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MOLECULAR INCLUSION CRYSTALS OF NOVEL HETEROCYCLIC HOST COMPOUNDS

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Abstract Inclusion phenomena of the solvents such as hexane, benzene, and dichloromethane in either the crystals or glassy states of the armed-1,4,8,12-tetrazacyclopentadecanes were observed, whereas only few inclusion was found in the armed 1,4,8,11-tetraazacyclotetradecanes. As further examples of undesigned inclusion hosts, the 1:2 adduct, obtained by Diels-Alder reaction of [2.2]paracyclophane with 4-phenyl-1,2,4-triazoline-3,5-dione, along with the 1:2 adducts from 5-cyano-1,4-diphenylpyridazino[4,5-*a*]-indolizines and dimethyl acetylenedicarboxylate (DMAD) are described.

INTRODUCTION

In order to explore the new host compounds having excellent binding abilities toward transition metal ions such as poisonous mercury (II), cadmium (II), lead (II), or chromium (VI) ions, we have prepared a variety of novel heterocyclic host molecules.[1] Specifically, high pressure S_NAr reactions (0.6-0.8GPa)[2] were applied for functionalization of

monoaza- and diaza-crown ethers to afford novel host compounds possessing heteroaromatic sidearms.[1] Binding properties of these compounds were investigated by liquid membrane transport, extraction as well as ^{13}C NMR titration experiments, whereas the structures of the complexes of (metal salt)-(host compound) were determined by X-ray crystallography.[1b] On the other hand, the design of and search for organic hosts capable of forming inclusion compounds either ions or uncharged molecules are of the current interests which stems from many points of views including analytical applications, transport processes, reaction catalysis, artificial enzyme mimicry, and others.[3] In the course of our studies, we have found the inclusion phenomena of the solvents such as hexane, benzene, and dichloromethane in either the crystals or glassy states of the armed-1,4,8,12-tetrazacyclopentadecanes. In contrast, only few inclusion was observed in the armed 1,4,8,11-tetraazacycloteradecanes. As further examples of undesigned inclusion hosts, the 1:2 adduct, obtained by Diels-Alder reaction of [2.2]paracyclophane with 4-phenyl-1,2,4-triazoline-3,5-dione, along with the 1:2 adducts from 5-cyano-1,4-diphenylpyridazino[4,5-*a*]-indolizines and dimethyl acetylenedicarboxylate (DMAD) will be described.

TETRAAZAMACROCYCLES

The modification of tetraaza-macrocyclic ligands to control and tune the redox properties of coordinated metal centers has been the subject of much interest.[3] Therefore, as a second stage of our project on armed oligocycles[4] as well as armed macrocycles that are directly connected to aromatic heterocycles, the high pressure S_NAr reactions[5] were applied to tetrakisheteroarylation of 1,4,8,12-tetrazacyclopentadecane and 1,4,8,11-tetraazacyclotetradecane,[6] since, to the best our knowledge, there seems no example of these related tetraazamacrocycles whose nitrogen atoms are directly connected to aromatic heterocycles. In a typical experiment, a mixture of 1,4,8,12-tetrazacyclopentadecane (**1**, 2

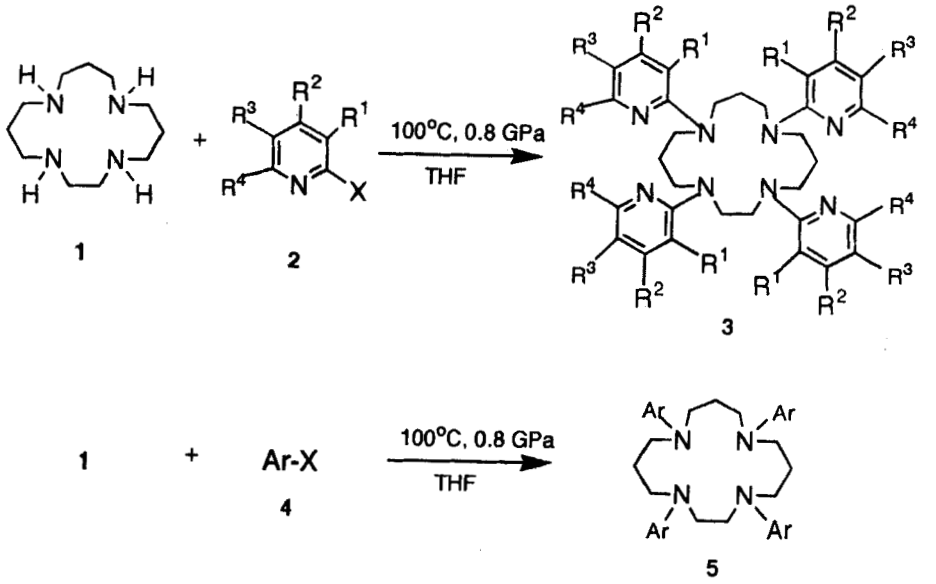


Table 1. Armed 1,4,8,12-Tetraazacyclopentadecanes (3)

Entry	Substituents					Reaction time	Yield	Mp	Inclusion
	R^1	R^2	R^3	R^4	X	(d)	(%)	(°C)	(Guest/Host)
1	H	H	H	H	F	4	61[a]	190 –192	none
2	H	H	CF_3	H	Cl	3	84	202 – 203	1/2 CH_2Cl_2
3	NO_2	H	H	H	Cl	5	86	66 – 67	1/2 benzene
4	Cl	H	Cl	H	Cl	4	82	110 –112	none
5	CF_3	H	Cl	H	Cl	4	91	113 –114	none
6						4	55	105 –106	1/2 hexane
7	CF_3	H	CF_3	H	Cl	4	83	glass	none
8	Cl	H	CF_3	H	Cl	5	92	glass	1/2 benzene
9	H	CF_3	CF_3	H	Cl	5	64	243 – 250	1/2 benzene

[a] Only trace amount of the product was obtained in refluxing toluene in our hands.

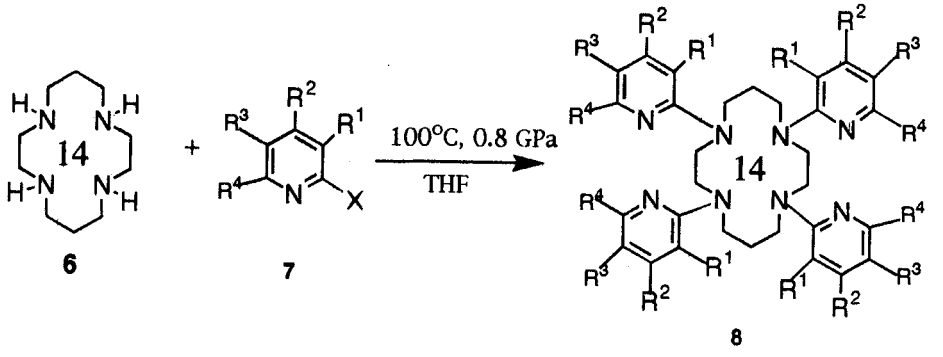
mmol), halogenoheterocycle (**2** or **4**, 10 mmol), and triethylamine (10 mmol) was diluted with tetrahydrofuran in an 8 ml polytetrafluoroethylene capsule that was compressed to 0.8 GPa and heated to 100°C for the stated time in Tables 1 and 2. Only low yields (<10%) of the products were obtained in the reactions of **1** with 2-chloropyridine or

Table 2. Armed 1,4,8,12-Tetraazacyclopentadecanes (5)

Entry	Halogenoheterocycles 4 Ar	X	Reaction time (d)	Yield (%)	Mp (°C)	Inclusion (Guest/Host)
10		Br	5	23	155–156	none
11		Cl	4	81	270–272	1/2 benzene
12		Cl	3	74	243–244	none
13		Cl	3	65	182–183	1/2 CH_2Cl_2

2-bromopyridine which does not possess an additional activating group, whereas an analogous reaction of **1** with 2-fluoropyridine produced **3** (R^1=R^2=R^3=R^4=H) in 61% yield. This is not unexpected because the relative reactivities in S_NAr reaction increase in the order C≤Br≤I≤F.[7] As expected in terms of resonance stabilization of Meisenheimer intermediate, the 2-chloropyridines **2** possessing an electron-withdrawing substituent at a or g position with respect to a leaving chloro atom produced the corresponding azamacrocycles **3** in good yields (entries 2–9). Interestingly, some of these products form, during usual work-up by chromatographic separation, inclusion complexes either with benzene or dichloromethane or hexane with a 2:1 (host/guest) stoichiometry. The stoichiometry is based upon elemental analysis as well as integrations by ^{1}H-nmr spectra. ^{1}H- and ^{13}C-nmr spectra were in accord with the structures **3** for all the compounds. The formation of inclusion compounds seems to depend on solvents used in work-up procedure ; for instance, the product from 2,5-dichloro-3-trifluoromethylpyridine forms the inclusion complex (host/hexane=1/2) when chromatographed using hexane/dichloromethane, whereas no inclusion complex was formed when ethyl acetate/dichloromethane was used as eluent. These inclusion complexes are probably of lattice type (*clathrate*) rather than of molecular type (*cavitate*),[4] though attempts to obtain a suitable crystal for an X-ray analysis have hitherto been unsuccessful.

The modification of the more symmetrical and more popular 14-membered analogue (cyclam) would be of interest because of the potentially intriguing thermal properties.[8] In comparison with the 15-membered macrocycles **3**,only few inclusion was observed in the armed



6 **7** **8**

Table 3. Armed 1,4,8,11-tetraazacyclotetradecanes (**8**)

Entry	Substituents					Reaction time (d)	Yield (%)	Mp (°C)
	R^1	R^2	R^3	R^4	X			
1	H	H	H	H	F	4	7[a)]	202–203
2	H	H	CF_3	H	Cl	6	62	170–171
3	CF_3	H	H	H	Cl	6	64	243–244
4	H	H	Cl	H	Cl	5	74	171–172
5	Cl	H	H	H	Cl	4	33	152–153
6	H	H	H	Cl	Cl	4	40	259–262
7	H	H	CF_3	CF_3	Cl	6	75	146–147
8	Cl	H	CF_3	H	Cl	6	71	157–158
9	Cl	H	Cl	H	Cl	4	63	174–176

[a] No product was obtained in refluxing toluene in our hands.

1,4,8,11-tetraazacycloteradecanes **8**; this is probably due to the highly symmetrical character and therefore much better packing properties of **8** in crystal state. This is also reflected in the much lower solubilities of **8** in most solvents. (Table 3) However, the armed 1,4,8,11-tetra-azacycloteradecane **8** (R^1=Cl, R^2=R^3=R^4=H) formed inclusion complex

with dichloromethane when recrystallized from dichloromethane.(Fig. 1) The host molecules are highly symmetrical in conformation, each guest molecule being between the pyridine sidearms of each host molecule that stands opposite to each other in parallel.

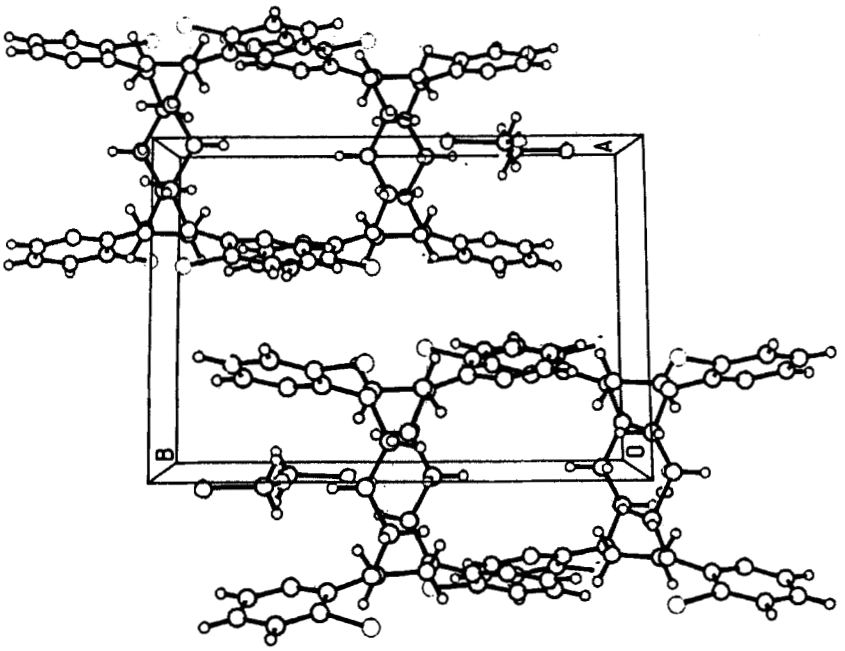
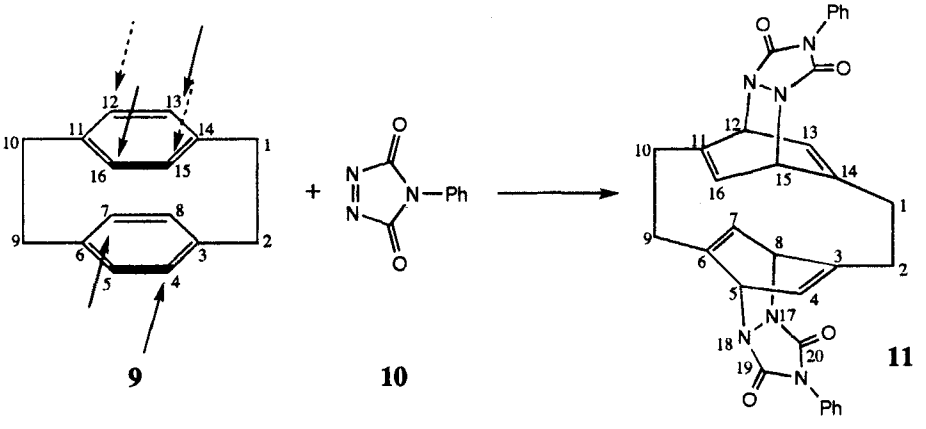


FIGURE 1 Molecular packing of the armed 1,4,8,11-tetraaza-cycloteradecane **8** (R^1=Cl, R^2=R^3=R^4=H)

1:2 ADDUCT OF [2.2]PARACYCLOPHANE WITH 4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE

Non-annelated arenes normally do not participate as diene components in Diels-Alder reactions.[10] To surmount this lack of reactivity, considerable improvements have been realized and still challenged via recourse to chemical modification of dienes[11] and dienophiles, catalysis by Lewis acids, and high temperature and high pressure[2] as well. From

the diene side, for example, this may be achieved by the incorporation of bridging structural units into arenes. Specifically, when simple aromatic 6π-electron systems, which are extremely sluggish in Diels-Alder additions, are incorporated into a [2n]cyclophane system such as [2.2]paracyclophane (**9**) that is a formal dimer of p-xylene, a dramatic increase in the rate of addition is observed in certain cases.[12] Indeed, the super dienophile, 4-phenyl-1,2,4-triazoline-3,5-dione (**10**) adds to **9** even at 20°C. However, Hoph et al. reported the 4,7:12,15-parallel bridge additions between **9** and **10** without any evidence,[12,13] in disagreement with the X-ray analysis of the 1:2 adduct obtained by Diels-Alder reaction of **9** with N-methylmaleimide which arises from 4,7:13,16-cross bridge additions rather than 4,7:12,15-parallel bridge additions.[14a] Therefore, Diels-Alder reaction of [2.2]-paracyclophane with



4-phenyl-1,2,4-triazoline-3,5-dione was reinvestigated.[14b] The stereochemistry of the 1:2 adduct was established to be **11** by the X-ray analysis,[15] the reaction taking place in the sense of 4,7:13,16-cross bridge additions rather than 4,7:12,15-parallel bridge additions (Fig.2). When the product was recrystallized from acetone/dichloromethane, it has proven that the needle crystal constitutes an inclusion complex of **11** with acetone (Fig. 2). The molecular packing of **11** is depicted in

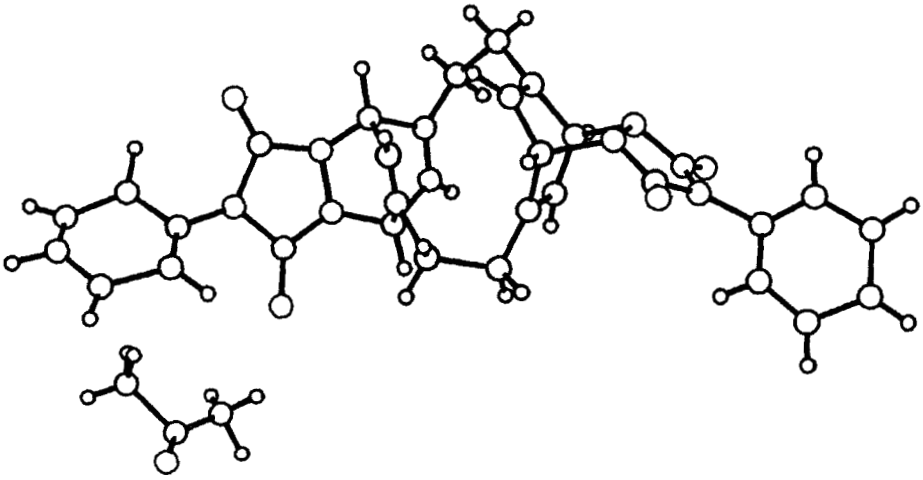


FIGURE 2 Molecular structure of **11**

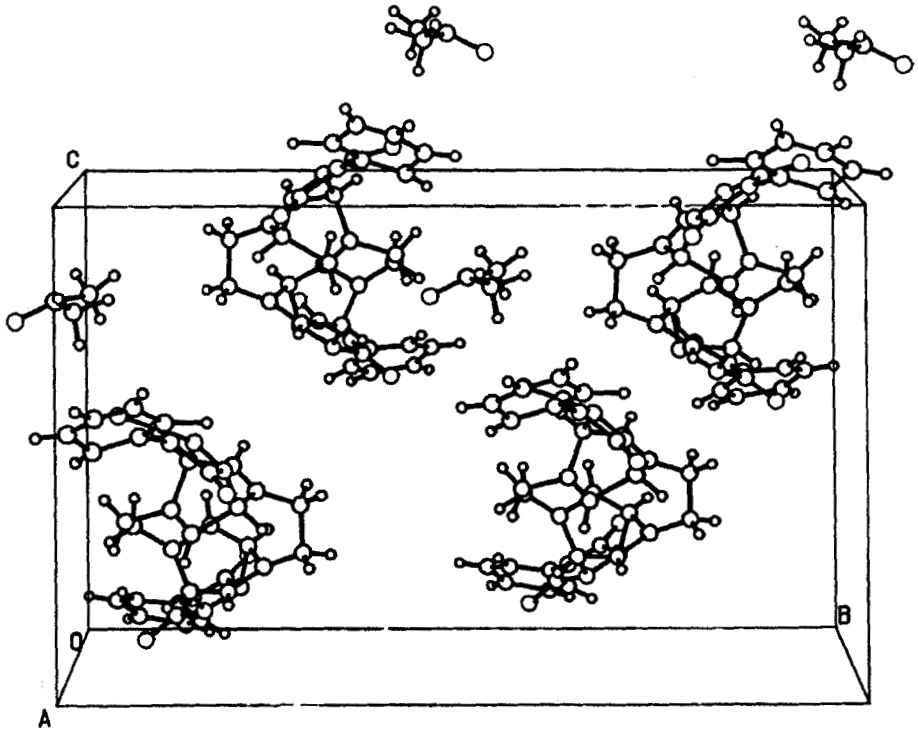


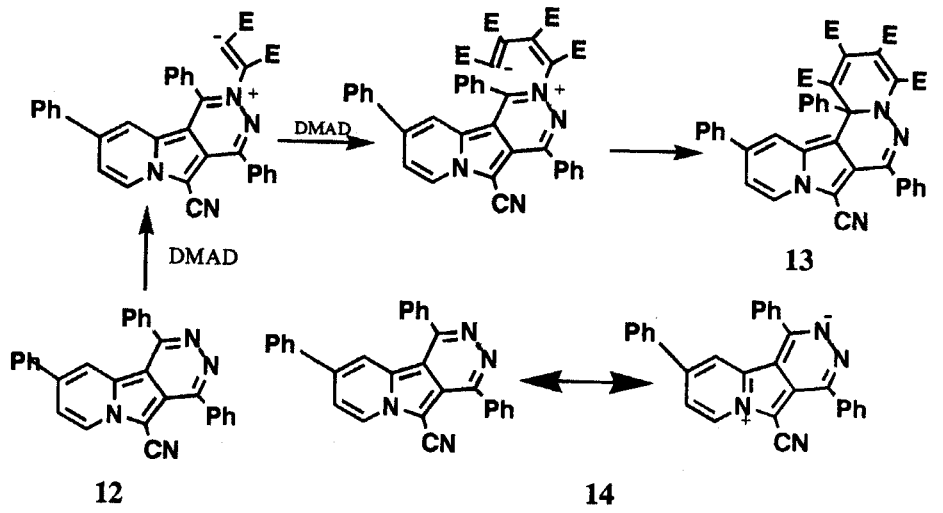
FIGURE 3 Molecular packing of **11**

Fig. 3. It is interesting to note that (a) the chiral molecule **11** is distorted in a spiral fashion in the crystal state, (b) the C=O bond of the guest molecule of acetone is bended more than 20 degree from the normal trigonal plane, (c) the enatiomeric 1:2 adduct constitutes the 1:1 chiral inclusion crystal packing, (d) each cavity that the guest acetone occupies is in chiral environment. The theoretical explanation based upon molecular orbital calculations regarding the crossbridge selectivity will be a subject of future communications.

8-CYANO-7,13c-DIPHENYL-12-PHENYL-1,2,3,4-TETRAMETHOXY-CARBONYL-13cH-PYRIDO[1',2':2,3]PYRIDAZINO[4,5-a]INDOLIZINE

Investigations of addition reactions of acetylenic esters to nitrogen-containing heterocycles have been stimulated partly because of the problems involved in unraveling the novel types of reactions and structures sometimes observed.[16] Since 1,2-pyridazine-fused 3-cyanoindolizines are readily available by 1,3-dipolar cycloaddition reactions of dicyanomethylides with dibenzoylacetylene, followed by treatment with hydrazine,[17] we examined reactions of 8-phenyl1,4-diphenylpyridazino[4,5-a]indolizine (**12**) with dimethyl acetylene-dicarboxylate (DMAD).[18]

Reaction of **12** with three equimolar amounts of DMAD in refluxing toluene for 41 h gave the 1:2 adduct (yellow crystals, mp 284-285 °C) in 40% yield, whose composition was based upon the mass spectral and microanalytical analysis The structure was confirmed to be 8-cyano-7,13c-diphenyl-12-phenyl-1,2,3,4-tetramethoxy-carbonyl-13cH-pyrido[1',2':2,3]pyridazino[4,5-a]indolizine (**13**) by an X-ray analysis.[19] Regiospecific formation of **13** could be explained by higher nucleophilicity of nitrogen at 2 position than that at 3 position due to the resonance hybrid (**14**), since the adducts probably arise from successive Michael additions shown in Scheme 3. The 1:2 adduct **13** was crystallized from hexane-dichloromethane giving yellow, prismatic crystals which proved



to be crystalline complexes with dichloromethane. The molecular packing of **13** • CH_2Cl_2 is depicted in Fig. 4 Intriguingly, the guest molecules of dichloromethane are included in the chimney that the host molecules of **13** construct along b axis.

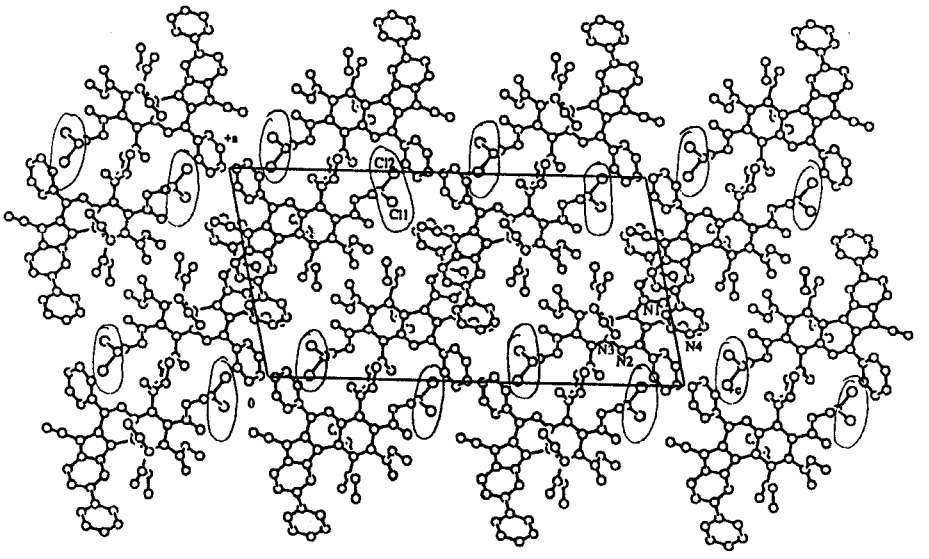


FIGURE 4 Molecular packing of **13** (Dichloromethane is circled for clarity).

ACKNOWLEDGMENTS

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9. Crystal data of **8** (R^1=Cl, R^2=R^3=R^4=H) $C_{31}H_{34}N_8Cl_6$, M=731.38, triclinic, space group $P\bar{1}$ (#2), a=10.42(1), b=14.557(8), c=12.13(1)Å, α=90.00(6)° β=105.78(8)°, γ= 90.03 (8)°, V=1772(3)Å^3, Z=2, Dc=1.371 gcm^{-3}, μ=5.20 cm^{-1}. The structure solution (direct methods) and refinement (full-matrix least-squares) was performed using the

TEXSAN software and based on 2677 observed intensities [F>3.0σ(F)] from 8570 measured data (2θ<55.1°). Final R and R_w values were 0.117 and 0.131.

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15. Crystal data of **11**: $C_{32}H_{26}N_6O_4$, M=558.60, monoclinic, space group Cc (#9), a=8.548(4), b=24.467(4), c=14.966 (2)Å, β=100.59 (2)°, V=3077(1)Å^3, Z=4, Dc=1.206 gcm^{-3}, μ=0.77 cm^{-1}. The structure solution (direct methods) and refinement (full-matrix least-squares) was performed using the TEXSAN software and based on 183 observed intensities [F>3.0σ(F)] from 818 measured data (2θ<55.0°). Final R and R_w values were 0.068 and 0.066.
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19. Crystal data of **13**: $C_{42}H_{32}N_4O_8Cl_2$, M=791.64, monoclinic, space group $P2_1/c$ (#14), a=15.005(2), b=8.9852(9), c=29.129(4)Å, β=100.92(1)°, V=3856.2(9)Å^3, Z=4, Dc=1.363 gcm^{-3}, μ=20.14 cm^{-1}. The structure solution (direct methods) and refinement (full-matrix least-squares) was performed using the TEXSAN software and based on 3001 observed intensities [F>3.0σ(F)] from 5481 measured data (2θ<120°). Final R and R_w values were 0.053 and 0.071.