using $Pd(dppf)(OAc)_2$ as catalyst. Filtration of the crude product through silica gel (300 mL) using EtOAc (500 mL) as solvent and flash chromatography using EtOAc as eluant followed by sublimation at 0.01 mm (bath temperature 80 °C) gave 1.90 g (89%) of **26** as white needles: mp 98–99 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 7.46 (dd, 1 H, J = 5 Hz, J = 9 Hz), 7.95 (d, 1 H, J = 9 Hz), 8.5 (t, 1 H, J = 2 Hz), 8.7 (d, 1 H, J = 5 Hz), 8.9 (d, 1 H, J = 2 Hz), 9.02 (d, 1 H, J = 2 Hz), 9.25 (d, 1 H, J= 2 Hz). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71, N, 13.08. Found: C, 67.58; H, 4.74; N, 13.05.

Methyl [3,4′-bipyridine]-5-carboxylate (27): from 2.2 g of methyl 5-bromonicotinate **25** and 2.5 g of 4-pyridineboronic acid[18] using $Pd(dppf)(OAc)_2$ as catalyst. Filtration of the crude residue through 200 mL of silica gel using 2 L of EtOAc and flash chromatography using EtOAc as eluant followed by sublimation at 0.01 mm (bath temperature 100 °C) gave 1.58 g (74%) of **27**: mp 122–124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 7.56 (d, 1 H, M = 7 Hz), 8.55 (t, 1 H, J = 2 Hz), 8.75 (d, 1 H, J = 7 Hz), 9.08 (d, 1 H, J = 2 Hz), 9.3 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{12}H_{10}N_2O_2 \cdot 0.1H_2O$: C, 66.72, H, 4.67; N, 12.98. Found: C, 66.73; H, 4.69; N, 12.75.

3-Bromo-2,4-dimethyl-6-methoxypyridine-5-carbonitrile (29). To a stirred solution of 0.98 g of sodium in 25 mL of absolute MeOH at 25 °C was added 6.63 g of 6-chloro-3-bromo-2,4-dimethylpyridine-5-carbonitrile[7] in 150 mL of absolute MeOH. After stirring at 25 °C for 16 h, 4 mL of glacial AcOH was added. The mixture was concentrated to dryness, taken up in 200 mL of CH_2Cl_2, washed with H_2O (50 mL) and saturated NaCl (50 mL), and dried over $MgSO_4$. After concentrating to dryness, the crude orange solid (6.81 g) was purified by flash chromatography eluting with 1:3 $CHCl_3$/hexanes. Recrystallization from Et_2O–hexanes gave 3.35 g (71%) of white prisms: mp 95–98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3 H), 2.65 (s, 3 H), 4.01 (s, 3 H). Anal. Calcd for $C_9H_9BrN_2O$: C, 44.84; H, 3.76; N, 11.62. Found: C, 45.04; H, 3.65; H, 11.41.

2,4-Dimethyl-6-methoxy-[3,4′-bipyridine]-5-carbonitrile (30). To a solution of $Pd(dppf)(OAc)_2$ (from 115 mg of $PdOAc_2$ and 276 mg of dppf) in 8 mL of DMF under N_2 atmosphere were added 1.2 g of **29**, 1.12 g of 4-pyridineboronic acid,[18] and 2.1 mL of Et_3N. The mixture was warmed to 90 °C for 27 h and then concentrated to dryness by short path distillation of the solvents. The black residue was dissolved in $CHCl_3$, washed with dilute aqueous NH_3 and saturated brine, and dried over Na_2SO_4. The crude product (1.56 g) was purified by flash chromatography, eluting with 2:3 Et_2O/hexanes. Recrystallization from heptane gave 263 mg (22%) of colorless crystals: mp 143–144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 2.22 (s, 3 H), 4.07 (s, 3 H), 7.10 (dd, 2 H, J = 5 Hz. J = 1 Hz), 8.74 (dd, 2 H, J = 5 Hz, J = 1 Hz); UV (MeOH) max 237 (ϵ 13 600) and 296 nm (ϵ 9100).

1,6-Dihydro-2,4-dimethyl-6-oxo-[3,4′-bipyridine]-5-carbonitrile (31). A solution of the methoxybipyridine **30** (101 mg, 0.424 mmol) in 2 mL of concentrated HCl was warmed to 100 °C for 1 h. The mixture was filtered, diluted with EtOH, and allowed to cool. The white solid which precipitates was collected by vacuum filtration and dried. Recrystallization from 1 N ethanolic HCl gave 95 mg (85%) of white crystalline **31** as the hydrochloride salt: mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6)[19] δ 2.06 (s, 3 H, C_2-methyl), 2.09 (s, 3 H, C_4-methyl), 7.82 (d, 2 H, J = 6.4 Hz), 8.92 (d, 2 H, J = 6.4 Hz); IR (KBr) 3450, 3100, 2920, 2860, 2220 (CN, s), 1660, 1620, 1540, 1510, 1450, 1380, 1300, 1240, 1210, 1080, 960, 810 cm^{-1}, ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.22, 20.11, 100.41, 115.76, 115.84, 128.27, 144.06, 149.52, 150.61, 157.80, 159.92; UV (MeOH) max 270 (ϵ 6700) and 345 nm (ϵ 10 300). Anal. Calcd for $C_{13}H_{11}N_3O \cdot HCl$: C, 59.66; H, 4.62; N, 16.06. Found: C, 60.00; H, 4.52; N, 16.25.

Acknowledgment. We thank Dr. Paul S. Anderson for his support and encouragement during this investigation.

Supplementary Material Available: Full experimental details including NMR data for compounds **8–19** (4 pages). Ordering information is given on any current masthead page.

(19) The methyl resonances at 2.06 and 2.09 ppm were assigned on the basis of long range heteronuclear correlations using 2-dimensional carbon–proton correlation experiments. The 2.06-ppm methyl group correlated with two carbons (115.76 and 149.52 ppm) while the 2.09-ppm methyl group correlated with three carbons (100.41, 115.76, and 157.80 ppm). Thus, the 2.06-ppm resonance is due to the C_2-methyl group, and the 2.09-ppm resonance is due to C_4-methyl group. The authors thank Drs. Steve M. Pitzenberger and Sandor L. Varga for both providing these spectral assignments and performing the NMR experiments.

(20) For a detailed experimental section, see the paragraph at the end of the paper about supplementary material.

Synthesis and Complexing Properties of Macrocycles Incorporating 2,2′-Biindazolyl Binding Subunits

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Substituted 2,2′-biindazoles **4** and **19–23** were prepared in 80–90% yields by thermal decomposition of *o,o′*-diazido azines **13–18**, which in turn were readily obtained from the corresponding 2-azidobenzaldehydes or 2-azidobenzophenones. The preference of these N,N′-linked azolyl dimers for an almost orthogonal conformation was clearly demonstrated by the strong deshielding of the H-3 signal in ^1H NMR spectra. Appropriate substituted indazolyl models were used for the full assignment of ^1H and ^{13}C NMR signals. The chemistry of 2,2′-biindazoles appears to be mainly governed by the ease of cleavage of the interconnecting N–N bond under reducing or strongly acidic conditions. Analogously, cine substitution to position 3 of one ring, with simultaneous loss of the other moiety, acting as a leaving group, was observed in 7,7′-dinitro derivatives. Despite these limitations, dimethyl derivatives **21**, **23**, and **38** were useful starting materials for 2,2′-biindazolyl-containing macrocycles **50–60** via NBS bromination (50–68% yield) and reaction with the disodium salt of tetraethylene glycol (9–17% yield). The sodium cryptate of the macrobicycle **61** was similarly obtained from the bis(bromomethyl) derivative **56** in a 63% yield, without high dilution techniques. ^1H NMR techniques and ion-transport experiments across a bulk $CHCl_3$ phase were used to evaluate the coordination properties of macrocycles **58–60**. Na^+ and K^+ ions coordinate on the crown moiety of **58**, as well as Hg^{2+}, whereas the $PdCl_2$ complex showed the expected coordination by the indazolyl nitrogen atoms. Alkali-metal ions were transported at moderate rates by **58–60**, and a high Na^+/Li^+ selectivity was observed for **60**. An allosteric effect was demonstrated on the complex **58**·$PdCl_2$, in which conformational changes induced by complexation caused transport rates by the crown to be lowered, without inversion of the K^+/Na^+ selectivity.

It is well-known that substitution of donor atoms in macrocyclic ligands causes important changes in their complexation behavior. In particular, introduction of nitrogen atoms belonging to heteroaromatic subunits

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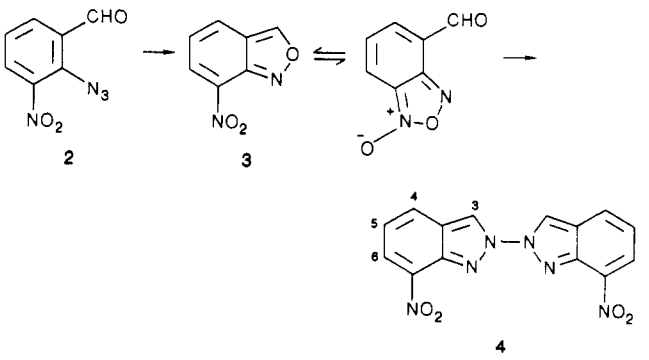
greatly enhances stability constants toward transition metals. Therefore, pyridine,[1] 2,2′-bipyridine,[2] 1,10-phenanthroline,[3] and terpyridine[4] subunits have been widely employed in the design of abiotic receptors. Of particular interest are macrobicyclic assemblies incorporating bipyridine and phenanthroline groups, combining within the same molecule both the inclusion properties of cryptands and the photoactivity of some of their complexes in electronic transfer processes.[5]

In contrast, receptor molecules having five-membered nitrogen heteroaromatics have been employed only occasionally in host–guest chemistry.[6,7] This is somewhat surprising, since azoles, besides common characteristics with pyridine and other azines (as are their good complexing ability and their wide range of basicities), have some unique properties not shared by other aromatic compounds. In particular, the tautomeric equilibria and the presence of acidic N–H protons, which could be useful in the design of proton-ionizable receptors.[7] Substitution of the N–H bond by a N–X bond is another consequence of the structural features of azoles, for it can only be introduced in pyridine and azines through quaternization of the aromatic ring. In that way, long-chain hydrophobic side arms or functionalized groups could be introduced into the receptor framework.

In this context, azolyl dimers linked through their pyrrolic nitrogen atoms are endowed with some peculiar properties that make them essentially different from 2,2′-bipyridines and analogues. Apart from the geometries of coordination, especially angles and distances, N,N′-linked biazoles differ from 2,2′-bipyridines in conformation as free ligands. For example, the free 2,2′-bipyridine most stable conformation takes place at a planar, anti conformation,[8] whereas in N,N′-linked biazoles the most stable form lies at an angle close to orthogonality.[9] An important consequence is that rings behave independently from each other, with little or no conjugation across the internuclear linkage. One advantage of this independency is the conservation of the basicity and coordinating properties of each heterocycle.

Scheme I



From the synthetic point of view, some of these dimers can be assembled rapidly. One example is 2,2′-biindazole (**1**), a close analogue of the 2,2′-bipyridine family. This article deals with the synthesis of a series of 2,2′-biindazoles functionalized in suitable positions for host design and the preparation and preliminary survey of properties of some crown derivatives.

Results and Discussion

Synthesis of 2,2′-Biindazoles. The first 2,2′-biindazolyl derivative was reported in 1961 by Joshi and Gambhir, who claimed the preparation of the 6,6′-dinitro derivative by reaction of 6-nitroanthranil with hydrazine acetate.[10] This result was questioned by Boulton 16 years later, for he was unable to reproduce the reaction.[11] In contrast, the reaction of hydrazine with 7-nitroanthranil (**3**), prepared from 2-azido-3-nitrobenzaldehyde (**2**), was straightforward and led to 7,7′-dinitro-2,2′-biindazole (**4**) in a 30% yield. This seemed to indicate the participation of the nitro group in helping the N–O bond of 7-nitroanthranil to be cleaved by isomerization to 4-formylbenzofuran *N*-oxide (Scheme I).[11]

The parent 2,2′-biindazole (**1**) can be easily obtained by a double nitrene insertion to azine derivatives. Yields were found to be much better when nitrenes were generated from thermal decomposition of the corresponding azides (**5** → **1**, or **5** → **6** → **1**, see Scheme II)[12] than from triethyl phosphite reduction of nitro derivatives (**7** → **1**).[13]

Thus, compounds **4** and **19–23** were obtained in high yields by thermal decomposition of the azines **13–18**, which in turn were prepared from the corresponding carbonyl compounds **2** and **8–12** (Scheme II).

By this method, 7,7′-dinitro-2,2′-biindazole (**4**) was obtained in a 73% overall yield, instead of the 13% reported by Boulton from the same aldehyde **2** (Scheme I).[11] In agreement with the Krbechek results, a mixture of indazole **24** and biindazole **22** was obtained when the azine **17** was heated for 1 h at 150 °C. **24** was easily transformed by further heating into **22** (80%).

Catalytic reduction of the dinitro derivative **19** afforded the corresponding 7,7′-diamino-2,2′-biindazole (**25**). Azines **13–18** were prepared from the acid-catalyzed reaction of

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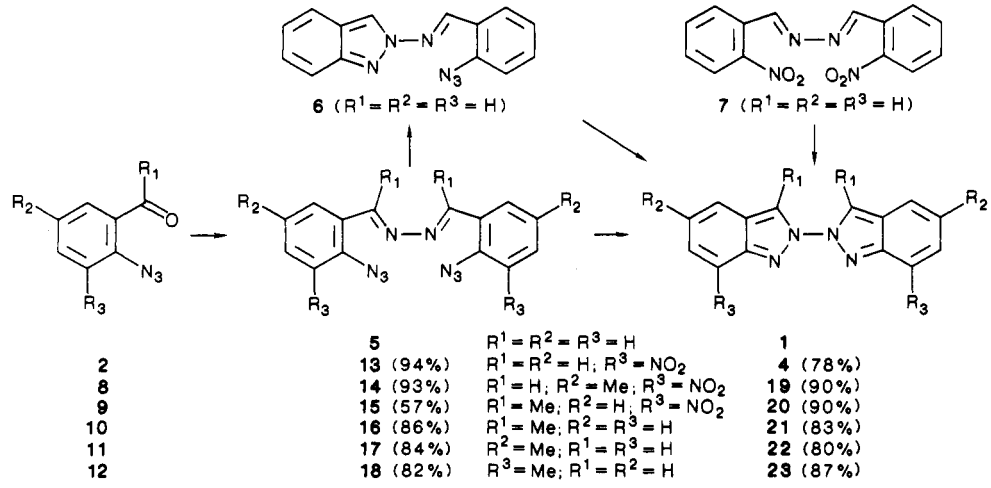
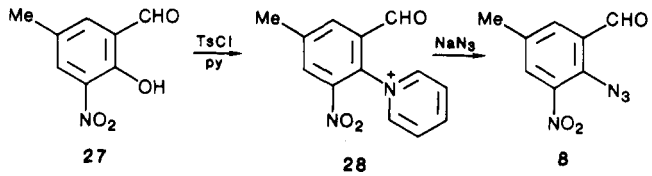
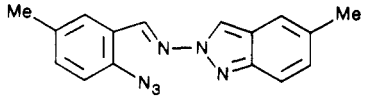
Scheme II

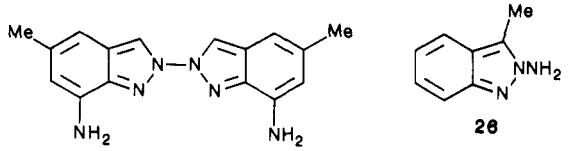


Scheme III



the adequate 2-azidobenzaldehyde (**2**, **8**, **11**, and **12**) or 2-azidoacetophenone (**9** and **10**) derivatives with hydrazide hydrate, in high yields. In the absence of acid catalyst, the reaction of 2-azidoacetophenone (**10**) with hydrazine afforded, beside the expected azine **16**, significant amounts of 2-amino-3-methylindazole (**26**). The formation of this material can be rationalized by the nitrene insertion on the hydrazone derivative of **10**.



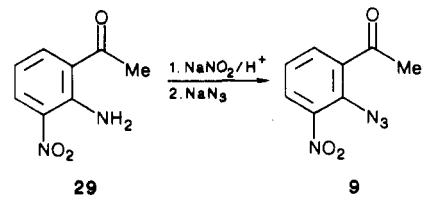


For the synthesis of 2-azido-5-methyl-3-nitrobenzaldehyde (**8**) from 5-methyl-3-nitrosalicylaldehyde (**27**), the method developed by Boulton for the synthesis of **2** was employed,[11] the azido group being introduced in a 69% overall yield by a double nucleophilic substitution of the tosyl derivative of **27** (Scheme III). However, when the same reaction was attempted on 3-nitro-2-hydroxyacetophenone a complex mixture resulted, in which the expected azide **9** was a minor product. The preparation of **9** was carried out by reaction of the diazonium salt of 2-amino-3-nitroacetophenone (**29**) with sodium azide (Scheme IV).

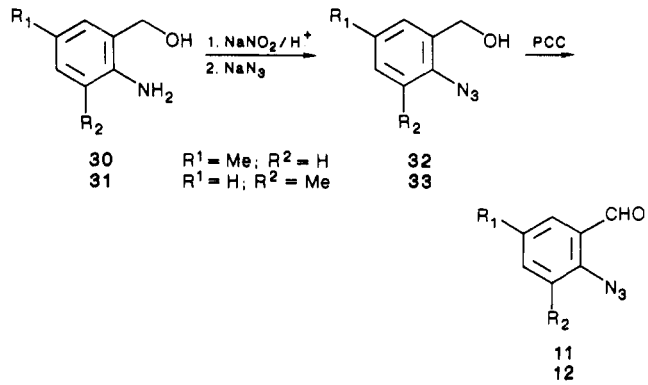
The same reaction was employed to prepare the azides **11** and **12** from 2-amino-5-methyl- and 2-amino-3-methylbenzyl alcohols (**30** and **31**) as starting materials, with overall yields of 76% and 69%, respectively (Scheme V). Alternatively, the introduction of the azido group could be delayed to the last step, using an oxime to protect the aldehyde function.[14] However, the overall yield of such

(14) Bamberger, E.; Demuth, E. *Chem. Ber.* **1901**, *34*, 1334.

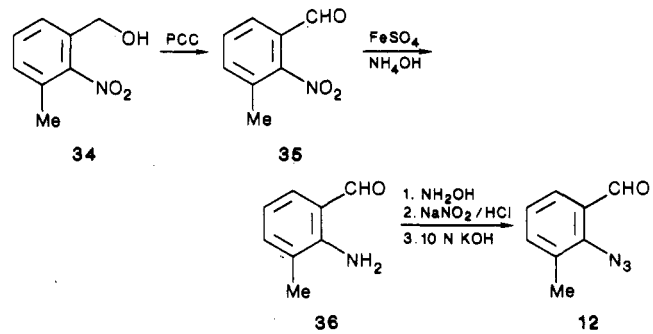
Scheme IV



Scheme V



Scheme VI



a sequence to obtain **12** from 3-methyl-2-nitrobenzyl alcohol (**34**) was only 4.9% (Scheme VI), and the reaction sequence of Scheme V was therefore preferred.

Finally, the reaction of 2–azido-3-methylbenzaldehyde (**12**) with 2-amino-3-methylindazole (**26**) afforded the intermediate **37**, which allowed us to prepare the unsymmetrically substituted 3,7′-dimethyl-2,2′-biindazole (**38**) in a 83% yield (Scheme VII).

NMR Study of 2,2′-Biindazoles. No NMR data have been so far reported in the literature for 2,2′-biindazoles.

Table I. ^{1}H NMR Data for 2,2'-Biindazoles and Related Structures

compd	solvent	H-3	H-4	H-5	H-6	H-7	CH_3	J_{4-5}	J_{6-7}	J_{5-6}	J_{4-7}	J_{4-6}	J_{5-7}	J_{3-7}
39	$CDCl_3$	7.67	7.56	7.02	7.22	7.68	3.80	8.3	8.5	6.7	1.0	1.1	0.8	0.8
	DMSO-d_6	8.20	7.65	7.00	7.20	7.59		8.5	8.7	6.6	1.0	1.0	0.9	1.0
26	$CDCl_3$		7.50	7.01	7.27	7.54	2.57	8.5	8.8	6.6		1.0	0.7	
	DMSO-d_6		7.58	6.93	7.16	7.43	2.53	8.2	8.5	6.6		1.3	0.8	
40	DMSO-d_6	9.02	7.85	7.24	7.45	7.72		8.6	8.9	6.6	0.9	1.0	0.8	0.9
41	$CDCl_3$	8.15	7.68	7.18	7.38	7.73		8.4	8.7	6.6	0.9	0.9		0.8
	DMSO-d_6	8.81	7.77	7.18	7.38	7.67		8.4	8.8	6.7	1.0	1.0	0.9	0.9
1	DMSO-d_6	9.14	7.85	7.23	7.45	7.76		8.5	8.8	6.7		1.1		
21	$CDCl_3$		7.65	7.16	7.41	7.69	2.49	8.4	8.8	6.5		1.2	0.9	
	DMSO-d_6		7.87	7.19	7.44	7.67	2.42	8.5	8.8			1.0	0.8	
22	$CDCl_3$	8.55	7.47		7.24	7.65	2.45		9.0			1.6		1.0
	DMSO-d_6	8.98	7.64		7.29	7.56	2.41		8.9					
23	$CDCl_3$	8.64	7.56	7.17	7.14		2.65	7.8						
	DMSO-d_6	9.09	7.65	7.13	7.22		2.54	8.1						
25	$CDCl_3$	8.32	6.85		6.40		2.35					1.1		
38	$CDCl_3$													
(3-CH_3 indazole)			7.64		7.39	7.67	2.54		9.0	6.5		1.1		
(7-CH_3 indazole)		8.30	7.56				2.63	9.0						

Table II. ^{13}C NMR Data for 2,2'-Biindazoles and Related Structures

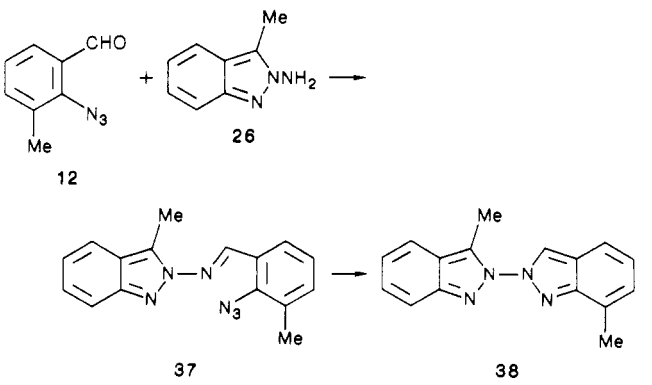
compd	solvent	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_3
39	$CDCl_3$	123.1	121.8	119.6	121.2	125.4	116.8	148.7	39.7
		^1J = 186.5		^1J = 162.5	^1J = 159.0	^1J = 157.5	^1J = 162.5		^1J = 140.0
				^3J = 7	^3J = 8	^3J = 9.5	^3J = 5.5		
	DMSO-d_6	124.3	121.8	120.4	120.9	125.2	116.8	148.3	
26	DMSO-d_6	127.9	119.5	119.2	119.7	124.8	115.8	144.0	9.1
40	DMSO-d_6	125.0	120.5	121.1	123.5	128.3	117.3	146.5	
41	DMSO-d_6	123.0	120.3	120.9	122.8	127.3	117.3	145.8	
1	DMSO-d_6	123.4	120.6	121.3	122.5	128.2	117.4	146.2	
21	DMSO-d_6	133.6	119.0	121.0	122.1	128.4	117.4	146.0	8.8
		^2J = 7.0	*a*	^1J = 162.5	^1J = 161.1	^1J = 160.8	^1J = 165.0	^3J = 10.1	^1J = 132.8
		^3J = 2.0		^3J = 7.6	^3J = 8.0	^3J = 8.4	^3J = 7.1	^3J = 6.1	
		^4J = 1.0			^2J = 1.4	^2J = 1.7	^2J = 1.6	^2J = 0.8	
22	DMSO-d_6	121.1	120.5	118.6	132.1	130.7	117.0	144.8	21.3
23	DMSO-d_6	123.0	120.0	118.2	123.4	126.5	126.8	146.4	16.5
		^1J = 192.3	*a*	^1J = 163.9	^1J = 167.4	*a*	^3J = 6.6	*a*	^1J = 127.3
				^3J = 7.5			^2J = 6.6		^3J = 4.9
25	DMSO-d_6	121.4	121.7	105.3	134.0	107.4	137.8	138.9	22.1
		^1J = 197.8	^2J = 7.8	^1J = 162.6	^2J = 5.8	^1J = 152		*a*	^1J = 125.3
		^3J = 1.5	^2J = 2.8	^3J = 5.5		*a*			
				^3J = 5.5					
38	DMSO-d_6								
(3-CH_3 indazole)		132.9	118.9	120.8	122.0	128.2	117.1	146.9[b]	8.8
(7-CH_3 indazole)		125.2	120.0	118.4	123.6	126.7	127.1	145.3[b]	16.6

[a] Complex multiplet. [b] These assignments could be reversed.

Except for the highly insoluble nitro derivatives **19** and **20**, ^{1}H and ^{13}C NMR spectra were recorded for the rest of 2,2'-biindazoles described above (Tables I and II). Whenever possible, spectra were registered in two solvents ($CDCl_3$ and DMSO-d_6). In order to make the assignment of the signals, data from the model compounds 2-methylindazole (**39**),[15] 2-amino-3-methylindazole (**26**), and the two biazolyl dimers 2-(1,2,4-triazol-4-yl)indazole (**40**) and 2-(1-pyrrolyl)indazole (**41**)[16] were also compiled.

From the ^{1}H NMR study of the model **39**, it is well-known[15a] that in DMSO-d_6 H-4 and H-7 are shifted to higher frequencies than H-5 and H-6. On the other hand, δ(H-7) < δ(H-4), a situation that is reversed when the spectrum is registered in $CDCl_3$.[17] For the assignment of H-5 and H-6, vicinal coupling constants may be used ($^3J_{4,5} < {}^3J_{6,7}$).[15a] The same criteria were used to assign the signals of 2,2'-biindazoles **21–23**, **25**, and **38** (see Table I).

Scheme VII

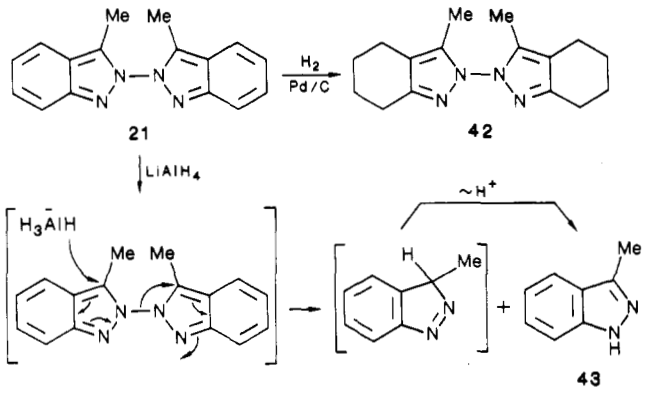


From the ^{1}H NMR data it may be concluded that the N-substituted indazole ring behaves as an electron-withdrawing group, causing most signals of the vicinal subunit to shift toward higher frequencies (compare to 2-methylindazole).

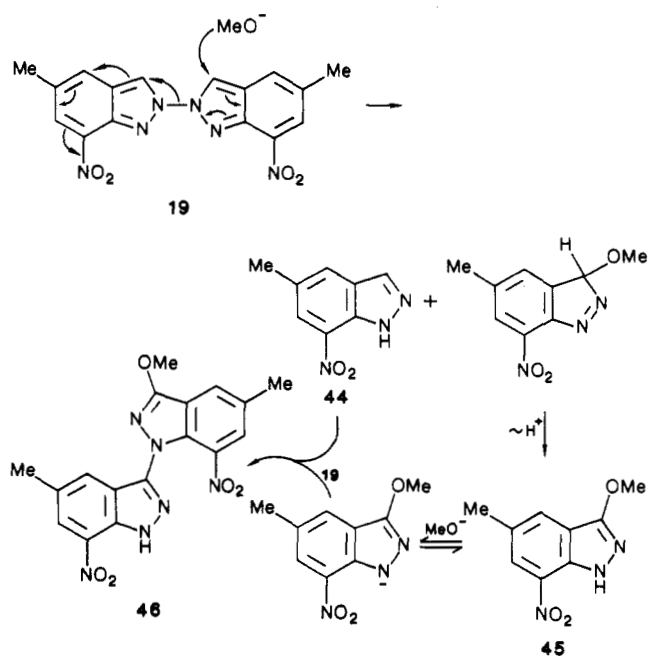
^{13}C NMR data for substituted indazoles are scarce. From the Elguero work on 2-methyl- and 2-acetylindazole,[15] it follows that $^1J_{CH}$ for a carbon atom situated α from a nitrogen atom is higher than $^1J_{CH}$ for a carbon

(15) (a) For ^{1}H NMR data, see: Elguero, J.; Fruchier, A.; Jacquier, R.; Scheidegger, H. *J. Chem. Phys.* **1971**, 1113. (b) For ^{13}C data, see: Begtrup, M.; Claramunt, R. M.; Elguero, J. *J. Chem. Soc.* **1978**, 99. Bouchet, P.; Fruchier, A.; Joncheray, G.; Elguero, J. *Org. Magn. Reson.* **1977**, *9*, 716.
(16) Castellanos, M. L.; Thesis, University of Barcelona, 1984.
(17) Palmer, M. H.; Findlay, R. H.; Kennedy, S. M. F.; McIntyre, P. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1695.

Scheme VIII



Scheme IX



atom on the benzo-fused ring, and that, from all carbocyclic atoms, C-7 is the one with a higher ^1J coupling constant and a chemical shift at a lower frequency.

Proton-coupled spectra were used for the assignments of 2,2′-biindazoles **21**, **23**, and **25** (see Table II). For the rest of compounds, assignments were made by comparison, taking into account the effect produced by a methyl group on the chemical shifts of aromatic protons.

The ^2J coupling constant of the C-3 signal of 3,3′-dimethyl-2,2′-biindazole (**21**) to the methyl protons has a value of 7.0 Hz. This high value has also been found in **23** (C-7, ^2J = 6.6 Hz) and in **25** (C-5, ^2J = 5.8 Hz) and agrees with the values found in the pyrazole series.[18] In the spectrum of **25**, the C-3a signal is coupled both to H-3 (^2J = 7.8 hz) and to H-4 (^2J = 2.8 Hz). The first coupling constant is similar to that found in pyrazoles, whereas the second shows a typical value for a two-bond coupling constant in benzene carbon atoms.[18] Finally, the spectrum of the unsymmetrical dimer **38** was assigned readily, since the chemical shifts of each moiety were quite coincident to the respective signals of both **21** and **23**.

Synthesis of Macrocycles. The chemistry of N,N′-linked biazoles closely resembles that of each bonded heterocyclic ring for the orthogonal conformation around the connecting N–N′ bond prevents conjugation of both rings. One important reaction, however, is the relative fragility of the connecting N–N′ bond under reductive, photolytic, or nucleophilic conditions.[19] Indeed, the only reported reaction on a 2,2′-biindazole was the catalytic cleavage (Raney Ni) of the parent compound **1** to indazole.[12] However, the N–N′ bond can be preserved under milder conditions, as we have already pointed out for the catalytic reduction (Pd/C) of **19** to **25**. Similarly, 3,3′-dimethyl-2,2′-biindazole (**21**) was hydrogenated (Pd/C) to the octahydro derivative **42** (a 1,1′-bipyrazole system) but suffered cleavage to 3-methylindazole (**43**) when the reduction was attempted with $LiAlH_4$ in tetrahydrofuran. The process, which could be reasonably explained by an initial attack of the hydride to position 3 of one of the rings, followed by heterolytic cleavage of the internuclear bond (Scheme VIII), has its precedent in the 1,1′-bibenzotriazole series.[20]

A first group of macrocycles could be developed from nitro derivatives of 2,2′-biindazole via direct substitution with dianions of suitable glycol derivatives. However, a preliminary test with sodium methoxide on 7,7′-dinitro-5,5′-dimethyl-2,2′-biindazole (**19**) afforded a complex mixture of components, none of which was the desired 7,7′-dimethoxy derivative. Column chromatography allowed us the separation of the three main components **44**–**46** in 17%, 15%, and 7% yields, respectively,[21] A rationale for their formation is proposed in Scheme IX. One of the indazolyl moieties acts as a leaving group while the nucleophile enters at position 3 of the other ring. Previous examples of such cine substitution have been observed in N,N′-linked biheteroaryl quaternary salts. For instance, *N*-pyridinium-substituted pyrazolium quaternary salts are transformed by nucleophiles into 1,5-disubstituted pyrazoles, the method having found synthetic interest in the pyrazole series.[19b,22] In this case, both nitro groups appear to be necessary for the reaction to take place (other 2,2′-biindazolyl derivatives were found to be stable to O-nucleophiles, see below): one activating a ring toward the addition of the methoxy anion, and the other activating the neighboring ring as a leaving group (see Scheme IX).

A second family of macrocyclic structures could arise from the alkylation of a protected and activated derivative of 7,7′-diamino-3,3′-dimethyl-2,2′-biindazole (**25**). Thus, the ditosyl derivative **47**, which was obtained quantitatively from **25**, was treated with sodium hydride (2 equiv) to give the dianion, which was alkylated either with the tosyl derivative of 2-methoxyethanol or with the ditosylate of tetraethylene glycol (dimethylformamide, 110 °C, no high-dilution conditions), affording the biindazolyl podand **48** and the coronand **49** in 56% and 16% yield, respectively (Scheme X). Unfortunately, all attempts to deprotect the tosyl groups caused the N–N′ bond to be broken. Indeed, reaction of the macrocycle **49** with sodium naphthalenide[23] afforded a mixture of the two secondary amines **50** and **51**, whereas this last compound was the only isolated product when the deprotection was attempted on podand **48** using hydrogen bromide/acetic acid/phenol.[24] The use of

(18) Bruix, M.; Claramunt, R. M.; Elguero, J.; de Mendoza, J.; Pascual, C. *Spectrosc. Lett.* **1984**, *17*, 757.

(19) (a) de Mendoza, J.; Millan, C.; Rull, P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 403. (b) Castellanos, M. L.; Llinàs, M.; Bruix, M.; de Mendoza, J.; Martín, M. R. *Ibid.* **1985**, 1209.

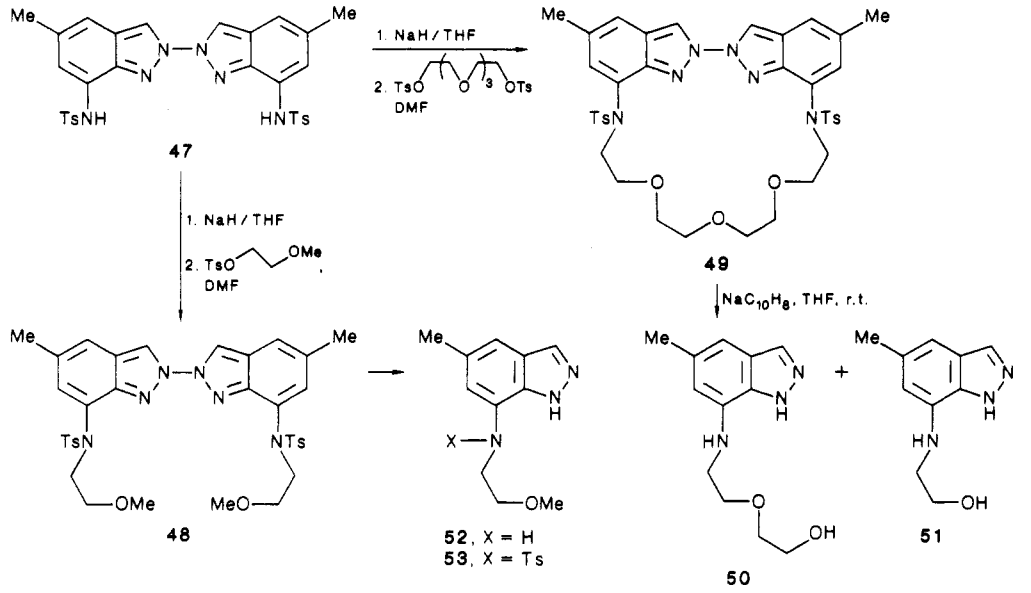
(20) Harder, R. J.; Carboni, R. A.; Castle, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 2643.

(21) All three compounds were fully characterized by routine methods. Only the structure of biindazole **46**, containing a N_1–$C_{3'}$ bond, raised some doubt, for it could have a N_2–$C_{3'}$ bond as well. No attempts were made to ascertain this point.

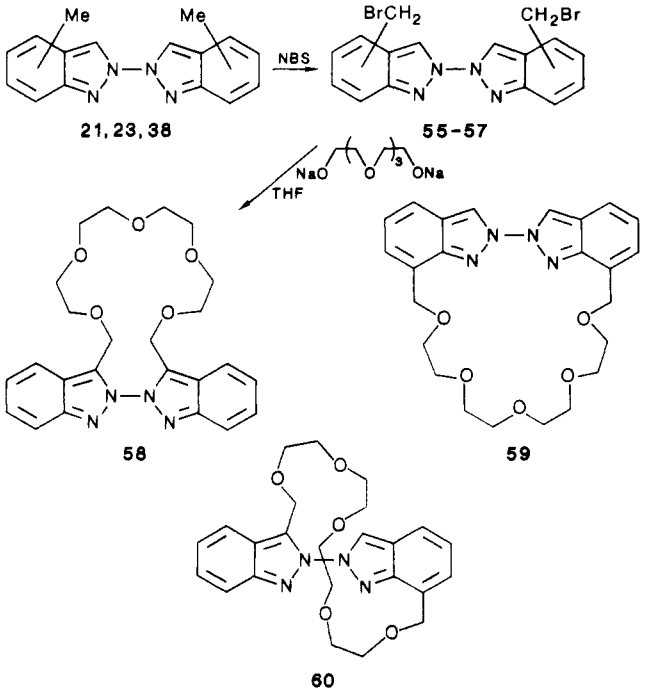
(22) Bruix, M.; Castellanos, M. L.; Martín, M. R.; de Mendoza, J. *Tetrahedron Lett.* **1985**, *26*, 5485.

(23) Biernat, J. F.; Luboch, E. *Tetrahedron* **1984**, *40*, 1927.

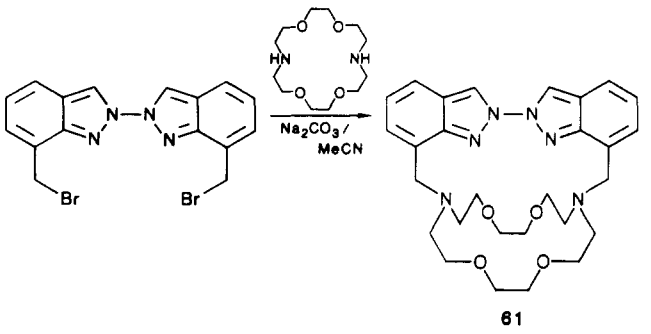
Scheme X



Scheme XI



Scheme XII



$LiAlH_4$[25] on podand **48** afforded either the amine **52** (18–24 h) or the tosylamide **53** (1 h), showing without any doubt that the N–N′ bond was cleaved before the tosyl group had been removed. Finally, hot sulfuric acid was tried on tosylamides **47** and **48**.[26] However, the fragility of the N–N′ bond was again emphasized, and the only isolated products were 7-amino-5-methylindazole (**54**) and 7-[(2-hydroxyethyl)amino]-5-methylindazole (**51**), respectively. Structure **54** was confirmed by an independent synthesis from 5-methyl-7-nitroindazole (**45**).

Dimethyl 2,2′-biindazole derivatives **21**, **23**, and **38** constitute useful starting materials for the synthesis of macrocycles, for they can be easily transformed into the respective bromomethyl derivatives. Thus, reaction with *N*-bromosuccinimide afforded intermediates **55–57** in 50–68% yield (Scheme XI). Coronands **58–60** were prepared in low yield (9–17%) by slow addition (ca. 8 h) of a tetrahydrofuran solution of the bis(bromomethyl)-2,2′-biindazole to a well-stirred suspension of the disodium salt of tetraethylene glycol. No attempts were made to improve yields by changing dilution or reaction time or temperature. On the other hand, reaction of the intermediate **56** with 1,7,10,16-tetraoxa-4,13-diazacyclooctadecane in acetonitrile in the presence of sodium carbonate, without adhering to high-dilution techniques, afforded a 63% yield of cryptand **61** (Scheme XII), isolated as the sodium cryptate. The high yield of this reaction could be ascribed both to a templating effect of the cation and to the relative rigidity of the aromatic part incorporated.

Coordination Properties. Both ^1H NMR techniques and experiments of ion-transport across bulk membranes were used to evaluate the complexation behavior of macrocycles **58–60**. Prior to this work, some 2,2′-bipyridine and biphenyl analogues of **58** were studied by Rebek to test the "allosteric effect", i.e., the conformation change of the crown moiety (which causes a modification in its coordination properties) induced by coordination of a second binding site (the bipyridine nitrogen atoms) to a transition metal.[27] Since the pioneering work of Rebek, no other bipyridine analogues have been investigated for

(24) Snyder, H. R.; Geller, H. C. *J. Am. Chem. Soc.* **1952**, *74*, 4864. Snyder, H. R.; Heckert, R. E. *Ibid.* **1952**, *74*, 2006. Boissons, R. A.; Preitner, G. *Helv. Chim. Acta* **1953**, *36*, 875. Searles, S.; Nukina, S. *Chem. Ber.* **1979**, *59*, 1077. Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.

(25) Pietraszkiewicz, M.; Jurczak, J. *Tetrahedron* **1984**, *40*, 2967.

(26) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2269.

(27) Rebek, J., Jr.; Trend, J. E.; Wattley, R. V.; Chakravorti, S. *J. Am. Chem. Soc.* **1979**, *101*, 4333. For an excellent review on allosteric effects in organic chemistry, see: Rebek, J., Jr. *Acc. Chem. Res.* **1984**, *17*, 258.

Table III. Transport Rates ($\times 10^{-8}$ mol·h^{-1}) of Alkali-Metal Ions across a $CHCl_3$ Phase

compd	Li^+	Na^+	K^+	Rb^+	Cs^+	Na^+/Li^+	K^+/Na^+
DB-18-C-6	0.56	16.71	177.40	169.93	78.67	29.83	10.61
58	0.28	2.42	8.47	10.31	7.37	8.64	3.50
58·$PdCl_2$		0.95	3.50				3.68
59	3.13	10.31	16.58	37.12	44.99	3.29	1.61
60	0.44	27.98	38.25	31.18	12.22	63.59	1.37

the search of improved models. The higher relative rigidity of the biindazolyl derivative **58**[28] as well as its somewhat different geometry was expected to significantly affect its coordination properties. Indeed, the association constant of **58** toward potassium ion, determined by NMR using the Cram extraction method,[29] was found to be midway (log K_a = 4.7) from those described by Rebek, following the same method, for the bipyridine (log K_a = 5.1) and biphenyl (log K_a = 4.5) analogues. The observed changes in the aliphatic signals of the NMR spectra of the sodium and potassium complexes of **58** revealed that the complexation takes place in the crown moiety. On the contrary, the palladium complex **58**·$PdCl_2$ showed the expected complexation by the indazolyl nitrogen atoms.[30] Surprisingly enough, mercury(II) seemed to coordinate preferentially to the crown moiety, since aliphatic signals of **58**·$HgCl_2$ were greatly distorted, whereas aromatic signals showed little variation, as for the alkali-metal complexes.[31]

Alkali-metal complexes of the macrocycles **59** and **60** were also studied qualitatively by ^1H NMR. For **59**, both alphatic and, to a lesser extent, aromatic signals showed changes upon complexation to Na^+ or K^+, according to the structure of the ligand. A similar change was observed for the potassium complex of **60**, but *not* for the sodium complex, for which aromatic protons remained unchanged upon complexation. This may be due to the flexible nature of the ligand: a five-oxygen cavity may form in the sodium complex, without altering the orthogonal conformation of the biindazolyl moiety, whereas a larger cavity is needed to accommodate the potassium ion, with participation of an additional nitrogen atom from the 7-substituted ring, as is clearly shown by CPK model inspection.

Transport rates of alkali-metal ions across a bulky chloroform phase were determined for macrocycles **58–60**, as a measure of their ionophoric ability, and for the complex **58**·$PdCl_2$ (only of Na^+ and K^+ ions) to test the allosteric effect. The results, compared to dibenzo-18-crown-6 under the same conditions (Table III), reveal that **58–60** transport alkali-metal ions at moderate rates. Macrocycle **59** was shown to be the best carrier for big cations, as expected from its larger cavity. The low selectivities found for **58** toward K^+, Rb^+, and Cs^+, as well as for **60** toward K^+ and Rb^+, could be due to their greater flexibility, which allows the cavity to adapt to the size of the cation. The K^+/Na^+ selectivity of **58** (3.50) is quite similar to that reported by Rebek for the bipyridine analogue (3.8).[27] On the other hand, the conformational changes induced by the complexation to a transition metal in **58**·$PdCl_2$ caused transport rates to be lowered, as in the bipyridine case, with a $W(CO)_4$ complex.[27] However, in the biindazolyl system K^+/Na^+ selectivity is not inverted.

Finally, values for macrocycle **60** were moderately high, with both better Na^+/Li^+ selectivity and transport rate of Na^+ than dibenzo-18-crown-8.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were registered on a Bruker WP 200 SY instrument, MS spectra on Hewlett-Packard 5985 and Hitachi Perkin Elmer RMU-6MG (70 eV, EI mode) instruments, and IR spectra on a Perkin Elmer 257 instrument. Abbreviations used are as follows: s, singlet; d, doublet; t, triplet, m, multiplet, br, broad. Elemental analyses were carried out at the Instituto de Química Orgánica General, CSIC, Madrid.

Silica gel (Merck 230–400 mesh) and DC-Alufolien 60 were used for flash and analytical chromatography, respectively. Thin layer plates were visualized by UV light, iodine, or (2,4-dinitrophenyl)hydrazine. Most chemicals were purchased from Aldrich Co. and used as received without further purification. Organic solvents were purified by standard procedures. N,N-Dimethylformamide (DMF) (Carlo Erba) were dried over 3-Å molecular sieves before use. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone and sodium under an argon atmosphere, immediately prior to use.

Transport rates measurements were performed at 25 °C with a glass cell composed of two concentric cylinders[32] containing 50 mL of a $CHCl_3$ solution of the macrocycle (7×10^{-4} M) and two aqueous phases. The source phase (I) consisted of 10 mL of an alkali picrate solution (2×10^{-3} M) and the nitrate of the same cation (10^{-1} M). The receiving phase (II) was made with 12.5 mL of pure water. Samples of phase II were periodically analyzed for picrate content (UV, 355 nm).

2-Hydroxy-5-methyl-3-nitrobenzaldehyde (27). Fuming nitric acid (*d* 1.5, 100 g) was added dropwise to a stirred and cooled (0 °C) solution of 2-hydroxy-5-methylbenzaldehyde[33] (66.30 g). The reaction mixture was poured into crushed ice, and the yellow solid was filtered and washed with water. The crude compound was dissolved in dichloromethane, and the solution was washed with a saturated solution of sodium bicarbonate, dried (Na_2SO_4), and evaporated, to give a residue which was recrystallized in acetic acid: yield 57.00 g (65%); yellow needles, mp 138–140 °C; IR (Nujol) 3260, 1690, 1620, 1580, 1530, 1300 cm^{-1}; MS, *m/z* (relative abundance) 181 (9.0, M^+), 164 (3.6), 163 (21.7), 151 (2.3), 135 (3.2), 134 (13.6), 133 (11.3), 105 (9.5), 77 (19.5), 57 (18.1), 40 (100); ^1H NMR ($CDCl_3$) δ 11.20 (s, 1 H, OH), 10.41 (s, 1 H, CHO), 8.12 (br s, 1 H, H-4), 7.89 (br s, 1 H, H-6), 2.41 (s, 3 H, CH_3). Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.11; H, 3.96; N, 7.84.

2-Azido-5-methyl-3-nitrobenzaldehyde (8). Tosyl chloride (2.20 g, 11 mmol) in pyridine (12 mL) was added to 2-hydroxy-5-methyl-3-nitrobenzaldehyde (**27**) (1.65 g, 9 mmol) in pyridine (6 mL). Yellow tosylate crystals were formed as soon as the slightly exothermic reaction ceased. The reaction mixture was heated at 90 °C for 2 h, and then the excess pyridine was removed

(28) The chiral nature of **58** was revaled by its ^1H NMR spectrum. Contrary to the Rebek bipyridine analogue, where the benzylic protons of the crown system appeared as a singlet, the structure being fixed only upon complexation,[27] an AB system was already observed in the free ligand **58**, a fact that could be explained by the impossibility of each indazolyl ring to rotate and pass through the crown cavity.

(29) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.

(30) The low field effect of the metal on the benzylic methylene signals (one doublet was deshielded by ca. 1 ppm) is noteworthy and has no parallel in the bipyridine analogue (a broad singlet).[27] This is indicative of the nonplanar conformation of **58**·($PdCl_2$). On the other hand, the complex was found to be stable in chloroform solution. Addition to the solution of small quantities of the free ligand **58** revealed that the Pd exchange was slow in the NMR timescale (two well separated spectra). However, important changes were observed after few hours, demonstrating the formation of new species in the solution.

(31) In good agreement with this behavior was the observation that Hg(II) was unable to give any definite complex with the model compound 3,3'-dimethyl-2,2'-biindazole (**16**).

(32) For a full description of the cell, see: Samat, A.; El Malouli-Bibout, M.; Chanon, M.; Elguero, J. *Nouv. J. Chim.* **1982**, *6*, 483.

(33) Tiemann, F.; Schotten, C. *Chem. Ber.* **1878**, *11*, 773.

in vacuo, affording the corresponding pyridinium salt **28** as an oil. The oil was dissolved in water (4 mL) and a solution of sodium azide (1.00 g, 15 mmol) in water (6 mL) was added. After stirring at room temperature for 10 h, the solid formed was filtered and washed with some water. From the filtrate an additional amount of solid was obtained by crystallization. The combined solids (1.60 g, 85%) were recrystallized in ethanol to give pure **8** (1.29 g, 69%), mp 68–69 °C: IR (Nujol) 2180, 2140, 1705, 1620, 1540, 1355 cm^{-1}; MS, m/z (relative abundance) 206 (2.5, M^+), 178 (20.0), 161 (4.0), 148 (15.0), 118 (19.1), 104 (21.3), 89 (66.0), 77 (100), 65 (70.2), 51 (50.0), 40 (44.5); ^1H NMR ($CDCl_3$) δ 10.40 (s, 1 H, CHO), 7.90 (m, 2 H, H-4 and H-6), 2.50 (s, 3 H, CH_3). Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.90; H, 2.74; N, 26.92.

2-Azido-3-nitroacetophenone (9). To a stirred solution of 2-amino-3-nitroacetophenone (**29**)[34] (0.270 g, 1.5 mmol) and concentrated hydrochloric acid (1.5 mL) in water (3 mL) was added dropwise, at 0 °C, a saturated aqueous solution of sodium nitrite (0.114 g, 1.5 mmol). After 1 h, an aqueous solution of sodium azide (0.107 g, 1.5 mmol) was added to the resulting clear solution, at a temperature below 5 °C. The mixture was allowed to warm to room temperature and after 15 min the yellow solid formed was filtered, washed, and dried in vacuo to give almost pure **9** (0.247 g, 80%): mp 80–81 °C; IR (KBr) 2160, 2130, 1680, 1600, 1530 cm^{-1}; MS, m/z (relative abundance) 206 (4.3, M^+), 179 (9.6), 178 (81.5), 163 (19.2), 148 (18.9), 147 (31.3), 120 (23.8), 103 (34.2), 90 (53.4), 89 (26.7), 88 (19.6), 86 (65.8), 84 (100); ^1H NMR ($CDCl_3$) δ 8.02 (dd, J = 8.1, 1.6 Hz, 1 H, H-4), 7.84 (dd, J = 8.1, 1.6 Hz, 1 H, H-6), 7.40 (t, J = 8.1 Hz, 1 H, H-5), 2.69 (s, 3 H, CH_3). Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.30; H, 3.01; N, 27.30.

2-Azido-5-methylbenzyl Alcohol (32). This compound was obtained from 2-amino-5-methylbenzyl alcohol (**30**)[35] (6.90 g, 50 mmol), following a similar method as for compound **9**. The crude reaction mixture was extracted with ether (2 × 80 mL), and the extract washed with brine (2 × 50 mL), dried ($MgSO_4$ and Na_2SO_4), and evaporated: yield 83%; yellow oil; IR (neat) 3350, 2120, 2080, 1590, 1495, 1300, 810 cm^{-1}; MS, m/z (relative abundance) 163 (9.8, M^+), 134 (6.2), 107 (37.0), 106 (100), 89 (12.6), 77 (27.9); ^1H NMR ($CDCl_3$) δ 7.10 (m, 3 H, Ar), 4.58 (s, 2 H, CH_2O), 2.33 (s, 3 H, CH_3). Anal. Calcd for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.95; H, 5.80; N, 25.52.

2-Azido-3-methylbenzyl Alcohol (33). Similarly, this compound was obtained from 2-amino-3-methylbenzyl alcohol (**31**)[35] in a 84% yield: yellow oil; IR (neat) 3400, 2140, 1475, 1315, 785 cm^{-1}; MS, m/z (relative abundance) 163 (10.2, M^+), 134 (10.2), 107 (56.7), 106 (100), 105 (11.0), 104 (18.0), 91 (23.6), 84 (70.1), 77 (39.4), 65 (18.9), 51 (46.5); ^1H NMR ($CDCl_3$) δ 7.00–7.20 (m, 3 H, Ar), 4.71 (s, 2 H, CH_2O), 2.62 (br s, 1 H, OH), 2.41 (s, 3 H, CH_3). Anal. Calcd for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.71; H, 5.56; N, 25.67.

2-Azido-5-methylbenzaldehyde (11). A mixture of 2-azido-5-methylbenzyl alcohol (**32**) (1.074 g, 6.6 mmol), pyridinium chlorochromate (2.120 g, 9.9 mmol), and dichloromethane (20 mL) was stirred for 1.5 h at room temperature. The reaction mixture was filtered on silica gel (dichloromethane), and the resulting solution was evaporated to give aldehyde **11** (0.880 g, 83%) as a yellow solid, mp 55.5–56.5 °C: IR (KBr) 2130, 2095, 1690, 1485, 1395, 1305, 1295, 1280, 820, 735 cm^{-1}; MS, m/z (relative abundance) 161 (11.2, M^+), 133 (60.7), 104 (100), 86 (25.8), 84 (28.1), 78 (52.8); ^1H NMR ($CDCl_3$) δ 10.32 (s, 1 H, CHO), 7.69 (m, 1 H, H-6), 7.43 (dd, J = 8.2, 2.1 Hz, 1 H, H-4), 7.17 (d, J = 8.2 Hz, 1 H, H-3), 2.37 (s, 3 H, CH_3). Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.34; H, 4.41; N, 26.14.

2-Azido-3-methylbenzaldehyde (12). Method A. Following the same procedure as for aldehyde **11**, 6.12 g (91%) of **12** was obtained from 2-azido-3-methylbenzyl alcohol (**33**) (6.77 g, 41.5 mmol), pyridinium chlorochromate (13.43 g, 62 mmol), and dichloromethane (40 mL). Pale yellow oil: IR (neat) 2760, 2150, 1700, 1590, 1470, 1400, 1310, 790 cm^{-1}; MS, m/z (relative abundance) 161 (10.8, M^+), 133 (19.9), 132 (10.8), 106 (10.0), 105 (55.0), 104 (100), 86 (29.1), 84 (44.6), 78 (45.8), 77 (44.2), 63 (16.7); ^1H NMR ($CDCl_3$) δ 10.34 (s, 1 H, CHO), 7.72 (br d, J = 7.6 Hz, 1 H, H-6), 7.43 (br d, J = 7.6 Hz, 1 H, H-4), 7.24 (t, J = 7.6 Hz, 1 H, H-5), 2.47 (s, 3 H, CH_3). Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.32; H, 4.54; N, 25.88.

Method B. A solution of sodium nitrite (0.410 g, 6 mmol) in water (2 mL) was added dropwise to a well-stirred suspension of the oxime of 2-amino-3-methylbenzaldehyde (**36**)[36] (0.890 g, 6 mmol) in concentrated hydrochloric acid (9 mL) at −5 °C. Stirring was continued until the initial white suspension was transformed into a yellow-orange solution (ca. 1 h), and then aqueous 10 N potassium hydroxide (10 mL) was added dropwise, keeping the temperature below 0 °C. After an additional hour at 0 °C, the mixture was left 5 h at room temperature and then steam distilled. The distillate was extracted with ether (3 × 50 mL), washed with brine (3 × 50 mL), dried ($MgSO_4$), and evaporated to give azide **12** (0.264 g, 28%), identical with the compound prepared by method A.

Preparation of Azines. General Procedure. To a solution of the corresponding azidoaldehyde or ketone in ethanol was added dropwise a solution of hydrazine hydrate (0.5 equiv) in ethanol. Acid catalysis was ensured by addition of 1–2 drops of acid (HCl or acetic acid), and the reaction mixture was heated to reflux until complete disappearance (TLC) of the starting material. Solid azines precipitated on cooling and were purified by crystallization in ethanol.

2-Azido-3-nitrobenzaldehyde azine (13) was obtained from 2-azido-3-nitrobenzaldehyde (**2**):[11] yield 94%; mp >300 °C; IR (Nujol) 2170, 1630, 1610, 1550, 1370 cm^{-1}; MS, m/z (relative abundance) 324 (100, $M^+ - 2 \times N_2$), 294 (7.0), 262 (20.0), 250 (22.4), 231 (7.1), 221 (15.0), 220 (17.9), 204 (40.8), 192 (78.0), 163 (51.7), 132 (46.1); ^1H NMR ($CDCl_3$) δ 9.00 (s, 2 H, CH=N), 8.36 (dd, J = 8.0, 1.6 Hz, 2 H, H-4 and -4′ or H-6 and -6′), 8.05 (dd, J = 8.0, 1.6 Hz, 2 H, H-6 and -6′ or H-4 and -4′), 7.34 (t, J = 8 Hz, 2 H, H-5 and H-5′). Anal. Calcd for $C_{14}H_8N_{10}O_4$: C, 44.22; H, 2.12; N, 36.83. Found: C, 43.98; H, 2.09; N, 36.72.

2-Azido-5-methyl-3-nitrobenzaldehyde azine (14) was obtained from 2-azido-5-methyl-3-nitrobenzaldehyde (**8**): yield 93% mp >310 °C; IR (Nujol) 2175, 1630, 1615, 1540, 1350 cm^{-1}; MS, m/z (relative abundance) 352 (100, $M^+ - 2 \times N_2$), 336 (2.5), 324 (6.5), 296 (2.6), 278 (15.0), 250 (10.2), 248 (11.8), 232 (23.0), 219 (38.9), 205 (14.5), 177 (23.0); ^1H NMR ($CDCl_3$) δ 9.08 (s 2 H, CH=N), 8.26 (d, J = 2.2 Hz, 2 H, H-4 and -4′), 7.96 (d, J = 2.2 Hz, 2 H, H-6 and -6′), 2.49 (br s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{12}N_{10}O_4$: C, 47.06; H, 2.96; N, 34.30. Found: C, 47.31; H, 3.03; N, 34.27.

2-Azido-3-nitroacetophenone azine (15) was obtained from 2-azido-3-nitroacetophenone (**9**): yield 57%: mp 133–134 °C; IR (KBr) 2150, 2130, 1600, 1590, 1525, 1430, 1340, 735 cm^{-1}; MS, m/z (relative abundance) 380 (1.5, $M^+ - N_2$), 352 (6.9), 245 (4.4), 231 (4.1), 218 (6.1), 206 (5.6), 192 (5.6), 178 (16.7), 177 (100), 176 (25.9), 161 (13.7), 147 (22.4), 131 (20.1), 130 (12.1), 116 (15.5), 104 (16.6), 102 (12.4); ^1H NMR ($CDCl_3$) δ 8.00 (dd, J = 8.2, 1.6 Hz, 2 H, H-4 and -4′ or H-6 and -6′), 7.73 (dd, J = 7.7, 1.6 Hz, 2 H, H-6 and -6′ or H-4 and -4′), 7.40 (dd, J = 8.2, 7.7 Hz, 2 H, H-5 and -5′), 2.33 (s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{12}N_{10}O_4$: C, 47.06; H, 2.96; N, 34.30. Found: C, 47.21; H, 3.18; N, 34.60.

2-Azidoacetophenone Azine (16). Following the general procedure, **16** was obtained from 2-azidoacetophenone (**10**),[37] in a 86% yield: mp 120–121 °C dec; IR (Nujol) 2170, 2120, 1620, 1500, 1370, 760 cm^{-1}; MS, m/z (relative abundance) 290 (15.0, $M^+ - N_2$), 276 (31.2), 262 (45.6), 248 (23.2), 233 (11.0), 220 (26.7), 206 (8.0), 195 (21.1), 132 (100), 131 (58.2); ^1H NMR ($CDCl_3$) δ 7.1–7.6 (m, 8 H, Ar), 2.27 (s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_8$: C, 60.37; H, 4.43; N, 35.20. Found: C, 60.15; H, 4.32; N, 35.28. When the reaction was carried out in the absence of acid catalyst, a mixture of two compound was obtained. Column chromatography (hexanes–ethyl acetate 3:1) afforded 13% of azine **16** and 18% of 2-amino-3-methylindazole (**26**), mp 153.5–154.5 °C (lit.[38] mp 154 °C).

2-Azido-5-methylbenzaldehyde azine (17) was obtained from

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2-azido-5-methylbenzaldehyde (**11**) in a 84% yield: mp 175–175.5 °C dec; IR (KBr) 2120, 2100, 1615, 1490, 1300, 820, 800 cm^{-1}; MS, m/z (relative abundance) 318 (4.9, M^+), 290 (15.5), 262 (32.1), 248 (22.6), 233 (55.0), 219 (53.1), 207 (52.3), 132 (26.6), 131 (52.1), 116 (21.5), 103 (37.9), 89 (40.5), 77 (100); ^1H NMR ($CDCl_3$) δ 8.90 (s, 2 H, CH=N), 7.96 (m, 2 H, H-6 and -6′), 7.31 (dd, J = 8.2, 2.2 Hz, 2 H, H-4 and -4′), 7.11 (d, J = 8.2 Hz, 2 H, H-3 and -3′), 2.38 (s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_8$: C, 60.37; H, 4.43; N, 35.20. Found: C, 60.09; H, 4.62; N, 34.90.

2-Azido-3-methylbenzaldehyde azine (18) was obtained from 2-azido-3-methylbenzaldehyde (**12**) in an 82% yield: mp 145–146 °C dec; IR (KBr) 2150, 1625, 1590, 1460, 1420, 1335, 790 cm^{-1}; MS, m/z (relative abundance) 318 (2.6, M^+), 290 (19.6), 262 (27.4), 233 (86.9), 219 (24.8), 132 (35.3), 131 (74.4), 116 (20.2), 103 (29.4), 89 (44.2), 77 (100); ^1H NMR ($CDCl_3$) δ 9.06 (s, 2 H, CH=N), 7.96 (dd, J = 7.6, 1.7 Hz, 2 H, H-6, and -6′), 7.29 (m, 2 H, H-4 and -4′), 7.19 (t, J = 7.6 Hz, 2 H, H-5 and -5′), 2.48 (s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_8$: C, 60.37; H, 4.43; N, 35.20. Found: C, 60.19; H, 4.45; N, 34.98.

7,7′-Dinitro-2,2′-biindazole (4). The Krbechek method[12] for the synthesis of 2,2′-biindazoles was employed. A solution of 2-azido-3-nitrobenzaldehyde azine (**13**) (0.150 g, 4 mmol) was heated for 2 h at 150 °C in 1,2-dichlorobenzene (15 mL). The initial yellow solution became darkish and a copious precipitate developed. The solvent was evaporated in vacuo and the resulting solid residue was recrystallized in nitrobenzene to give 0.100 g (78%) of **4** as brown crystals; mp >300 °C (lit.[11] mp 323 °C).

5,5′-Dimethyl-7,7′-dinitro-2,2′-biindazole (19). The same method as for compound **4** was used, from 2-azido-5-methyl-3-nitrobenzaldehyde azine (**14**) (0.500 g, 1 mmol) in 30 mL of 1,2-dichlorobenzene: yield 0.388 g (90%); mp >300 °C; IR (Nujol) 1520, 1325, 1305, 1240, 760 cm^{-1}; MS, m/z (relative abundance) 352 (100, M^+), 336 (2.5), 324 (6.5), 296 (2.5), 278 (15.0), 250 (10.1), 248 (12.0), 232 (22.9), 219 (39.0), 205 (15.0), 177 (23.2). Anal. Calcd for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 53.93; H, 3.44; N, 23.43.

7,7′-Diamino-5,5′-dimethyl-2,2′-biindazole (25). A well-stirred mixture of 5,5′-dimethyl-7,7′-dinitro-2,2-′biindazole (**19**) (1.00 g, 3 mmol), 10% Pd/C (0.40 g), and ethyl acetate (175 mL) was refluxed under hydrogen for 20 h. The hot reaction mixture was filtered and the solution was concentrated in vacuo to a small volume and cooled. Filtration of the solid formed afforded yellow crystals of **25** (0.58 g, 70%): mp 222–225 °C; IR (Nujol) 3440, 1630, 1620, 1580, 1060 cm^{-1}; MS, m/z (relative abundance) 293 (9.0), 292 (45.7, M^+), 263 (1.4), 148 (9.3), 147 (100), 146 (74.6), 131 (2.8), 120 (5.6), 119 (32.9), 118 (12.4), 117 (3.8); ^1H and ^{13}C NMR, see Tables I and II. Anal. Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 65.74; H, 5.72; N, 28.85.

3,3′-Dimethyl-7,7′-dinitro-2,2′-biindazole (20) was prepared as for compound **4**, from 2-azido-3-nitroacetophenone azine (**15**) (0.130 g, 0.3 mmol) in 20 mL of 1,2-dichlorobenzene. **20**: yield 0.101 g (90%); mp >300 °C; IR (KBr) 1640, 1515, 1430, 1380, 1340, 1310, 880, 790 cm^{-1}; MS, m/z (relative abundance) 352 (5.2, M^+), 335 (5.2), 306 (3.1), 178 (11.7), 177 (100), 176 (23.0), 147 (13.0), 131 (11.8), 104 (9.3). Anal. Calcd for $C_{16}H_{12}N_6O_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 54.56; H, 3.62; N, 23.58.

3,3′-Dimethyl-2,2′-biindazole (21) was prepared as for compound **4**, from 2-azidoacetophenone azine (**16**) (4.00 g, 12.5 mmol) in 100 mL of 1,2-dichlorobenzene. The crude brown solid was purified by column chromatography (hexanes–ethyl acetate 3:1). **21**: yield 2.73 g (83%), colorless crystals; mp 143–144 °C; IR (Nujol) 3095, 1635, 1535, 1255, 1170, 915, 755 cm^{-1}; MS, m/z (relative abundance) 262 (8.1, M^+), 233 (3.7), 149 (3.5), 133 (10.3), 132 (100), 131 (47.2), 102 (12.6); ^1H and ^{13}C NMR, see Tables I and II. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.23; H, 5.13; N, 21.08.

5,5′-Dimethyl-2,2′-biindazole (22) was prepared similarly, from 2-azido-5-methylbenzaldehyde azine (**17**) (4.31 g, 13.5 mmol) in 125 mL of 1,2-dichlorobenzene. The solid residue was triturated with n-hexane, filtered, and washed with ether: yield 80%. An analytically pure sample was obtained by column chromatography (hexanes–ethyl acetate 5:1). **22**: mp 218.5–219.5 °C; IR (Nujol) 1520 cm^{-1}; MS, m/z (relative abundance) 262 (100, M^+), 234 (21.8), 233 (51.6), 219 (43.7), 207 (40.2), 206 (28.5), 192 (13.8), 132 (12.7), 131 (39.4); ^1H and ^{13}C NMR, see Tables I and II. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.40; H, 5.64; N, 21.50. When the reaction time was shortened to 1 h, a similar workup afforded only 30% of the desired biindazole **22**. Evaporation of the filtrate and column chromatography of the residue (toluene) afforded 32% of **2-[(2-azido-5-methylbenzylidene)amino]-5-methylindazole (24)**: mp 107–108 °C; IR (KBr) 2140, 2120, 1590, 1530, 1490, 1345, 1305, 1285, 1170, 1120, 990, 970, 805 cm^{-1}; MS, m/z (relative abundance) 291 (10.5), 290 (52.4, M^+), 262 (41.9), 248 (25.6), 234 (31.0), 233 (88.1), 232 (15.8), 220 (18.3), 219 (89.0), 218 (26.6), 208 (18.3), 207 (100), 206 (63.6); ^1H NMR ($CDCl_3$) δ 9.73 (s, 1 H, CH=N), 8.07 (d, J = 1.0 Hz, 1 H, H-3), 7.98 (m, 1 H, H-4′), 7.61 (d, J = 8.9 Hz, 1 H, H-7), 7.40 (m, 1 H, H-4), 7.31 (ddd, J = 8.2, 2.1, 0.6 Hz, 1 H, H-6′), 7.15 (m, 2 H, H-3′ and -6), 2.41 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: 66.51;, H, 4.86; N, 29.11. This material was transformed into **22** by further heating in 1,2-dichlorobenzene for 2 h at 150 °C (80%).

7,7′-Dimethyl-2,2′-biindazole (23) was prepared as for **22**, from 2-azido-3-dimethylbenzaldehyde azine (**18**): yield 87%; mp 165–166 °C; IR 1520 cm^{-1}; MS, m/z (relative abundance) 262 (63.3, M^+), 234 (34.4), 233 (100), 219 (23.3), 192 (11.1), 132 (11.1), 131 (35.6), 102 (25.6); ^1H and ^{13}C NMR, see Tables I and II. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 72.97; H, 5.07; N, 21.35.

2-[(2-Azido-3-methylbenzylidene)amino]-3-methylindazole (37). A solution of 2-azido-3-methylbenzaldehyde (**12**) (0.547 g, 3 mmol) and 2-amino-3-methylindazole (**26**) (0.500 g, 3 mmol) in ethanol (5 mL) containing 1 drop of concentrated hydrochloric acid was stirred at room temperature for 10 h. The yellow solid formed during the reaction was filtered (0.643 g). Concentration of the filtrate afforded another crop of product (0.175 g). Total yield of **37** was 83%: mp 114–115 °C; IR (KBr) 2120, 1635, 1600, 1420, 1370, 1335, 1270, 755 cm^{-1}; MS, m/z (relative abundance) 290 (15.9, M^+), 262 (11.4), 248 (3.5), 233 (7.3), 220 (4.7), 219 (8.5), 218 (4.8), 133 (9.5), 132 (100), 131 (42.5); ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H, CH=N), 8.00 (m, 1 H, H-6′), 7.61 (m, 2 H, H-4 and -7), 7.0–7.4 (m, 4 H, H-4′, -5′, -5, and -6), 2.78 (s, 3 H, CH_3-Het), 2.48 (s, 3 H, CH_3-Ar). Anal. Calcd for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.50; H, 4.79; N, 29.14.

3,7′-Dimethyl-2,2′-biindazole (38). This compound was prepared following the general procedure, from 2-[(2-azido-3-methylbenzylidene)amino]-3-methylindazole (**37**) (0.630 g, 2 mmol) in 30 mL of 1,2-dichlorobenzene. After evaporation of the solvent, the crude oil was purified by chromatography (hexanes–ethyl acetate 3:1) to give 0.504 g (88%) of **38**, yellowish crystals: mp 89–90 °C; IR (KBr) 1635, 1525, 1450, 1400, 1355, 1130, 955, 905, 800, 790, 745 cm^{-1}; MS, m/z (relative abundance) 262 (16.4, M^+), 233 (6.6), 219 (6.3), 133 (8.9), 132 (100), 131 (31); ^1H and ^{13}C NMR, see Tables I and II. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.50; H, 5.50; N, 21.60.

3,3′-Dimethyl-4,4′,5,5′,6,6′,7,7′-octahydro-2,2′-biindazole (42). A suspension of 3,3′-dimethyl-2,2′-biindazole (**21**) (0.100 g, 0.4 mmol) and 10% Pd/C (0.04 g) in ethyl acetate (15 mL) was shaken in hydrogen for 2 days at room temperature. The mixture was filtered and the solution evaporated to give **42** as a colorless solid (0.062 g, 60%): mp 120–121 °C; IR (Nujol) 1600, 1165, 970, 940 cm^{-1}; MS, m/z (relative abundance) 271 (18.7), 270 (94.5, M^+), 202 (10.9), 137 (23.2), 136 (55.0), 135 (100), 134 (35.5), 133 (7.4), 108 (60.1); ^1H NMR ($CDCl_3$) δ 2.57 (t, J = 6.0 Hz, 4 H, H-7 and -7′), 2.37 (t, J = 6.0 Hz, 4 H, H-4 and -4′), 1.93 (s, 6 H, CH_3), 1.67–1.75 (m, 8 H, H-5, -5′, -6, and -6′); ^{13}C NMR ($CDCl_3$) δ 148.6 (C-7a), 135.6 (C-3), 113.5 (C-3a), 23.3, 23.2, 20.2 (C-4, -5, -6, and -7), 8.50 (CH_3). Anal. Calcd for $C_{16}H_{22}N_4$: C, 71.08; H, 8.20; N, 20.72. Found: C, 71.27; H, 8.42; N, 20.44.

Reaction of 3,3′-Dimethyl-2,2′-biindazole (21) with Lithium Aluminum Hydride. A suspension of **21** (0.233 g, 1 mmol) in ether (5 mL) was added at room temperature, under nitrogen, to a stirred suspension of lithium aluminum hydride (0.104 g, 2.7 mmol) in ether (5 mL). The mixture was stirred for 24 h at room temperature. To the reaction mixture was added, successively, ethyl acetate (1 mL), 12% aqueous sodium hydroxide (1 mL), and water (1 mL). Salts were separated and the ethereal solution was dried ($MgSO_4$) and evaporated, affording 3-methylindazole (**43**) (0.182 g, 78%): mp 105–106 °C (lit.[39] mp 113 °C).

(39) Fischer, E.; Tafel, A. *Liebigs Ann. Chem.* **1885**, *227*, 317.

Reaction of 5,5′-Dimethyl-7,7′-dinitro-2,2′-biindazole (19) with Sodium Methoxide. A mixture of **19** (0.250 g, 0.7 mmol) and sodium methoxide (0.500 g, 9 mmol) was refluxed in absolute methanol (25 mL) for 3 days. The solvent was eliminated and the residue submitted to column chromatography (toluene–ethyl acetate 9:1). The following compound were eluted successively. **5,5′-Dimethyl-3-methoxy-7,7′-dinitro-1,3′-biindazole (46)** (0.006 g, 2%): mp 187–189 °C; IR (Nujol) 3240, 1650, 1565, 1530, 1330, 1300, 985 cm^{-1}; MS, m/z (relative abundance) 382 (41.6, M^+), 335 (4.0), 321 (4.9), 320 (3.1), 307 (3.5), 206 (4.0), 205 (2.7), 176 (4.0), 165 (4.4), 164 (13.3), 161 (16.8), 118 (10.2), 89 (28.3), 63 (11.1), 44 (21.7), 40 (100); ^1H NMR ($CDCl_3$) δ 10.88 (s, 1 H, NH), 8.27 (m, 2 H, H-6 and -6′), 8.02 (m, 1 H, H-4 or -4′), 7.85 (m, 1 H, H-4′ or -4), 4.19 (s, 3 H, OCH_3), 2.62 (br s, 3 H, CH_3), 2.57 (br s, 3 H, CH_3); high-resolution MS calcd for $C_{17}H_{14}N_6O_5$ 382.1026, found 382.0999. **5-Methyl-3-methoxy-7-nitroindazole (45)** (0.022 g, 15%): mp 190–191 °C; IR (Nujol) 3340, 1650, 1585, 1525, 1300 cm^{-1}; MS, m/z (relative abundance) 207 (100, M^+), 206 (17.0), 161 (8.0), 160 (8.9), 146 (13.4), 118 (9.8); ^1H NMR ($CDCl_3$) δ 10.30 (br s, 1 H, NH), 8.13 (br s, 1 H, H-6), 7.81 (br s, 1 H, H-4), 4.13 (s, 3 H, OCH_3), 2.50 (s, 3 H, CH_3). Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.91; H, 4.14; N, 20.00. A third compound was identified as 5-methyl-7-nitroindazole (**44**), mp 191–192 °C (lit.[40] mp 192.5 °C).

5,5′-Dimethyl-7,7′-bis(*p*-toluenesulfonamido)-2,2′-biindazole (47). Tosyl chloride (0.34 g, 1.8 mmol) in pyridine (2 mL) was added to an ice-cooled suspension of 7,7′-diamino-5,5′-dimethyl-2,2′-biindazole (**25**) (0.25 g, 0.8 mmol) in pyridine (1 mL). The mixture was stirred at room temperature for 16 h. Water (2 mL) and 2 N hydrochloric acid (2 mL) were added, and the solution was extracted with dichloromethane (2 × 20 mL). The organic phase was washed with 2 N hydrochloric acid (3 × 20 mL) and with a saturated solution of sodium bicarbonate (1 × 20 mL) and then dried (Na_2SO_4) and evaporated to give **47** (0.51 g, 100%): mp 246–249 °C; IR (Nujol) 3295, 3180, 1605, 1565, 1170, 1100, 1050, 820, 750 cm^{-1}; MS, m/z (relative abundance) 602 (2.6), 601 (6.5), 600 (14.8, M^+), 446 (2.8), 301 (13.0), 290 (7.3), 147 (19.2), 146 (100), 139 (18.4), 119 (19.4), 105 (12.7); ^1H NMR ($CDCl_3$) δ 8.21 (s, 2 H, H-3 and -3′), 7.12 and 7.73 (AA′BB′ system, 8 H, Ts), 7.46 (br s, 2 H, TsNH), 7.21 (m, 2 H, H-4, and -4′), 7.03 (m, 2 H, H-6 and -6′), 2.32 (m, 6 H, CH_3-Ar), 2.25 (s, 6 H, CH_3-Ts). Anal. Calcd for $C_{30}H_{28}N_6O_4S_2$: C, 59.98; H, 4.70; N, 13.99. Found: C, 59.61; H, 4.84; N, 13.55.

5,5′-Dimethyl-7,7′-bis[*N*-(2-methoxyethyl)-*p*-toluenesulfonamido]-2,2′-biindazole (48). Sodium hydride (0.020 g, 0.8 mmol) was added to a cooled (0 °C) and stirred solution of **47** (0.226 g, 0.4 mmol) in DMF (3 mL), under argon. After 1 h, the resulting solution was warmed to 110 °C and a solution of 2-methoxyethanol tosylate (0.182 g, 0.8 mmol) in DMF (2 mL) was added slowly via syringe. After 16 h at 110 °C, the solvent was evaporated in vacuo and the solid residue was treated with water and extracted with dichloromethane (2 × 25 mL). The extract was dried (Na_2SO_4) and the solvent evaporated. Treatment of the new residue with a mixture of dichloromethane–ether (10:1) afforded 0.151 g (56%) of **48** as a colorless solid: mp 222–223 °C; IR (Nujol) 3145, 1605, 1170, 1160, 1105, 745 cm^{-1}; MS, m/z (relative abundance) 716 (5.9, M^+), 658 (5.6), 600 (7.1), 561 (8.1), 406 (45.7), 374 (32.3), 361 (36.2), 204 (32.2), 173 (36.8), 172 (100), 170 (34.8), 158 (66.7), 157 (41.3), 155 (72.4), 132 (45.0), 131 (56.6); ^1H NMR ($CDCl_3$) δ 8.03 (s, 2 H, H-3 and -3′), 7.14 and 7.58 (AA′BB′ system, 8 H, Ts), 7.38 (m, 2 H, H-4 and -4′), 7.29 (m, 2 H, H-6 and -6′), 4.07 (t, J = 6.3 Hz, 4 H, CH_2O), 3.47 (t, J = 6.3 Hz, 4 H, CH_2N), 3.25 (s, 6 H, OCH_3), 2.46 (s, 6 H, CH_3-Ar), 2.29 (s, 6 H, CH_3-Ts). Anal. Calcd for $C_{36}H_{40}N_6O_6S_2$: C, 60.32; H, 5.62; N, 11.72; S, 8.94. Found: C, 60.20; H, 5.65; N, 11.53; S, 8.61.

3,21-Dimethyl-6,18-ditosyl-6,15,18,26,29,30-hexaaza-9,12,15-trioxapentacyclo[24.2.1.2^{23,25}.0^{5,28}.0^{19,30}]henetriaconta-1(27),2,4,19,21,23,28,30-octaene (49). Sodium hydride (0.065 g, 2.5 mmol) was added to a stirred solution of **47** (0.780 g, 1 mmol) in DMF (25 mL), at 0 °C under argon. After 1 h the solution was warmed to 110 °C and a solution of tetraethylene glycol ditosylate (0.653 g, 1 mmol) in DMF was added dropwise during 1 h (syringe pump). After 30 h at 110 °C the solvent was evaporated in vacuo, and the residue was treated with some water and extracted with dichloromethane (2 × 50 mL). The extract was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (hexanes–ethyl acetate 1:1) to give pure **49** (0.157, g 16%) as a colorless solid: mp 251–253 °C; IR (KBr) 3160, 1610, 1550, 1460, 1365, 1185, 1100, 1050, 820, 750 cm^{-1}; MS, m/z (relative abundance) 759 (0.9, M^+), 671 (0.6), 605 (2.4), 604 (4.0), 576 (2.8), 458 (5.2), 449 (9.8), 448 (33.4), 303 (10.3), 301 (19.1), 261 (10.9), 216 (12.4), 186 (12.2), 146 (39.6), 91 (100); ^1H NMR ($CDCl_3$) δ 7.92 (s, 2 H, H-3 and -3′), 7.17 and 7.57 (AA′BB′ system, 8 H, Ts), 7.34 (s, 2 H, H-4 and -4′), 7.07 (s, 2 H, H-6 and -6′), 3.94 (t, J = 6.3 Hz, 4 H, CH_2(γ or δ)), 3.42 (t, J = 6.3 Hz, 4 H, CH_2(δ or γ)), 3.08 (t, J = 6.3 Hz, 4 H, $CH_3\beta$), 2.92 (t, J = 6.3 Hz, 4 H, $CH_2\alpha$), 2.40 (s, 6 H, CH_3-Ar), 2.38 (s, 6 H, CH_3-Ts). Anal. Calcd for $C_{38}H_{42}N_6O_7S_2$: C, 60.14; H, 5.58; N, 11.07; S, 8.45. Found: C, 60.01; H, 5.41; N 11.11; S, 8.68.

Attempted Detosylation of Biindazolyl Derivatives 47, 48, and 49. A. With Sodium Naphthalenide. A solution of the coronand **49** (0.250 g, 0.33 mmol) in THF (20 mL) was added slowly to a stirred solution of sodium (0.230 g, 10 mmol) and naphthalene (1.280 g, 12 mmol) in THF (20 mL), at room temperature and under argon. After 10 h at room temperature, the solvent was removed in vacuo and the solid was treated several times with 20% hydrochloric acid and filtered. The combined filtrates were treated with an excess of aqueous sodium hydroxide solution and extracted with ethyl acetate (2 × 25 mL). The extract was washed with water, dried (Na_2SO_4), and evaporated. Column chromatography (dichloromethane–ethanol 9:1) of the residue afforded **7-[(2-hydroxyethyl)amino]-5-methylindazole (51)** (0.020 g, 6%): mp 196–197 °C; IR (KBr) 3400, 1600, 1540, 1345, 1090, 970, 820 cm^{-1}; MS, m/z (relative abundance) 192 (8.5), 191 (64.5, M^+), 161 (13.0), 160 (100), 133 (78.3), 132 (27.6), 131 (35.4), 118 (17.4); ^1H NMR ($CDCl_3$) δ 7.91 (s, 1 H, H-3), 6.92 (br s, 1 H, H-4), 6.36 (br s, 1 H, H-6), 3.91 (t, J = 5.0 Hz, 2 H, CH_2O), 3.42 (t, J = 5.0 Hz, 2 H, CH_2N), 3.0–4.0 (br s, 3 H, NH and OH), 2.39 (s, 3 H, CH_3). Further elution of the column afforded **7-[[2-(2-hydroxyethoxy)ethyl]amino]-5-methylindazole (50)** (0.030 g, 10%): mp 159–160 °C; MS, m/z (relative abundance) 235 (61.0, M^+), 160 (100), 147 (8.2), 146 (11.9), 133 (47.0), 119 (13.8), 118 (15.2); ^1H NMR ($CDCl_3$) δ 7.87 (s, 1 H, H-3), 6.85 (br s, 1 H, H-6), 3.65–3.75 (m, 4 H, OCH_2CH_2OH), 3.49–3.53 (m, 2 H, CH_2O), 3.31–3.36 (m, 2 H, CH_2N), 2.37 (s, 3 H, CH_3). When the same procedure was applied to the podand **48**, column chromatography (dichloromethane–ethanol 95:5) afforded **5-methyl-7-[(2-methoxyethyl)amino]indazole (52)** (22%): mp 138.5–139.5 °C; IR (Nujol) 3340, 3170, 3100, 1600, 1320, 1120, 950, 860 cm^{-1}; MS, m/z (relative abundance) 205 (60.1, M^+), 160 (100), 133 (47.4), 132 (15.3), 131 (13.2); ^1H NMR ($CDCl_3$) δ 7.97 (s, 1 H, H-3), 6.91 (br s, 1 H, H-4), 6.33 (br s, 1 H, H-6), 3.67 (t, J = 5.0 Hz, 2 H, CH_2O), 3.43 (t, J = 5.0 Hz, 2 H, CH_2N), 3.35 (s, 3 H, OCH_3), 2.40 (s, 3 H, CH_3). Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.41; H, 7.47; N, 20.19.

B. With Lithium Aluminum Hydride. Lithium aluminum hydride (0.10 g, 3 mmol) was added to a stirred suspension of the podand **48** (0.20 g, 0.3 mmol) in ether (20 mL). The mixture was refluxed for 1.5 h. A similar workup as for the reduction of biindazole **21** (see above) afforded a residue which was purified by chromatography (hexanes–ethyl acetate 1:1) to give **5-methyl-7-[*N*-(2-methoxyethyl)-*p*-toluenesulfonamido]-indazole (53)** (0.11 g, 55%) as a crystalline colorless solid: mp 120–121 °C; IR (KBr) 3420, 1600, 1455, 1350, 820, 765 cm^{-1}; MS, m/z (relative abundance) 359 (58.0, M^+), 314 (18.9), 204 (100), 159 (59.0), 158 (34.2), 132 (49.6), 131 (48.8), 91 (99.5); ^1H NMR ($CDCl_3$) δ 10.71 (br s, 1 H, NH), 7.97 (s, 1 H, H-3), 7.24 and 7.54 (AA′BB′ system, 4 H, Ts), 7.47 (br s, 1 H, H-4), 6.65 (br s, 1 H, H-6), 3.84 (t, J = 5.6 Hz, 2 H, CH_2O), 3.41 (t, J = 5.6 Hz, 2 H, CH_2N), 3.26 (s, 3 H, OCH_3), 2.42 (s, 3 H, CH_3-Ar), 2.33 (s, 3 H, CH_3-Ts). Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89; N, 11.69. Found: C, 60.30; H, 5.74; N, 11.52. When the reflux time was prolonged for 18 h, only indazole **52** (27%), identical with that obtained by the sodium naphthalenide reduction of **48**, was isolated by column chromatography (dichloromethane–ethanol 95:5).

C. With Hydrogen Bromide/Phenol/Acetic Acid. A mixture of the podand **48** (0.157 g, 0.2 mmol), phenol (0.390 g),

(40) Gabriel, S.; Stelzner, R. *Chem. Ber.* **1896**, *29*, 305.

and 33% HBr in acetic acid (7 mL) was heated to 80 °C for 20 h. Evaporation of the mixture afforded a reddish residue, which was treated with water (10 mL) and washed with dichloromethane to eliminate the phenol. The aqueous phase was made alkaline by adding diluted potassium hydroxide and was extracted with ethyl acetate (2 × 20 mL), washed with water, dried (Na_2SO_4), and evaporated to give indazole **51** (0.036 g, 43%), identical with that obtained from the sodium naphthalenide reduction of coronand **49**.

D. With Sulfuric Acid. A solution of podand **48** (0.204 g, 0.3 mmol) in concentrated sulfuric acid (2 mL) was heated to 110 °C for 2 h. After cooling, the mixture was diluted with water, made alkaline with aqueous potassium hydroxide, and extracted with ethyl acetate (2 × 25 mL). The extract was washed with brine (25 mL), dried (Na_2SO_4), and evaporated, to give indazole **51** (0.055 g, 51%). The same procedure, applied to biindazole **47**, afforded 7-amino-5-methylindazole (**54**), mp 161–163 °C (lit.[41] mp 172 °C), in a 35% yield. Structure **54** was confirmed by spectral data and also by an independent synthesis from 5-methyl-7-nitroindazole (**44**). Thus, catalytic reduction of **44** (10% Pd/C, ethanol, room temperature, 50 min) gave 71% of **54**.

NBS Bromination of Dimethyl-2,2′-biindazoles 21, 23, and 38. General Procedure. A mixture of the appropriate biindazole (3.8 mmol) and *N*-bromosuccinimide (7.6 mmol) was refluxed in carbon tetrachloride (50–100 mL) for 24 h (48 h for the 7,7′-dimethyl derivative **23**). The reaction mixture was cooled and in the case of **21** and **23** the solid that appeared was filtered, dissolved in dichloromethane, and purified by chromatography (dichloromethane). For **38** the solid was filtered and washed with carbon tetrachloride. The filtrate was evaporated and the residue triturated with ether. Yields of bis(bromomethyl) derivatives **55**, **56**, and **57** were 54%, 50%, and 68%, respectively.

3,3′-Bis(bromomethyl)-2,2′-biindazole (55): mp 181–182 °C dec; IR (Nujol) 3060, 1645, 1195, 1115, 755 cm^{-1}; MS, *m/z* (relative abundance) 422 (2.0), 420 (4.2), 418 (2.2, M^+), 341 (15.7), 339 (15.8), 232 (34.4), 231 (70.7), 212 (9.1), 210 (9.7), 132 (31.3), 131 (88.5), 130 (22.4), 102 (100); ^1H NMR ($CDCl_3$) δ 7.72 (m, 4 H, H-4, -4′, -7, and -7′), 7.41 (m, 2 H, H-6 and -6′), 7.25 (m, 2 H, H-5 and -5′), 4.67 (s, 4 H, CH_2Br). Anal. Calcd for $C_{16}H_{12}N_4Br_2$: C, 45.74; H, 2.88; N, 13.34; Br, 38.04. Found: C, 46.10; H, 3.13; N, 13.09; Br, 37.68.

7,7′-Bis(bromomethyl)-2,2′-biindazole (56): mp 213–214 °C; IR (KBr) 3130, 1625, 1530, 1435, 1390, 1360, 1315, 1215, 810, 750 cm^{-1}; MS, *m/z* (relative abundance) 422 (8.0), 420 (11.4), 418 (8.0, M^+), 341 (56.8), 339 (63.2), 260 (12.8), 259 (40.8), 231 (26.4), 205 (16.0), 131 (47.2), 130 (55.2), 102 (100); ^1H NMR ($CDCl_3$) δ 8.87 (s, 2 H, H-3 and -3′), 7.74 (m, 2 H, H-4 and -4′), 7.47 (m, 2 H, H-6 and -6′), 7.19 (m, 2 H, H-5 and -5′), 4.95 (s, 4 H, CH_2Br). Anal. Calcd for $C_{16}H_{12}N_4Br_2$: C, 45.74; H, 2.88; N, 13.34; Br, 38.04. Found: C, 46.10; H, 2.87; N, 13.64; Br, 37.39.

3,7′-Bis(bromomethyl)-2,2′-biindazole (57): mp 128.5–129 °C; IR (KBr) 3120, 1630, 1430, 1390, 1345, 1210, 745 cm^{-1}; MS, *m/z* (relative abundance) 422 (2.7), 420 (5.0), 418 (2.7, M^+), 341 (20.8), 339 (24.2), 261 (20.6), 260 (30.0), 259 (41.4), 233 (13.6), 232 (30.7), 231 (42.1), 132 (35.2), 131 (88.1), 130 (29.8), 102 (100); ^1H NMR ($CDCl_3$) δ 8.55 (s, 1 H, H-3′), 7.75 (m, 2 H, H-4, -4′), 7.17–7.50 (m, 5 H, H-5, -5′, -6, -6′, and -7), 4.91 (s, 4 H, CH_2Br). Anal. Calcd for $C_{16}H_{12}N_4Br_2$: C, 45.74; H, 2.88; N, 13.34; Br, 38.04. Found: C, 45.85; H, 2.94; N, 13.60; Br, 37.61.

1,2,3,33-Tetraaza-12,15,18,21,24-pentaoxapentacyclo-[24.7.0.0^{2,10}.0^{4,9}.0^{27,32}]tritriaconta-3,5,7,9,26,28,30,32-octaene (58). A suspension of tetraethylene glycol (0.570 g, 3 mmol) and sodium hydride (0.175 g, 7 mmol) in THF (50 mL) was stirred for 1 h at 0 °C under argon. The suspension was allowed to warm to room temperature and then a solution of 3,3′-bis(bromomethyl)-2,2′-biindazole (**55**) (1.120 g, 3 mmol) in THF (100 mL) was added dropwise, via syringe pump, over a period of 8 h. Stirring was maintained for an additional period of 12 h after the addition was complete, and the solvent was removed to give a residue which was extracted with dichloromethane (2 × 50 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by chromatography (ethyl acetate), affording an almost colorless oil (0.158 g, 17%), which crystallized on standing: mp 119–120 °C; IR (neat) 3090, 2915, 1720, 1635, 1470, 1350, 1150–1100, 740 cm^{-1}; MS, *m/z* (relative abundance) 452 (3.6, M^+), 275 (13.5), 259 (11.0), 258 (33.4), 173 (13.5), 161 (10.8), 160 (10.6), 159 (11.0), 148 (11.5), 147 (60.4), 146 (40.3), 145 (21.5), 144 (18.8), 132 (21.1), 131 (93.6), 118 (16.9), 102 (100); ^1H NMR ($CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2 H, H-4 and -4′), 7.72 (d, *J* = 8.9 Hz, 2 H, H-7 and -7′), 7.42 (m, 2 H, H-5 and -5′), 7.21 (m, 2 H, H-6 and -6′), 4.78 and 4.86 (AB system, *J* = 13.3 Hz, 4 H, $ArCH_2O$), 3.55 (m, 16 H, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 146.5 (C-7a), 133.6 (C-3), 128.0 (C-6), 123.3 (C-4), 120.3 (C-5), 120.1 (C-3a), 118.0 (C-7), 70.7, 70.6, 70.5, 70.2, and 61.7 (CH_2O). Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.95; H, 6.30; N, 12.69. Metal complexes were prepared by mixing equimolecular amounts of the macrocycle and the corresponding inorganic salt. **58**·NaSCN complex (**58** in ethyl acetate, NaSCN in methanol, reflux 1 h, yield 56%): mp 180–181 °C; ^1H NMR ($CDCl_3$) δ 7.86 (m, 2 H), 7.73 (m, 2 H), 7.43 (m, 2 H), 7.26 (m, 2 H), 4.94 and 5.19 (AB system, *J* = 12.3 Hz, 4 H), 2.83–3.73 (m, 16 H). **58**·KSCN complex (**58** in ethyl acetate, KSCN in methanol, reflux 1 h, yield 70%): oil; ^1H NMR ($CDCl_3$) δ 7.86 (m, 2 H), 7.71 (m, 2 H), 7.42 (m, 2 H), 7.24 (m, 2 H), 4.91 and 5.11 (AB system, *J* = 12.4 Hz), 2.97–3.71 (m, 16l H); ^{13}C NMR ($CDCl_3$) δ 146.1, 132.2, 128.1, 123.5, 120.1, 120.0, 117.8, 69.7, 69.5, 69.2, 69.0, 62.2. **58**·$HgCl_2$ complex (**58** and $HgCl_2$ in ethanol, room temperature, 1 h, yield 75%): mp 165–167 °C; ^1H NMR ($CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.42 (m, 2 H), 7.22 (m, 2 H), 4.83 and 5.20 (AB system, *J* = 12.8 Hz, 2 H), 3.55 (m, 16 H); ^{13}C NMR ($CDCl_3$) 146.5, 133.1, 128.3, 123.5, 120.9, 120.4, 117.9, 70.6, 70.4, 70.3, 70.1, 61.7. **58**·$PdCl_2$ complex (**58** and bis(acetonitrile)dichloropalladium in acetonitrile, room temperature, 1 h, yield 76%); mp 172–175 °C dec; ^1H NMR ($CDCl_3$) δ 7.68 (m, 2 H), 7.44 (m, 2 H), 7.02 (m, 4 H), 5.05 and 5.85 (AB system, *J* = 13.0 Hz, 4 H), 3.57 (m, 16 H).

1,2,30,33-Tetraaza-10,13,16,19,22-pentaoxapentacyclo-[22.5.2.2^{2,8}.0^{4,32}.0^{28,31}]tritriaconta-3,5,7,24,26,28,30,32-octaene (59). Following a similar method as for coronand **58**, this compound was obtained from **56**. Purification was achieved by chromatography (ethyl acetate–methanol 95:5): yield 10%; mp 145–146 °C; IR (KBr) 3110, 1635, 1540, 1360, 1135, 1090, 945, 805 cm^{-1}; MS, *m/z* (relative abundance) 321 (3.1, M^+ – 131), 275 (8.6), 259 (11.7), 247 (2.9), 231 (6.7), 218 (4.6), 204 (5.5), 189 (5.0), 173 (8.6), 159 (13.5), 147 (26.7), 146 (18.1), 145 (20.1), 144 (16.3), 132 (21.3), 131 (100), 130 (52.7), 129 (10.9); ^1H NMR ($CDCl_3$) δ 8.52 (s, 2 H, H-3 and -3′), 7.70 (dd, *J* = 8.5, 0.9 Hz, 2 H, H-4, -4′), 7.37 (d, *J* = 6.7 Hz, 2 H, H-6 and -6′), 7.19 (dd, *J* = 8.5, 6.7 Hz, 2 H, H-5 and -5′), 4.99 (s, 4 H, $ArCH_2O$), 3.33–3.75 (m, 16 H, OCH_2CH_2O). **59**·NaSCN complex (**59** in ethyl acetate and NaSCN in methanol, reflux 1 h, yield 65%): oil; ^1H NMR ($CDCl_3$) δ 8.58 (s, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 6.6 Hz, 2 H), 7.12 (m, 2 H), 4.91 (s, 4 H), 3.54–3.74 (m, 16 H). **59**·KSCN complex (**59** in ethyl acetate, KSCN in methanol, reflux 1 h, yield 70%): oil; ^1H NMR ($CDCl_3$) δ 8.66 (s, 2 H), 7.73 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 6.7 Hz, 2 H), 7.14 (dd, *J* = 8.5, 6.7 Hz, 2 H), 4.95 (s, 4 H), 3.52–3.65 (m, 16 H).

1,2,3,31-Tetraaza-12,15,18,21,24-pentaoxapentacyclo-[24.5.2.0^{2,10}.0^{4,9}.0^{30,33}]tritriaconta-3,5,7,9,26,28,30,32-octaene (60) was obtained similarly as coronand **58**: yield 9%; colorless oil; IR (neat) 2900, 1685, 1618, 1352, 1100, 940, 751 cm^{-1}; MS, *m/z* (relative abundance) 452 (6.2, M^+), 275 (22.0), 261 (11.3), 260 (14.2), 259 (25.6), 258 (24.0), 231 (11.1), 218 (10.5), 190 (11.4), 189 (12.6), 173 (19.9), 172 (12.1), 161 (10.2), 160 (16.9), 159 (16.1), 157 (12.8), 147 (57.9), 146 (35.7), 145 (40.2), 144 (25.0), 132 (25.7), 131 (100), 130 (35.0), 119 (12.5), 118 (21.3), 117 (14.5), 102 (93.5); ^1H NMR ($CDCl_3$) δ 8.42 (s, 1 H, H-3′), 7.18–7.80 (m, 7 H, H-4, -4′, -5, -5′, -6, -6′, and -7), 5.02 (s, 2 H, $ArCH_2O$ at C-7′), 4.96 (s, 2 H, $ArCH_2O$ at C-3), 3.61 (m, 16 H, OCH_2CH_2O). Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.58; H, 6.15; N, 12.65. **60**·NaSCN complex (**60** in ethyl acetate and NaSCN in methanol, reflux, 1 h, yield 52%): mp >330 °C; ^1H NMR ($CDCl_3$) δ 8.41 (s, 1 H), 7.20–7.80 (m, 7 H), 5.03 (s, 2 H), 4.94 (s, 2 H), 3.60 (m, 16 H). **60**·KSCN complex (**60** in ethyl acetate and KSCN in methanol, reflux 1 h, yield 61%): oil; ^1H NMR ($CDCl_3$) δ 8.52 (s, 1 H), 7.10–7.80 (m, 7 H), 5.04 (s, 2 H), 5.03 (s, 2 H), 3.63 (m, 16 H).

Sodium Bromide Complex of 2,2′-Biindazole-7,7′-diylbismethylene-1,10-diaza-18-crown-6 (61). A stirred suspension of 7,7′-bis(bromomethyl)-2,2′-biindazole (**56**) (0.100 g, 0.2 mmol),

(41) von Auwers, K.; Frese, E. *Chem. Ber.* **1926**, *59*, 544.

1,10-diaza-18-crown-6 (0.062 g, 0.2 mmol), and sodium carbonate (0.055 g, 0.6 mmol) was refluxed in dry acetonitrile (35 mL) for 2 h under argon. The reaction mixture was allowed to cool, the resulting suspension was filtered, and the filtrate was evaporated. Column chromatography (chloroform–ethanol 95:5) of the residue afforded **61**·NaBr·$2H_2O$ (63%) as a colorless gummy material: IR (KBr) 3455, 2880, 1630, 1545, 1390, 1360, 1100, 945 cm^{-1}; MS, *m/z* (relative abundance) 520 (3.1, M^+), 459 (2.5), 446 (6.5), 445 (21.2), 261 (10.7), 260 (19.1), 259 (28.2), 246 (21.6), 232 (9.4), 231 (10.3), 216 (21.2), 172 (21.0), 158 (13.7), 157 (10.1), 145 (11.6), 132 (16.1), 131 (100), 130 (19.9), 102 (17.1), 77 (10.4); ^1H NMR ($CDCl_3$) δ 9.48 (s, 2 H, H-3 and -3′), 7.87 (m, 2 H, H-4 and -4′), 7.26 (m, 2 H, H-6 and -6′), 7.12 (m, 2 H, H-5 and -5′), 3.95 (s, 4 H, $ArCH_2N$), 3.60 (m, 12 H, OCH_2CH_2O), 3.25 (m, 4 H, OCH_2CH_2O), 2.70 (m, 8 H, CH_2N). Anal. Calcd for $C_{28}H_{36}N_6O_4NaBr·2H_2O$: C, 50.99; H, 6.07; N, 12.75; Br, 12.11. Found: C, 50.98; H, 6.00; N, 12.69; Br, 12.25.

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Conjugate Addition of Methanol to α-Enones: Photochemistry and Stereochemical Details

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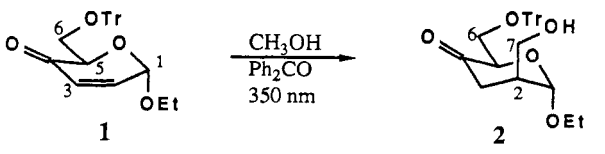
Previous studies seemed to indicate that the benzophenone-initiated photoaddition of methanol to the carbohydrate-derived α-enone **1** occurred more readily than to comparable carbocyclic α-enones. A mechanistic study was therefore undertaken (a) to establish the mechanistic details of the photoaddition reaction and (b) to compare the quantum yields of the carbohydrate and carbocyclic substrates. Evidence is presented that shows that the only important photochemical event is hydrogen abstraction (to give $^{\bullet}CH_2OH$) and that energy transfer to the enone substrate is not a factor. The course of addition of $^{\bullet}CH_2OH$ to **1** has been monitored by ESR spectroscopy, and the spectrum is best interpreted as involving the initial formation of an equilibrium mixture of the pseudochair and pseudoboat intermediates **26** and **27**, respectively. The quantum yields were determined for **1**, **5**, and **11** in order to discover the effect of (a) the pendant oxygen (**1** vs **5**) and (b) the ring oxygen (**5** vs **11**). The latter two give both axial and equatorial photoadducts, and within experimental error, there was no detectable difference in their reactivities. However, for the axial adduct formation, the carbohydrate enone **1** was found to be more reactive than oxane **5** or carbocycle **11**.

Introduction

In 1972, Fraser-Reid and co-workers reported that the carbohydrate-derived α-enone **1** undergoes efficient benzophenone-initiated photoaddition of methanol to give the hydroxymethyl adduct **2** (Scheme I).[2] In subsequent studies aimed at extending the scope of this process,[3,4] two general observations were made. Firstly, a wide variety of other oxygenated compounds of the type RCH_2OH, $RCH(OR')_2$, and RCHO also served as excellent addends.

Scheme I



1 **2**

Secondly, the α-enone **1** appeared to react faster and give better yields than its carbocyclic counterparts. A sampling of the data relating to the latter observation is shown in Table I.

In subsequent years, the Fraser-Reid group has also observed unusual reactivity for enone **1**, as compared with other α-enones, in a variety of cycloaddition reactions.[5]

(1) Taken in part from the Ph.D. Thesis of Z.B., University of Maryland, 1986.
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(4) Fraser-Reid, B.; Anderson, R. C.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3986.
(5) For convenient summaries of these reactions, see: Fraser-Reid, B. *Acc. Chem. Res.* **1975**, *8*, 192; **1985**, *18*, 347.

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