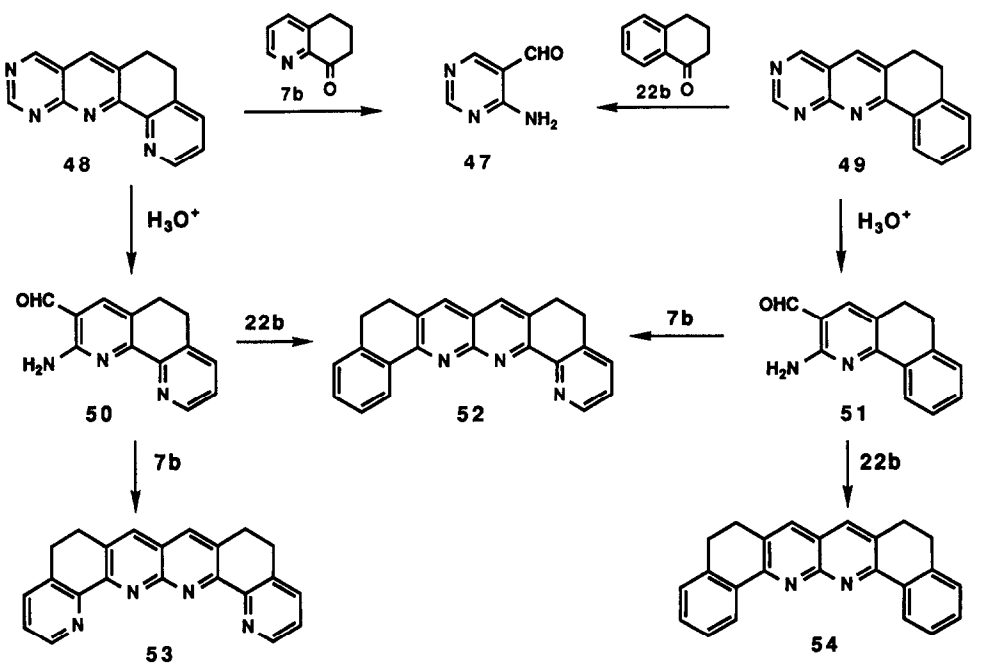
Again it is interesting to note that even the highly distorted tetramethylene-bridged derivatives complex with Ru(II). We have examined the x-ray crystal structure of the complex $Ru(\mathbf{38d})_2(PF_6)_2$ and found that, as expected, both tpys adopt the *meso* conformation and the average dihedral angle between adjacent pyridine rings in the coordinated ligand is about 33° It is interesting that ^1H NMR can be used as a sensitive probe of the conformation of such complexes. Figure 7 illustrates the octahedral geometry of a bis-tpy Ru(II) complex. Note that the proton $H_{6'}$ is held approximately over

the plane of the central pyridine ring of the orthogonal ligand causing it to be considerably shielded. This shielding is sensitive to the conformation of the ligand and as the length of the polymethylene bridges of **38** is increased, $H_{6'}$ is pushed somewhat deeper into the face of the orthogonal ligand and its resonance moves upfield.[44]

4. LARGER POLYAZA CAVITIES

Caluwe and coworkers have elegantly demonstrated how 4-aminopyrimidine-5-carboxaldehyde (**47**) may be employed as a masked derivative of 1,1-diamino-2,2-ethylenedicarboxaldehyde leading to the facile preparation of a variety of [1,8]naphthyridine derivatives.[45] Scheme 1 shows how this molecule can be used in condensations with **7b** and 1-tetralone (**20b**) to provide systems **52-54** which differ only in the number of nitrogens in their molecular cavity.[46a] The key to this process is the facile hydrolysis of the pyrimidopyridine intermediates **48** and **49** to provide the aminoaldehydes **50** and **51** which then undergo a second Friedländer reaction.

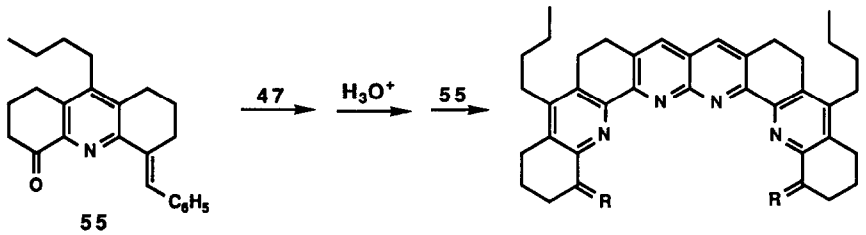
Scheme 1.



We found that when **53** was treated with dirhodium tetraacetate a complex was formed wherein the ligand **53** has replaced one acetate bridge and furthermore binds the two axial dirhodium sites using its distal pyridine nitrogens. This complex is analogous to one prepared earlier from a species similar to **53** but lacking the dimethylene bridges.[46b] Of greater

interest was the possibility that the benzo and dibenzo analogs **52** and **54** might complex in a similar manner and subsequently undergo metallation at the axial site(s). We were able to form the complex of **52** with $Rh_2(OAc)_4$ but the endo benzo-proton remained present in the NMR spectrum, appearing considerably downfield at 11.33 ppm. In this complex it is interesting to note that the dimethylene bridge connecting the naphthyridyl unit with the phenyl ring is conformationally rigid while the corresponding bridge to the pyridyl ring is conformationally mobile, reflecting the relative congestion on either side of the dirhodium core. The complex with **54** could not be prepared.[46a]

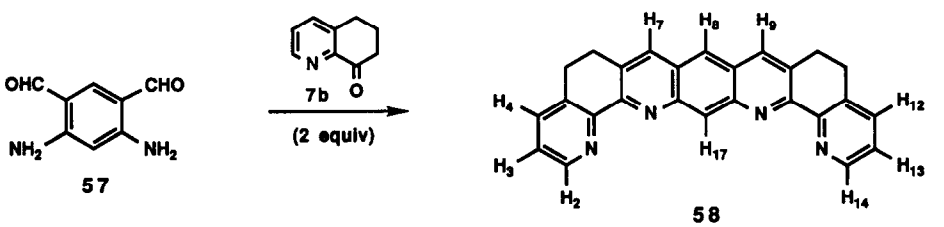
Bell and Liu have reported the two-fold condensation of **47** with the pyridyl ketone **55** to provide a derivative of **54** bearing two benzylidene groups which may undergo subsequent oxidative cleavage to provide the diketone **56b**.[47] The incorporation of two *n*-butyl groups improves the solubility of such systems.



55

56a R = CHC_6H_5
b R = O

Starting from *m*-xylene, one is able to prepare the diaminodialdehyde **57** in four steps.[48] In a synthetic sense, this molecule is a benzologue of the masked diaminodialdehyde encompassed by **47**. In this case both aminoaldehyde moieties can react simultaneously with the pyridyl ketone **7b** to produce the tetraaza cavity **58**.[49] The interior C-H appears at 9.45 ppm in the ^1H NMR and is diagnostic of the environment in the cavity. By treatment of **58**



57

58

with $Ru(bpy)_2Cl_2$ we were able to prepare only the mononuclear complex with the ruthenium binding to a dihydrophenanthroline subunit. The ^1H NMR of this complex is very complex due to lack of symmetry leading to non-equivalence of all aromatic protons. We solved the problems associated with the interpretation of this spectrum by substituting bpy-d_8 for bpy in the ruthenium(II) reagent. Figure 8 illustrates the NMR spectra for the protio and deuterio complexes and from the latter we can clearly make out the ten signals arising from **58** and by

analogy with other systems assign each one of them as shown. More recently we have synthesized tpy-d_{11} in a manner analogous to that employed for bpy-d_8 and ruthenium complexes employing this auxiliary ligand show a similar simplification in their aromatic region.[50]

The aminoaldehydes **50** and **51** (Scheme 1) are useful synthons in reactions with other ketones. The 2:1 reaction with cyclic 1,2-diketones provides the cavity-shaped molecules **59** and **60**[51] while reaction with the pyridyl diketones **37** provides **61** and **62**.[52] Note that for **60** and **62** every non-bridgehead position within the interior of the cavity is an sp^2 nitrogen making for a very electron rich cavity. In principle the outermost bridge lengths can also be varied by substituting higher homologs of **7b** and **20b** into Scheme 1 We have utilized only dimethylene bridges because these favor chelation at the outermost biaryl moiety.

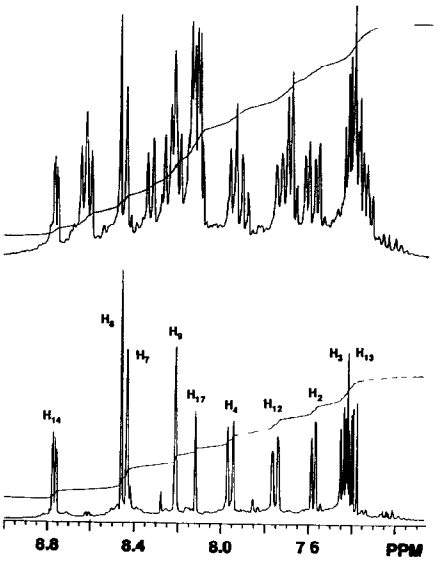
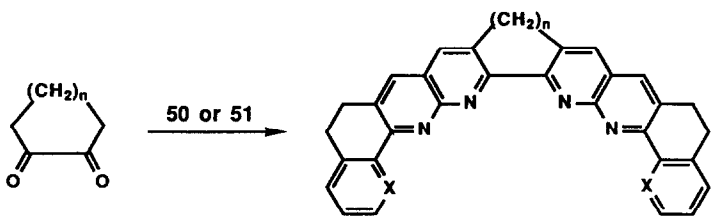


Figure 8 Downfield regions of the ^1H NMR spectra of Ru(bpy)$_2$(**58**)[PF_6]$_2$ (top) and Ru(bpy-d_8)$_2$(**58**)[PF_6]$_2$ at 25°C in CD_3CN Reprinted with permission from ref 49 Copyright (1989) American Chemical Society

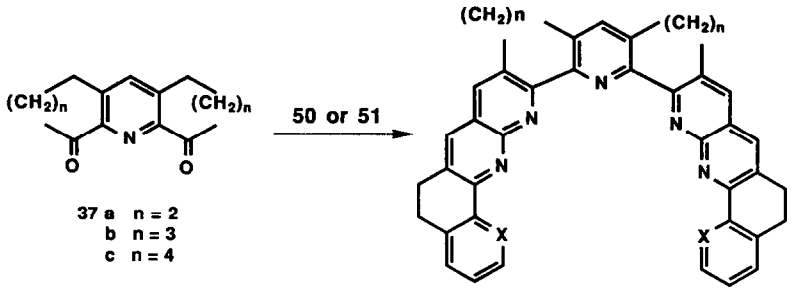


9 a n = 2
b n = 3
c n = 4

59 a X = CH, n = 2 (73%)
b n = 3 (61%)
c n = 4 (78%)
60 a X = N, n = 2 (63%)
b n = 3 (65%)
c n = 4 (88%)

One of our initial objectives in preparing such large cavities was to examine their possible chelation with the lanthanides. These metals have large ionic radii, high coordination numbers, and relatively non-specific chelation geometries. Thus we hoped that two or even three of our large cavity ligands could surround a lanthanide cation and complexes with interesting ligand-to-metal energy transfer states might result. We were unsuccessful in binding these large cavities to europium(III) and a study is currently in progress to determine the limitations of binding tpy and [1,8]naphthyridine ligands to this metal.

In reactions with Ru(II) we have found that two molecules of **61** will bind in a tridentate fashion through the central tpy moiety. We have been so far unsuccessful in forming RuL_3^{2+} complexes of any of these species. More interesting perhaps are reactions of these systems



37 a n = 2
b n = 3
c n = 4

61 a X = CH, n = 2 (98%)
b n = 3 (88%)
c n = 4 (65%)
62 a X = N, n = 2 (87%)
b n = 3 (87%)
c n = 4 (74%)

with $Ru(bpy)_2Cl_2$. This species binds only to the outermost dihydrophenanthroline subunit of **60** and **62** as the more interior bidentate sites are too congested due to the bulky bpy auxiliary ligands. For **60a** we are able to prepare a mononuclear complex but not a binuclear one again due to congestion within the molecular cavity. For **60b** and **60c** we are able to prepare both mononuclear and binuclear complexes and for the binuclear complex of **60c** an x-ray analysis has been performed (see Figure 9).[51]

Several interesting stereochemical features are in evidence. The bridging ligand has adopted a helical conformation with a dihedral angle of 74° for twisting about the central bond. The complex may now be considered as having three chiral centers, two associated with the Ru(II) centers and one with the tetramethylene bridge of **60c**. Of 8 possible diastereomers only the pair Δ,d,Δ; Λ,l,Λ is observed, indicating that, once again, coordination has been diastereoselective. In more recent work we have been successful in preparing heterobinuclear complexes of some of these large cavities using both Ru(II) and Os(II).[52]

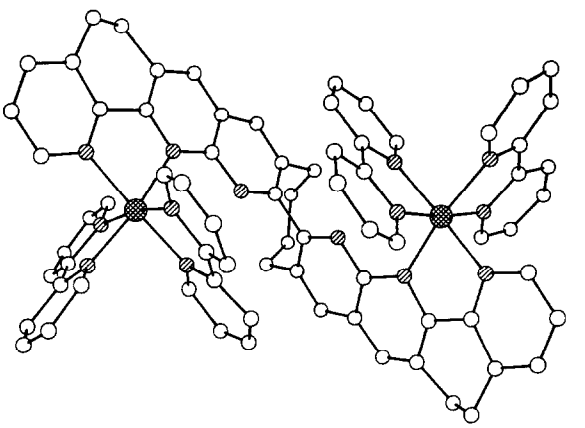
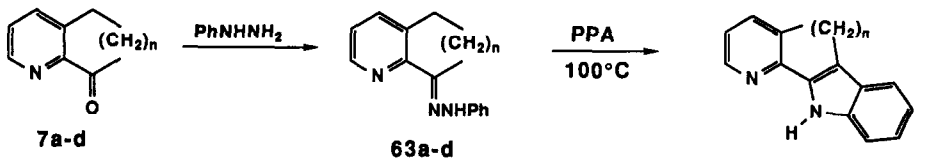


Figure 9 View of the $(bpy)_2Ru(\mathbf{60c})Ru(bpy)_2^{4+}$ cation The thermal ellipsoids are 20% envelopes and the hydrogens have been omitted for clarity Reprinted with permission from ref 51 Copyright (1988) American Chemical Society

5. INDOLE CONTAINING SYSTEMS

Up to this point all the polyaza systems which we have discussed have been prepared by variations of the Friedländer condensation. There is another very useful synthetic reaction which allows for the specific introduction of indole moieties into our organized assemblies. This reaction is the Fischer indole synthesis.[53]

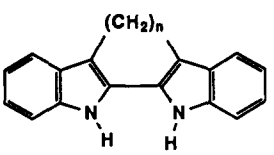


7a-d

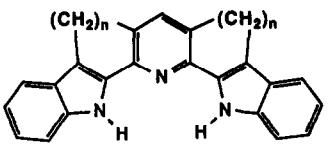
63a-d

64a n = 1 (95%)
b n = 2 (65%)
c n = 3 (62%)
d n = 4 (59%)

The phenylhydrazones **63** may be obtained by treatment of the pyridyl ketones **7** with phenylhydrazine. If these species are heated with polyphosphoric acid (PPA) to 100°C for several hours, Fischer cyclization occurs and the bridged 2-(2'-pyridyl)indoles **64** are obtained. Like the Friedländer condensation, this reaction can be carried out in a double-barrelled fashion to effect two sequential indolizations. When the cyclic 1,2-diketones **9** are employed, milder conditions are required and only modest yields of the desired 2,2'-biindoles **65** are obtained accompanied by substantial amounts of the monoketone intermediates.[54] The pyridyl diketones **37** react smoothly in this sequence affording good yields of the corresponding bridged 2,6-di(2'-indolyl)pyridines **66**.[54a]

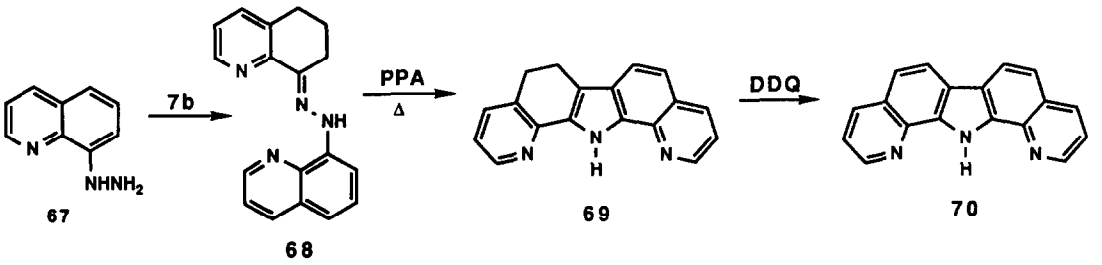


65 c n = 3 (23%)
d n = 4 (21%)

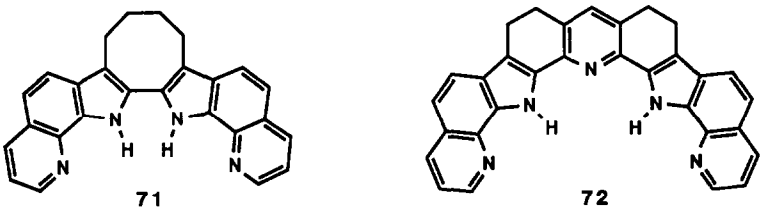


66b n = 2 (84%)
c n = 3 (82%)
d n = 4 (84%)

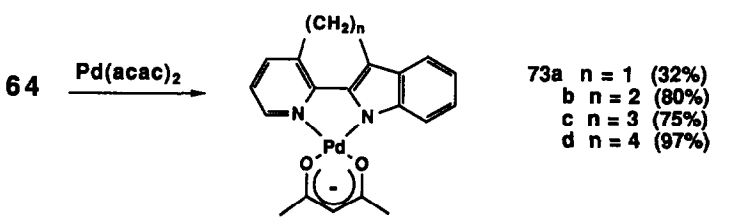
To introduce more useful functionality into the cavities of these systems we developed a modification involving 8-quinoline hydrazine (**67**) which can be prepared by the stannous chloride reduction of the diazo derivative of 8-aminoquinoline. This hydrazine condenses easily with **7b** to provide **68** which can be cyclized under Fischer conditions to provide **69**. Subsequent dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the fully aromatized dipyridocarbazole **70**.[55]



Double cyclizations similar to those employed for the phenylhydrazones may also be effected. Thus 1,2-cyclooctananedione provides 68% of **71** accompanied by a small amount of monoketone intermediate. The diketopyridine **37b** undergoes the same sequence to afford **72** in 77% yield.[55]



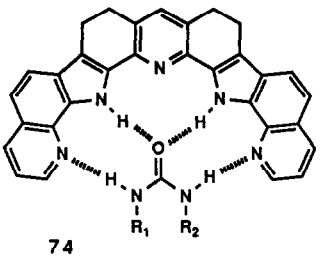
From a conceptual point of view 2-(2'-pyridyl)-indoles **64** may be considered as lower homologues of 2-(2'-pyridyl)-quinolines **22**. The former species will have a slightly less favorable "bite angle" for bidentate chelation but, more importantly, they have one of their nitrogen lone pairs tied up in the indole N-H bond. In order to chelate, these molecules must deprotonate and hence would serve as negatively charged ligands. We have tested this hypothesis by cyclopalladation of **64** with palladium 2,4-pentanedionate. These reactions occur smoothly even for the tetramethylene bridged systems to provide the species **73**. The lowest yield is, in fact, obtained for the most planar monomethylene-bridged system **64a** where presumably the even less favorable bite angle impedes the cyclometallation step.[54a]



The environment within the cavity of molecules such as **64** is interesting in another light. We have a hydrogen bond donor and acceptor arranged in a 1,4-fashion with respect to one another. There is a clear propensity for intramolecular hydrogen bonding as is evidenced by

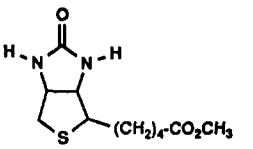
the position of the N-H signal in the NMR. For **64a-d** these resonances occur respectively at 10 98, 11.91, 10.02, and 9.32 ppm. An upfield shift indicates decreased intramolecular H-bonding and is quite consistent with structure.[54a]

For larger systems such as **72** the existence of alternating donor and acceptor sites around the inside of the molecular cavity has another interesting implication. This molecule is a particularly good receptor for urea derivatives.[55] Thus **72** not only solubilizes urea in chloroform but also forms complexes with a variety of substituted ureas Figure 10 shows the probable structure of the complex and the calculated association constants for several differ-



74

	K_a
$R_1 = R_2 = CH_3$	05
R_1 = n-Bu, R_2 = H	80
$R_1, R_2 = CH_2CH_2$	3530
Methyl Biotin (75)	3000
Butyrolactam	13



75

Figure 10 Association constants (±15%) for host-guest complexes of **72** with various substituted ureas calculated by the method of Horman and Dreux [56]

ent guests. Note that the weakest binder is dimethylurea whose most favorable binding conformation is hindered by its two N-methyl groups. The steric problem is partially alleviated for *n*-butylurea while bridging the two nitrogens as in imidazolidone provides an excellent fit. An X-ray structural analysis of this complex has been recently completed and is illustrated in figure 11 which shows all four H-bonds falling in the range 2.12 - 2.28 Å. Molecular mechanics calculations are in progress to simulate this process.

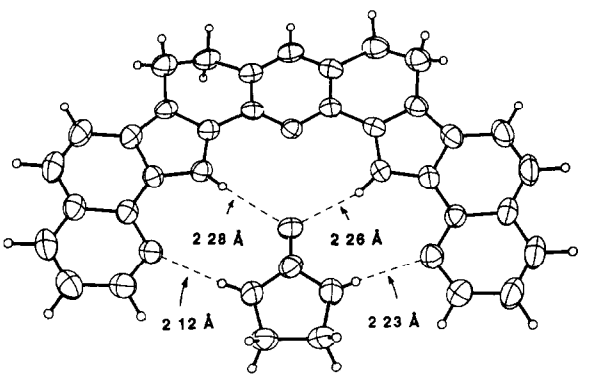


Figure 11 ORTEP drawing of the host-guest complex of **74** with imidazolidone, indicating critical hydrogen bonds

The binding appears to be fairly general in that methyl biotin which possesses the essential binding element binds quite well. Even a simple amide such as butyrolactam, which is only capable of forming three H-bonds, still associates reasonably well. It is particularly significant that this molecule binds urea with its carbonyl group pointed *inward* permitting the incorporation of a wide variety of guests. Other hosts, such as Bell's naphthyridine derivative **56b**, bind urea

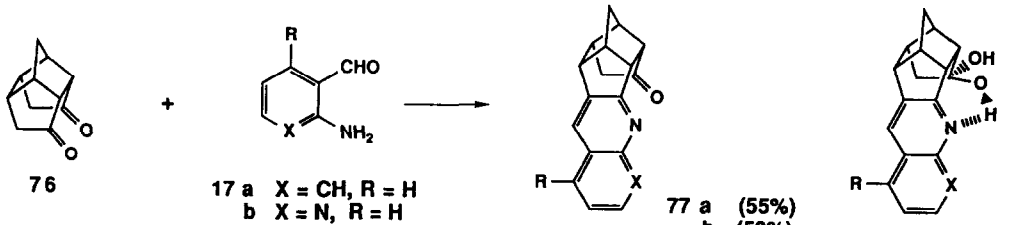
only through its N-H bonds with the carbonyl pointing outward.[47] One of the earliest examples of this type of host-guest binding was a bridged 2,2'-biquinoline derivative shown by Kelly and Maguire to bind uric acid.[57]

6. RIGID *SYN*-ORTHOCYCLOPHANES

The cavity-shaped molecules which we have discussed up to this point have all been comprised of covalently bound aromatic rings linked by polymethylene bridges whose function was to control conformation. The "cavity", as such, lies more or less in the mean plane of the aromatic rings which make up the molecule. This section deals with a different type of cavity in which the aromatic rings comprising the cavity are arranged in approximately parrallel planes rather than in the same plane.

Once again the synthetic strategy relies upon condensation reactions of a diketone with appropriately oriented carbonyl groups, tetracyclo[6.3.0 $0^{4,11}$.$0^{5,9}$]undecane-2,6-dione (TCU-2,6-dione, **76**). This material can be readily prepared in three steps from benzoquinone and cyclopentadiene.[58]

In the process of examining the Friedlander chemistry of **76** we also investigated the methoxy substituted derivatives **17c,d** which may be prepared by reduction of the corresponding nitro compounds. These materials show improved Friedländer reactivity presumably due to the electron donating influence of the methoxy groups as well as their steric inhibition of the competing self-reaction of the aminoaldehyde. As we will see later, their Friedlander products make excellent precursors for 8-hydroxyquinolines and 5,8-quinoline quinones [59]



76

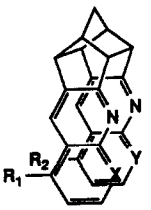
17 a X = CH, R = H
b X = N, R = H
c X = $COCH_3$, R = H
d X = $COCH_3$, R = OCH_3

77 a (55%)
b (50%)
c (90%)
d (80%)

78

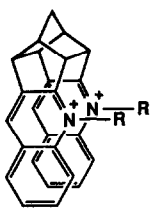
We find that, regardless of the ratio of **17**:**76**, we are only able to obtain the mono-condensation products **77** from the Friedlander reaction under normal conditions. Treatment of the isolated ketones **77** with a second equivalent of **17** then affords reasonable yields of the layered compounds **79**.[60] The stepwise nature of this reaction offers an advantage in making available unsymmetrical species such as **79c,e**. When the reaction is run under Dean-Stark conditions to separate the water formed, the symmetrical doubly condensed compounds **79a,b,d,f** may be obtained directly Our explanation for this unusual behavior is the propensity for the initially formed mono-ketone to hydrate with a water molecule given off

in the first step. As is illustrated in the hypothetical structure **78**, such a hydrate would be stabilized by hydrogen bonding with the quinoline nitrogen. However, we were never able to isolate such a geminal diol.

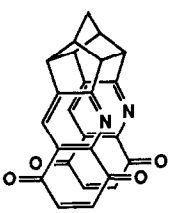


79 a X = Y = CH, $R_1 = R_2 = H$ (57%)
b X = Y = N, $R_1 = R_2 = H$ (60%)
c X = CH, Y = N, $R_1 = R_2 = H$ (40%)
d X = Y = $COCH_3$, $R_1 = R_2 = H$ (58%)
e X = $COCH_3$, Y = CH, $R_1 = OCH_3$, $R_2 = H$ (78%)
f X = Y = $COCH_3$, $R_1 = R_2 = OCH_3$ (90%)

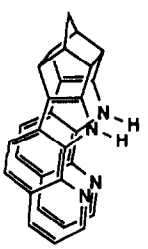
The parent layered quinoline **79a** can be functionalized at nitrogen. Treatment with methyl iodide or 1,3-dibromopropane leads to the diquaternary salts **80a,b** while *m*-chloroperbenzoic acid provides the di-N-oxide **80c**. We have examined the reduction of **80a** by cyclic voltammetry and find that the two N-methylquinolinium moieties reduce independently at potentials of -0.72 and -1.10 V which clearly bracket the value of -0.90 V for N-methyl-2,3-cyclopentenoquinolinium bromide.[59]



80 a R = CH_3
b R = $CH_2CH_2CH_2$
c R = O^-



81



82

When the tetramethoxy species **79f** is treated with ceric ammonium nitrate in the presence of the catalyst 2,6-picoline dicarboxylic acid N-oxide, the methoxy groups can be oxidatively cleaved to directly afford the layered quinoline quinone **81** in good yield.

TCU-2,6-dione is also amenable to Fischer indole cyclizations. Treatment of **76** with **67** affords the corresponding bis-hydrazone which upon heating with PPA cyclizes to give the layered pyridoindole **82** Treatment of this molecule with two equivalents of palladium 2,4-pentanedionate effects two cyclopalladations analagous to what is observed in compound **73**. The palladium acetonylacetonate moieties lie in approximately parallel planes but the metals do not appear to interact strongly with one another.[61]

An x-ray structure analysis of **79a** indicates that the mean planes of the two quinoline rings are not really parrallel but rather describe a dihedral angle of 50.5°. Furthermore these rings are bridged between their nitrogens by a hydrogen bonded water molecule which persists even after sublimation This water bridge causes the quinolines to be canted slightly toward one another such that the N-N distance is 3.65 Å while the corresponding C_4-$C_{4'}$ distance is

3.81 Å. The distance between the outermost carbons on each ring increases to about 6.84 Å All these structural features are extremely well reproduced by a simple molecular mechanics treatment[6] which, even without the H-bonded water, varies no more than .05 Å in its interquinoline distances. For this reason we feel that other similar systems can be faithfully simulated by such calculations.

Besides the obvious objective of using these TCU derivatives to orient species such as metals in parallel planes, we also hoped to examine the feasibility for intercalation of a guest into the hydrophobic region between the aromatic rings. A likely guest would be an *n*-phenylalkyl amine where the amino group could H-bond between the quinoline nitrogens and the phenyl moiety could sandwich between the benzo portions of the quinoline rings. Examination of a series of such guests did not evidence any intercalative binding due most likely to the narrowness of the hydrophobic cavity.

The crystal packing diagram for **79a** illustrated in figure 12 sheds more light on this situation. The molecules are arranged in a ΛVΛVΛV fashion which allows for convenient stacking of the aromatic rings. Furthermore the benzo-portion of one quinoline ring is pointing directly toward the cavity of a facing molecule in a clear attempt to intercalate. Efforts are currently underway to construct the benzoquinoline analog of this molecule where the cavity size should be sufficiently large to allow intercalative binding.

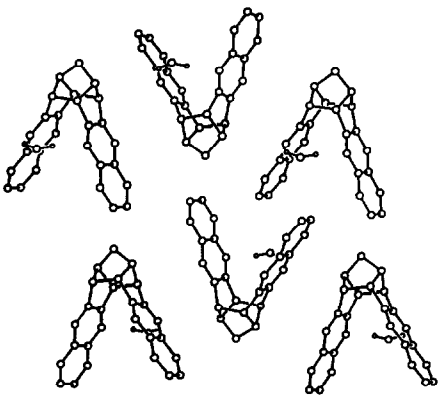
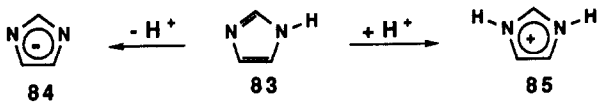


Figure 12. Crystal packing diagram for 2,3;6,7-bis(2',3'-quinolino)TCU (**79a**) Hydrogens have been omitted for clarity. Reprinted with permission from ref. 59. Copyright (1991) American Chemical Society

7. BRIDGED 2,2'-BIIMIDAZOLES

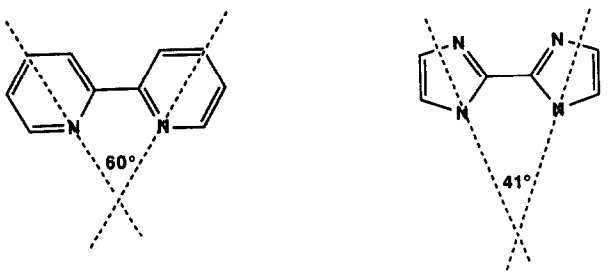
As an aromatic nucleus, imidazole is intriguing in that it can exist as a protonated or deprotonated species while retaining its aromaticity. Both charged forms exhibit symmetry which is lacking in the parent molecule. When these species are incorporated in the dimeric analogue, 2,2'-biimidazole (**86**), several important applications become apparant. The biimidazolium dication may behave as an effective two electron acceptor analogous to **30** while the corresponding dianion possesses two bidentate chelating sites and might serve as a bridging ligand.

The five-membered rings of **86** present a 1,4-diaza system that differs geometrically from what one finds in 2,2'-bipyridine. Measurements from Dreiding models indicate that the chelation angle for **86** is only 41° as compared with an angle of 60° for bpy meaning that its

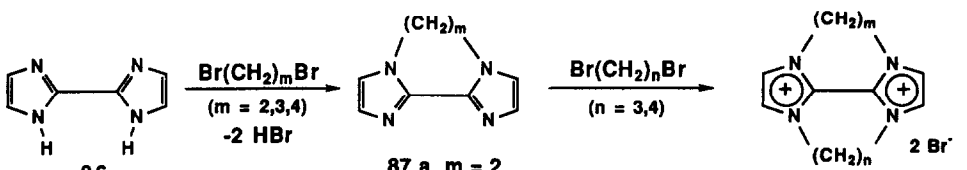


84 83 85

participation in octahedral complexation should be affected. Furthermore, assuming that the 2,2'-bond length is the same for both molecules, the N,N'-distance for **86** is greater than for bpy. Bridging between these sites should be affected and the dihedral angle between the imidazole rings in bridged systems would be reduced. MMX calculations predict an angle of 41° for **87c** as compared with that of 58° predicted for **4d**.



The preparation of bridged derivatives of 2,2'-biimidazole is considerably more straightforward than in the case of bpy. Treatment of **86** with one equivalent of 1,n-dihaloalkane in the presence of base leads to the neutral species **87**.[62] Reaction with a second equivalent of 1,n-dihaloalkane quaternizes the two basic nitrogens of **87** and provides the diquaternary salts **88**.[63] Due to the increased N,N'-distance, the shortest doubly bridged system which can be prepared is **88a**. Treatment of **87a** with 1,2-dihaloethane did not provide the salt **88** having m = n = 2. For the case of 2,2'-bibenzimidazole, the salt **89** has been reported, although in yields of only 30-43%.[64] Hünig has commented on the difficulty of preparing this salt by the direct treatment of 2,2'-bibenzimidazole with 1,2-dibromoethane.

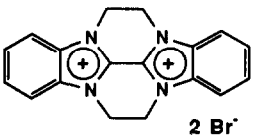


86

87 a m = 2
b m = 3
c m = 4

88 a m = 2, n = 3
b m = 2, n = 4
c m = n = 3
d m = 3, n = 4
e m = n = 4

One might expect that annulation of a benzo-ring at the 4,5-position of **86** would cause an increase in the N_1-C_2-N_3 bond angle, leading to a decrease in the N,N'-distance, which, in turn, would enable more facile bridging.



89

The sensitivity of these systems to the N,N'-distance is well demonstrated by the tetramethylene-bridged species **87c** which, unlike its bipyridine analog **4d**, is found to be conformationally mobile at room temperature on the NMR time scale.[63] Cooling a sample of **87c** to -70°C causes the two original signals at 1.96 and 3.90 ppm to split into four while the imidazole protons remain unchanged (figure 13). From this experiment we can estimate a coalescense temperature of -55°C and thus calculate the free energy of activation for the conformational inversion process to be 10.6 Kcal/mole. This lower barrier should mean that these systems are better able to attain the planar conformation preferred for bidentate coordination. Both **87b** and **87c** are able to form tris-complexes of the type RuL_3^{2+}. The most planar system **87a** cannot form such a tris-complex because now the dimethylene bridge pulls the two coordinating nitrogens away from one another creating a very unfavorable bite angle.[65]

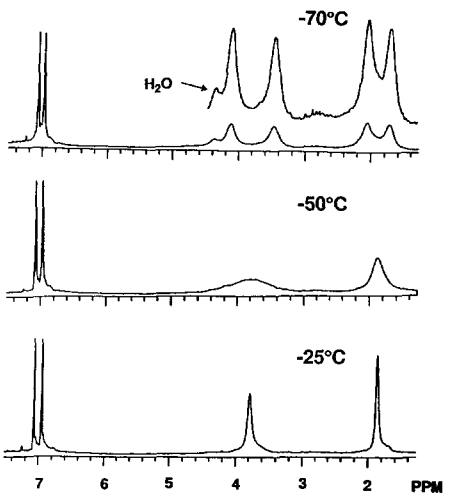
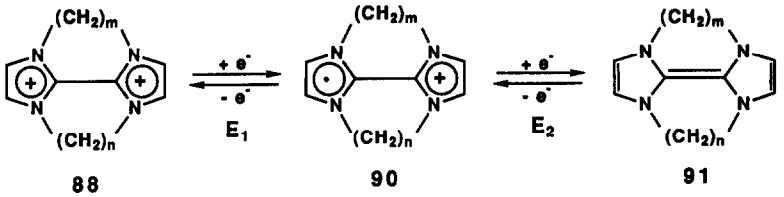


Figure 13 Variable temperature 300 MHz ^1H NMR study of 1,1'-tetramethylene-2,2'- biimidazole (**87c**) in $CDCl_3$ Reprinted with permission from ref. 63 Copyright (1989) American Chemical Society

As was the case for the N,N'-bridged bipyridinium salts mentioned earlier, the doubly-bridged biimidazolium salts **88** can also undergo two one electron reductions. The addition of one electron will generate the radical cation **90** and the second electron will produce the neutral species **91** This fully reduced species is interesting because it is a derivative of tetraaminoethylene. Such molecules are useful because of their very low ionization potentials. Furthermore **91** is an aza analogue of tetrathiafulvalene (TTF) which is an important electron donor in many charge transfer systems. An important feature of **90** and **91** are the bridges which should allow for mediation of their redox properties.



88 90 91

We find that as the system **88** becomes less planar, its reduction is shifted to more negative potential. This shift indicates that **90** and **91** are less stable when deprived of a more delocalized, planar structure. The less planar systems also show poor reversibility as is illustrated in figure 14. Only the first reduction for **88b** is clearly reversible, while **88c** shows only one quasi-reversible wave, and **88d** shows a single irreversible wave (in DMSO). In all these cases, the reduction potentials are too negative to allow for the isolation of a stable radical cation or neutral species.[63]

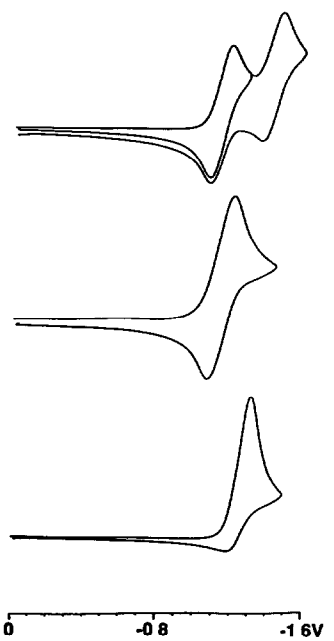
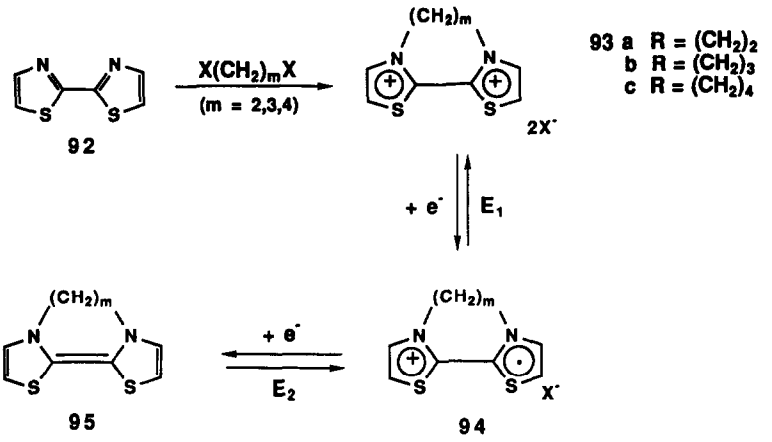


Figure 14 Cyclic voltammograms of bimidazolium salts **88b** (top), **88c** (middle), and **88d** (bottom) in DMSO containing 0.1 M TBAP at 25°C with a sweep rate of 200 mV/sec Reprinted with permission from ref 63 Copyright (1989) American Chemical Society

We were able to mediate these reduction processes by the preparation of bridged 2,2'-bithiazolium salts **93** which are intermediate in structure between the bimidazolium salts **88** and the tetrathiafulvalinium dication.[66] Thus treatment of 2,2'-bithiazole (**92**) with 1,n-dihaloalkanes resulted in the formation of the bithiazolium salts **93**.

Table 6 compares the redox behavior for several of the diquaternary salts discussed thus far. In particular, notice that both reduction potentials for **93a** appear almost midway between the comparable potentials for **88a** and the TTF dication. It appears that the redox properties of these systems can be tailored by judicious choice of the heteroatom and control of planarity via bridging.



The radical cations **94a,b** are both reasonably stable as their hexafluorophosphate salts and exhibit a strong ESR signal in acetonitrile solution. The tetraphenylborate of **94a** is air stable and efforts are currently underway to obtain crystals of these materials for structural analysis and conductivity measurements.

Table 6. Reduction Potentials Measured by Cyclic Voltammetry[a]

Compound	E_1	E_2
93a	-0.50 (100)	-0.13 (100)
93b	-0.57 (85)	-0.13 (85)
93c		-0.42 (320)
88a	-1.38 (110)	-1.14 (50)
33 (m = n = 2)	-0.89 (80)	-0.39 (80)
TTF	+0.33[b]	+0.77[b]

(a) Potentials, given in the oxidative direction to be consistent with other literature values, are in volts vs SCE for saturated solutions in DMSO, 0 1 M in TBAP recorded at 25±1°C at a scan rate of 200 mV/sec The difference between cathodic and anodic peak potentials (mV) is given in parenthesis (b) Measured in CH_3CN, reference 67

8. SUMMARY AND FUTURE DIRECTIONS

The work described here has been concerned with three particular aspects of polyaza cavity-shaped molecules: design, synthesis, and function. From the design viewpoint we have focussed on azapolyaryl systems having nitrogens positioned inside the cavity of the molecule

Polymethylene bridging between covalently bound azaaromatic rings has been employed to control the conformations of these systems. For the most part, the bridge lengths were determined by the ring size of a cyclic ketone in an early phase of the synthetic sequence. The carbonyl groups of ketones such as **7**, **9**, **37**, and **76** are oriented in such a way as to dictate the conformation of their eventual condensation products. The synthetic sequences have been purposely kept simple, relying primarily on Friedländer condensations to build up pyridine, quinoline, and 1,8-naphthyridine rings; and Fischer cyclizations to prepare indoles, pyridylindoles, and pyridoindoles. Other more straightforward bridging procedures leading to N,N'-bridged systems have been exploited whenever possible.

The physical properties of these cavity-shaped molecules have been explored particularly with regard to the influence of conformation on such features as light absorption, basicity, and NMR shielding and deshielding. Most importantly the effects of ligand conformation on chelation have been examined and more elaborate systems such as **46**, **60**, **62**, and **82** have been used to incorporate two metals in specifically controlled environments. The use of 1,4-diaza sites for chelation has not been limited to pyridine nitrogens Phenylpyridines and pyridylindoles such as **27** and **64** have been used to chelate metals via participation of C-H or N-H bonds. Indoles operating in concert with pyridines have been used to sequester organic substrates via the formation of host-guest complexes. A detailed discussion of how both electronic and steric effects can be used to specifically tune the photochemical and electrochemical properties of transition metal complexes is beyond the scope of this review but suffice it to say that such effects are both regular and predictable [68] A wide variety of quinones such as **81** are currently under investigation along with diquaternary salts such as **33**, **88**, and **93** as potential mediators in electron transfer processes.

The future looks bright. We have prepared and are exploring in detail three types of molecular components. tunable transition metal complexes, host-guest systems capable of acting as substrate binding sites, and reversible electron transfer mediators. Using principles being developed in the rapidly expanding field of supramolecular chemistry, we hope to bring these components together to construct molecular devices capable of accomplishing useful chemistry.

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