Amides and Sulfonamides: Efficient Molecular Padlocks for the Template Synthesis of Azacyclam (1,3,5,8,12-Pentaazacyclotetradecane) Macrocycles†

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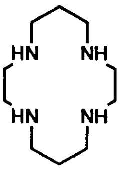
Amides and sulfonamides, both aliphatic and aromatic, acted as efficient locking fragments, in the presence of formaldehyde and base (triethylamine), in closing the open-chain tetramine 1,9-diamino-3,7-diazanonane around labile metal centres prone to a square type of co-ordination, *i.e.* Ni^{II} and Cu^{II}, to give a pentaazamacrocyclic complex of the azacyclam family. The product of the copper(II) template reaction involving methanesulfonamide as a locking fragment (3-methanesulfonyl-1,3,5,8,12-pentaazacyclotetradecane)dinitratocopper(II), was obtained in crystalline form and its crystal and molecular structure determined from single-crystal X-ray diffraction data, collected with the use of Cu-Kα radiation: trigonal, space group *R*3*c*, $a = b = c = 14.997(3)$ Å, $\alpha = \beta = \gamma = 98.48(2)°$, $Z = 6$. Only the four secondary amine nitrogen atoms of the macrocycle are bound to the Cu^{II}, giving a regular square stereochemistry. The tertiary nitrogen atom N(1), which presents distinct sp^2 structural features, is not involved in the co-ordination. The axial positions of the elongated octahedron are occupied by oxygen atoms of the nitrate ions. A kinetic investigation was carried out on the copper(II) template reactions involving diprotic acids as locking fragments, including amides, amines and carbon acids, such as nitroethane and diethyl malonate: for the systems investigated the rate of the template reaction seems to be related to the strength of the diprotic acid. This suggests that the monodeprotonated form of the acid is present in the rate-determining step of the cyclisation process.

The metal complexes of the 14-membered cyclic tetramine 1,4,8,11-tetraazacyclotetradecane, cyclam **I**, represent reference systems in the co-ordination chemistry of azamacrocycles. Comparison with tetramine macrocycles of different atomicity (from 12 to 16) has shown that cyclam complexes display the highest thermodynamic[1] and kinetic[2] stability. Furthermore, as the especially strong in-plane M–N interactions considerably raise the energy of the highest-occupied d level, co-ordination by cyclam favours the abstraction of electrons from the encircled metal centre and opens the way to unusually high oxidation states.[3] Moreover, its cyclic nature helps such oxidised complexes to persist in solution. Finally, cyclam can be obtained on a multigram scale through the convenient nickel(II) template procedure discovered by Barefield in 1972.[4]

More recently, another template synthesis of cyclam analogues was proposed by Suh and Kang:[5] this procedure involves condensation of the primary amine groups of an open-chain ligand co-ordinated to Ni^{II} or Cu^{II} (*e.g.* two molecules of ethylenediamine) with formaldehyde and a primary amine NRH_2. We followed this route to prepare the pentaazamacrocycle azacyclam **II**.[6]

An X-ray investigation on the low-spin $[Ni^{II}(azacyclam)][ClO_4]_2$ complex showed that: (*i*) the tertiary nitrogen atom is definitively not involved in co-ordination to the metal, (*ii*) it presents an intermediate hybridisation between sp^3 and sp^2, and (*iii*) it is so poorly basic that it is protonated only in 1 mol dm^{-3} strong acid solution.[6] As a consequence, azacyclam behaves as a four-co-ordinating tetramine and its co-ordination mode is very similar to that of cyclam. In particular, $[Ni^{II}(azacyclam)]^{2+}$ displays a solution behaviour very similar to that of $[Ni^{II}(cyclam)]^{2+}$: for instance, it exhibits an extreme resistance to demetallation, persisting in strongly acidic media, and can be easily oxidised to the solution-stable nickel(III) state.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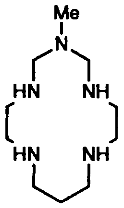
II

We have now found that the NH_2 group of any kind of amide (carboxamides and sulfonamides, both aliphatic and aromatic) works well as a locking fragment (or molecular padlock) in syntheses of the type depicted in Scheme 1, assisted by metal(II) centres (M = Ni or Cu). This behaviour fits well with the observation that the molecule used as a locking fragment should present distinctive acidic properties and, in particular, should behave as a diprotic acid. In this sense the primary amido group is a much stronger acid than the primary amine group. The use of $RCONH_2$ and RSO_2NH_2 molecules as locking fragments offers the opportunity to obtain, through a convenient one-pot procedure, complexes of Ni^{II} and Cu^{II} with a cyclam-like macrocycle carrying the desired functional group R on its backbone.

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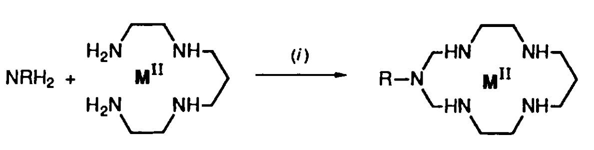
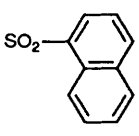
† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.



R	M = Cu	M = Ni
Me		**1b**
COMe	**2a**	**2b**
COPh	**3a**	**3b**
SO_2Me	**4a**	**4b**
SO_2Ph	**5a**	**5b**
$SO_2C_6H_4Me$-*p*	**6a**	**6b**
$SO_2C_6H_4CO_2H$-*p*	**7a**	
	**8a**	**8b**

Scheme 1 (*i*) CH_2O, base, EtOH

Experimental

Physical Measurements.—The UV/VIS spectra were measured on a Hewlett-Packard 8452 diode-array spectrophotometer. Melting points were recorded on a Gallenkamp apparatus in open capillaries.

Materials.—Unless otherwise stated, commercial grade chemicals were used without further purification. 1,9-diamino-3,7-diazanonane was prepared as described for the analogous 1,10-diamine-4,7-diazadecane,[7] distilled at reduced pressure [125 °C, 5 × 10^{-2} Torr (*ca.* 6.65 Pa)] and stored over NaOH in a refrigerator.

Synthesis of Naphthalene-2-sulfonamide.—Naphthalene-2-sulfonyl chloride (10 mmol) was dissolved in diethyl ether (25 cm^3) and treated, under magnetic stirring, with 32% aqueous NH_3 (80 cm^3). A white precipitate formed overnight, which was filtered off, washed with water and dried *in vacuo*. Yield: 72%, m.p. 211–212 °C (Found: C, 58.1; H, 4.4; N, 6.8. Calc. for $C_{10}H_9NO_2S$: C, 58.0; H, 4.3; N, 6.8%).

Template Synthesis of Macrocyclic Complexes. General Method.—Copper(II) nitrate or nickel(II) chloride (10 mmol) was dissolved in ethanol (40 cm^3) in a round-bottomed flask equipped with a reflux condenser, a thermometer and a dropping funnel. A solution of 1,9-diamino-3,7-diazanonane (10 mmol) in ethanol (20 cm^3) was added dropwise to the magnetically stirred solution of the metal salt. The solution was warmed to 50 °C and the chosen amide (carboxamide or sulfonamide, 10 mmol, dissolved in the minimum volume of ethanol, *i.e.* 20–100 cm^3) was added dropwise. Then, triethylamine (3 cm^3, in one portion) and 40% aqueous formaldehyde (10 cm^3, in three or four portions during the reaction) were added through the dropping funnel. Heating and magnetic stirring were maintained for 4–7 d. In some preparations the complex precipitated during the reaction: in this case it was filtered off through a sintered glass funnel, washed with cold ethanol and acetone, dried *in vacuo* and eventually recrystallised. Otherwise, at the end of heating, the solution was filtered to eliminate small amounts of metal hydroxide and concentrated to favour the precipitation of the metal complex. In a few cases no precipitate was obtained by this procedure and it was necessary to add aqueous $HClO_4$ to precipitate the metal complex as a perchlorate. Yields, elemental analysis results and spectral data are reported in Table 1.

It should be noted that all the nickel(II) complexes exist in the investigated solvents of varying donating tendencies as a mixture of the paramagnetic octahedral form and of the diamagnetic square form. This situation, which is common to metal complexes of 14-membered tetraazamacrocycles, prevented characterisation using NMR techniques.

CAUTION: Perchlorate salts of metal complexes are potentially explosive, and due care must be employed when handling them. In particular, such compounds should never be heated as solids.

X-Ray Diffraction Study of Salt **4a**.—X-Ray measurements were carried out, at room temperature, on a Siemens A.E.D. diffractometer on line with an IBM personal computer using nickel-filtered Cu-Kα radiation ($\bar{\lambda}$ = 1.541 78 Å). The lattice parameters were determined by a least-squares fit of $37(\theta,\chi,\varphi)_{hkl}$ reflections found in a random search of the reciprocal lattice in the range $33 < \theta < 40°$.

Crystal data. $C_{10}H_{25}CuN_7O_8S{\cdot}1.33H_2O$, M = 490.97, trigonal, space group $R\bar{3}c$, $a = b = c$ = 14.997(3) Å, $\alpha = \beta = \gamma$ = 98.48(2)°, U = 3250(1) $Å^3$, Z = 6, D_c = 1.505 g cm^{-3}, $F(000)$ = 1538, μ(Cu-Kα) = 27.92 cm^{-1}.

The intensities of the $\pm h$, $+k$, $+l$ reflections were determined by analysis of the profiles, obtained in the θ–2θ scan mode, according to the Lehmann and Larsen method.[8] The intensity of one standard reflection collected every 100 showed no significant fluctuation. A total of 6109 reflections (2069 unique) were measured in the range $3 \leqslant \theta \leqslant 70°$. The 1946 unique reflections, having $I \geqslant 2\sigma(I)$, were considered observed and used in the analysis. The intensities were corrected for Lorentz and polarisation effects, but not for absorption.

The structure was solved by direct methods using SHELX 86[9] and completed and refined with SHELX 76.[10] A full-matrix least-squares refinement was carried out. 285 Parameters were refined: the overall scale factor, atomic coordinates and anisotropic thermal parameters for all the non-hydrogen atoms. The water molecules found in the lattice were treated with isotropic thermal parameters. One water molecule lies on a three-fold crystallographic axis; a second is statistically distributed between two different positions with occupancy factors 0.55 [O(2w)] and 0.45 [O(3w)] respectively. The hydrogen atoms were taken in their calculated positions with the geometrical constraint C–H 1.0 Å and refined 'riding' on the corresponding C or N atoms except for the methyl hydrogens which were refined as a rigid body with a common isotropic thermal parameter. Two water hydrogens were found in the Fourier Δ*F* map and refined. Unit weights were used in the last cycles of refinement. The final *R* was 0.054. The highest peak in the final Fourier Δ*F* map was 1.06 e $Å^{-3}$ close to the Cu atom. Final atomic coordinates for the non-hydrogen atoms are given in Table 2.

The atomic scattering factors were obtained by analytical approximation according to the literature.[11] Geometrical calculations were performed by PARST.[12] Perspective plots of the molecule were obtained by PLUTO.[13] All calculations were performed on the Gould Encore 91 computer of the Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles.

Results and Discussion

Template Synthesis of Azacyclam Complexes of Ni^{II} *and* Cu^{II}.—The general synthetic procedure involves moderate heating of ethanol–water solutions (90 : 10) 0.01–0.05 mol dm^{-3} in the metal salt, $NiCl_2{\cdot}6H_2O$ or $Cu(NO_3)_2{\cdot}3H_2O$, and containing equimolar amounts of the open-chain tetramine 1,9-diamino-3,7-diazanonane, and of the NRH_2 molecule used as a padlock. The solution contained also 2 equivalents of triethylamine and an excess of formaldehyde. In some cases the

Table 1 Experimental data for macrocyclic complexes of Cu^{II} and Ni^{II}

Complex	Salt	Colour	Yield (%)	Analysis[a] (%) C	H	N	λ_{max}[b]/nm	ε[b]/dm^3 mol^{-1} cm^{-1}
2a	NO_3	Violet	28	30.2 (30.7)	5.9 (5.8)	22.4 (22.7)	518	78
3a	NO_3	Violet	45	38.7 (39.0)	5.7 (5.5)	19.6 (19.9)	518	86
4a	NO_3	Violet	53	25.9 (25.7)	5.55 (5.4)	20.5 (21.0)	520	87
	ClO_4	Pink-violet		22.3 (22.2)	4.8 (4.65)	12.9 (12.9)		
5a	NO_3	Violet	43	33.6 (33.9)	5.25 (5.1)	18.3 (18.45)	526	89
6a	NO_3	Violet	45	35.15 (35.4)	5.5 (5.5)	17.9 (18.05)	526	93
	ClO_4	Pink-violet		30.6 (30.4)	4.7 (4.6)	13.0 (13.3)		
7a	NO_3	Violet	33	33.75 (33.5)	4.9 (4.75)	17.0 (17.1)	524	88
	ClO_4	Pink		29.9 (29.7)	4.3 (4.2)	10.7 (10.8)		
8a	NO_3	Violet	30	39.3 (39.4)	5.1 (5.0)	16.8 (16.9)	520	85
2b	ClO_4	Orange-yellow	14	26.8 (26.4)	4.9 (5.0)	14.1 (14.0)		
3b	ClO_4	Orange-yellow	13	33.9 (34.1)	4.6 (4.8)	12.7 (12.4)		
4b	Cl	Pale violet	42	29.0 (29.4)	6.3 (6.2)	16.8 (17.1)		
5b	Cl	Pale violet	27	37.7 (38.2)	5.6 (5.7)	14.6 (14.9)		
6b	Cl	Pale violet	24	39.2 (39.6)	6.1 (6.0)	14.2 (14.4)		
	ClO_4	Orange		30.9 (30.65)	4.7 (4.7)	11.1 (11.2)		
8b	Cl	Pale violet	62	43.4 (43.8)	5.5 (5.6)	13.2 (13.4)		
	ClO_4	Orange		34.8 (35.2)	4.4 (4.5)	10.6 (10.8)		

[a] Required values are given in parentheses. [b] In water.

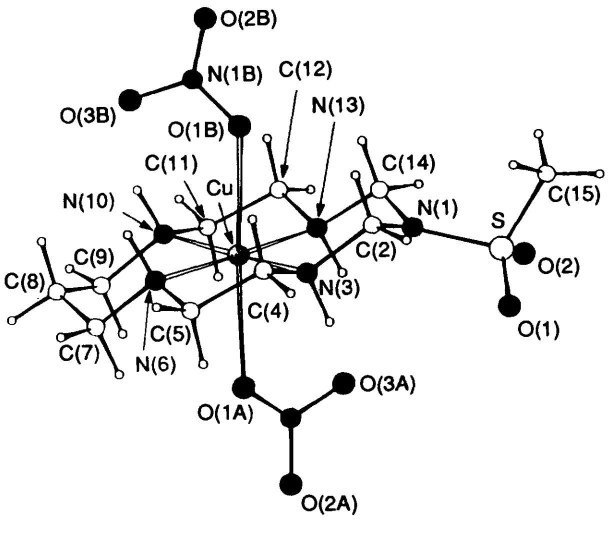


Fig. 1 Perspective view of the complex (3-methanesulfonyl-1,3,5,8,12-pentaazacyclotetradecane)dinitratocopper(II)

azacyclam complex precipitated during the course of the reaction, in other cases precipitation occurred after concentration or through addition of perchloric acid; in the latter case the complex was obtained in the form of a perchlorate salt. Yields for the investigated reactions are summarized in Table 1.

All the obtained complexes display typical macrocyclic inertness: addition of strong acid, hydrochloric or perchloric, to their aqueous (when soluble), ethanol or acetonitrile solutions did not cause any decomposition, as indicated by the persistence of the absorption bands of the metal tetramine chromophore. In the case of the copper(II) complex obtained with methanesulfonamide as a locking fragment, crystals suitable for X-ray analysis were grown from aqueous ethanol.

Crystal and Molecular Structure of (3-*Methanesulfonyl*-1,3,5,8,12-*pentaazacyclotetradecane*)*dinitratocopper*(II)–*Water* (3/4). The crystal structure determination of the dinitrate of **4a** shows that it exists in the stoichiometric composition [CuL(NO_3)$_2$]·1.33H_2O (L = 3-methanesulfonyl-1,3,5,8,12-pentaazacyclotetradecane) and that two nitrate oxygen atoms are axially co-ordinated to the metal centre. Fig. 1 shows a perspective view of the molecular complex.

The four secondary amine nitrogens of the azacyclam ligand are bound to the metal centre [average Cu–N distance 2.011(8) Å] in a square (although slightly distorted) planar arrangement (Fig. 1), whereas the average Cu–O axial distance is 2.543(9) Å (Table 3). The Cu is only 0.003(2) Å out of the least-squares plane defined by the four co-ordinated nitrogens and the orientations of the Cu–O bonds slightly deviate [3.2(2)–4.4(3)°] with respect to the normal to the CuN_4 plane.

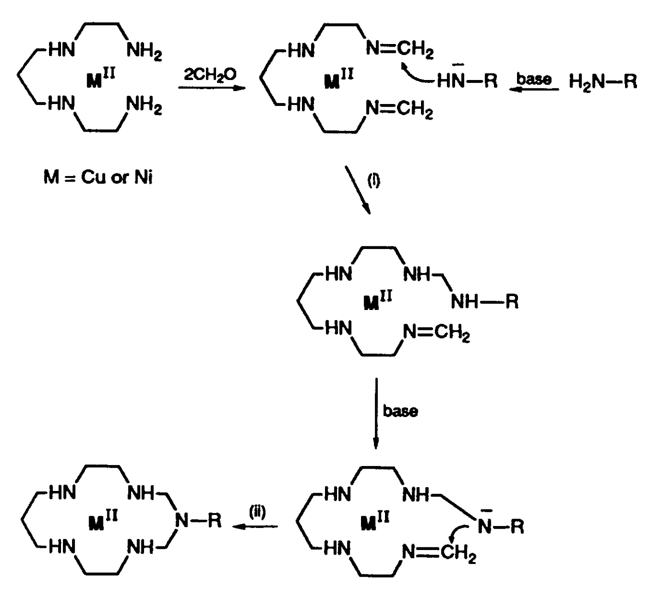
The two NH hydrogens of one six-membered chelate ring lie up and the two NH hydrogens of the other six-membered ring lie down with respect to the co-ordination plane, as observed in [Cu^{II}(cyclam)][ClO_4]$_2$;[14] flattened chair and *gauche* conformations are observed for the six- and five-membered chelate

Table 2 Fractional atomic coordinates (× 10^4) with estimated standard deviations (e.s.d.s) in parentheses for the non-hydrogen atoms of **4a**·1.33H_2O (nitrate salt)

Atom	*X*/*a*	*Y*/*b*	*Z*/*c*
Cu	7 262(1)	4 734(1)	998(1)
N(1)	7 050(5)	5 114(5)	−1 047(5)
C(2)	7 889(6)	4 804(7)	−744(6)
N(3)	7 746(5)	4 200(5)	−66(5)
C(4)	8 610(7)	3 878(7)	278(6)
C(5)	8 396(8)	3 411(7)	1 100(7)
N(6)	8 066(5)	4 045(5)	1 750(5)
C(7)	7 649(8)	3 586(7)	2 433(7)
C(8)	7 391(8)	4 252(7)	3 133(7)
C(9)	6 588(7)	4 688(7)	2 801(7)
N(10)	6 813(5)	5 294(5)	2 144(5)
C(11)	6 029(7)	5 732(7)	1 820(7)
C(12)	6 222(7)	6 162(6)	1 017(7)
N(13)	6 445(5)	5 449(5)	317(5)
C(14)	6 788(7)	5 823(6)	−415(6)
S	6 639(2)	4 924(2)	−2 151(2)
O(1)	6 732(5)	4 022(5)	−2 508(5)
O(2)	5 776(5)	5 220(5)	−2 235(5)
C(15)	7 412(10)	5 664(9)	−2 622(9)
N(1A)	5 165(6)	3 265(5)	248(6)
O(1A)	5 907(6)	3 419(6)	776(6)
O(2A)	4 635(6)	2 522(6)	131(6)
O(3A)	4 983(6)	3 828(6)	−239(6)
N(1B)	8 885(5)	6 629(6)	1 847(6)
O(1B)	8 568(6)	6 051(6)	1 155(6)
O(2B)	9 295(7)	7 350(6)	1 820(8)
O(3B)	8 759(7)	6 419(8)	2 591(5)
O(1W)	5 110(24)	5 110(24)	5 110(24)
O(2W)	8 865(28)	7 792(28)	10 005(27)
O(3W)	7 577(44)	8 213(43)	9 236(46)

Table 3 Relevant bond distances (Å) and angles (°)

Cu–N(3)	1.962(8)	Cu–N(10)	2.048(8)
Cu–N(6)	2.026(8)	Cu–N(13)	2.009(8)
Cu–O(1A)	2.560(8)	Cu–O(18)	2.526(9)
N(1)–C(2)	1.440(12)	N(13)–C(14)	1.431(13)
C(2)–N(3)	1.476(13)	C(14)–N(1)	1.456(12)
N(3)–C(4)	1.496(12)	N(1)–S	1.646(8)
C(4)–C(5)	1.555(15)	S–O(1)	1.414(8)
C(5)–N(6)	1.452(14)	S–O(2)	1.423(8)
N(6)–C(7)	1.478(14)	S–C(15)	1.780(15)
C(7)–C(8)	1.474(15)	C(8)–C(9)	1.509(16)
C(9)–N(10)	1.477(14)	N(10)–C(11)	1.484(14)
C(11)–C(12)	1.492(15)	C(12)–N(13)	1.495(12)
N(3)–Cu–N(6)	87.0(3)	N(10)–Cu–N(13)	85.9(3)
N(6)–Cu–N(10)	90.9(3)	N(13)–Cu–N(3)	96.2(3)
N(6)–Cu–N(13)	176.8(3)	N(10)–Cu–N(3)	177.4(3)
C(2)–N(1)–C(14)	116.6(7)	C(12)–N(13)–C(14)	112.7(7)
N(1)–C(2)–N(3)	109.9(7)	C(2)–N(3)–C(4)	111.4(7)
N(13)–C(14)–N(1)	110.7(7)	C(14)–N(1)–S	121.7(6)
N(3)–C(4)–C(5)	104.9(8)	S–N(1)–C(2)	118.5(6)
C(4)–C(5)–N(6)	109.5(8)	N(1)–S–O(1)	107.5(4)
C(5)–N(6)–C(7)	112.2(8)	N(1)–S–O(2)	105.9(4)
N(1)–S–C(15)	104.8(6)	O(1)–S–O(2)	122.1(5)
N(6)–C(7)–C(8)	111.4(9)	O(1)–S–C(15)	106.2(6)
C(7)–C(8)–C(9)	115.0(9)	O(2)–S–C(15)	109.1(6)
C(8)–C(9)–N(10)	111.6(9)	C(9)–N(10)–C(11)	111.9(8)
N(10)–C(11)–C(12)	109.2(8)	C(11)–C(12)–N(13)	108.3(8)
O(1A)–Cu–O(1B)	177.6(3)		



Scheme 2

rings in both compounds. Nevertheless, significant differences are observed in the two complexes when the absolute configurations of the chiral centres of the molecules are considered. In the cyclam perchlorate complex the Cu^{II} lies on a centre of symmetry, so that the asymmetric nitrogen donor atoms in the co-ordination plane may assume only one configuration (*RRSS*). In the copper(II) pentaazamacrocyclic nitrate complex investigated here the presence of a tertiary amine nitrogen replacing a CH_2 group of cyclam, as well as the different space-group symmetry, allow the existence of both *RSRS* and *SRSR* enantiomers. Noticeably, a small but significant strain seems to affect the six-membered chelate ring N(1)–C(2)–N(3)–Cu–N(13)–C(14). The Cu $\cdots$ N(1) distance [3.180(8) Å] is significantly shorter than Cu $\cdots$ C(8) [3.369(11) Å], which involves the opposite six-membered chelate ring. The unusual closeness of the N(1) atom to the Cu^{II} seems to be ascribed to a sort of compression of the triaza six-membered ring. Such a compression probably originates from the shortening of the N(1)–C(2) and N(1)–C(14) bonds [1.440(12) and 1.456(12) Å] with respect to C(8)–C(7) and C(8)–C(9) [1.474(15) and 1.509(16) Å] observed in the opposite unstrained six-membered ring. On the other hand a Cu $\cdots$ CH_2 distance [3.352(7) Å], quite similar to that observed here [3.369(11) Å], could be calculated for the corresponding interatomic distance in [Cu^{II}(cyclam)][ClO_4]$_2$.[14] Moreover, the C–N–C and C–N–S bond angles involving N(1) [116.6(7) and 118.5(6)°, respectively] indicate a pronounced sp^2 character of the tertiary amine nitrogen of the N(1)C_2S group, as expected for an amide nitrogen atom. The unusual *N*-methanesulfonyl group shows geometrical parameters in good agreement with those observed in tertiary mesylamine derivatives[15] and adopts a staggered conformation of the S–Me bond with respect to the N(1)–C(2) and N(1)–C(14) bonds of the N(1)C(2)C(14) moiety.

Intermolecular N–H $\cdots$ O hydrogen bonds involving macrocyclic NH groups and nitrate ligands from different complexes determine the molecular packing. On the other hand, there is no evidence for hydrogen bonds involving the zeolitic water molecules.

Kinetics of the Copper(II) *Template Synthesis of Azacyclam Macrocycles.*—A possible mechanistic pathway for the metal template synthesis of azacyclams is illustated in Scheme 2. Such a mechanism was first suggested by Sargeson for the cobalt(III)-directed synthesis of the sepulchrand macrotricycle (1,3,6,8,10,13,16,19-ocataazabicyclo [6.6.6] eicosane).[16] No detailed kinetic investigations were carried out to throw light on this type of reaction. However, it seems probable that a crucial step is that of (i) in Scheme 2, which involves nucleophilic attack of the NRH$^-$ anion on one of the two C=N double bonds which form through the Schiff-base condensation of formaldehyde with the terminal primary amine groups of the co-ordinated open-chain tetramine.

An investigation of the dynamic aspects of the formation of azacyclam complexes was carried out on those reactions that

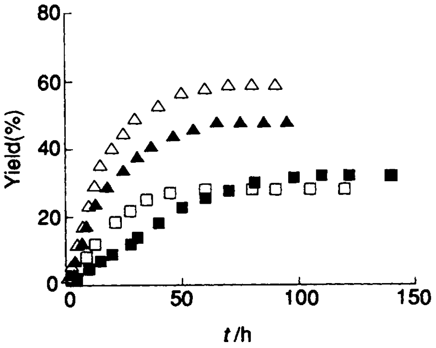


Fig. 2 Time-dependent variation of the yield for the formation of copper(II) complexes with cyclam-like macrocycles in template processes. Locking fragments: (△) nitroethane, (▲) benzenesulfonamide, (□) diethyl malonate and (■) acetamide

Table 4 Relevant parameters associated with reaction profiles of the type in Fig. 2 for the investigated locking fragment. The slope refers to the least-squares straight-line fitting of the experimental points of the initial part of the profile; the plateau indicates the average of the values for the final part of the profile

Locking fragment	Slope (% h^{-1})	Plateau (%)
$MeCONH_2$	0.40	33
$PhCONH_2$	0.52	46
$PhSO_2NH_2$	1.67	47
$NPhH_2$	0.51	28
$NPrH_2$	0.45	57
$EtNO_2$	2.40	58
$CH_2(CO_2Et)_2$	0.97	28

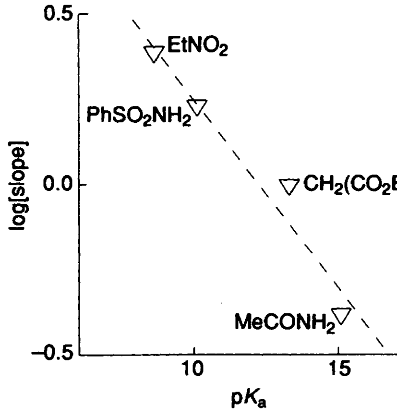


Fig. 3 Linear relationship between the acidity constant K_a of the locking fragment and the slope of the initial straight-line portion of the reaction profile in Fig. 2. Quantities are expressed in log units

involve Cu^{II} as a templating agent. In particular, a 150 cm^3 solution in ethanol–water (90:10) and 0.05 mol dm^{-3} in $Cu(NO_3)_2$, 1,9-diamino-3,7-diazanonane, triethylamine, and the amide (or other diprotic acids, see below) used as a locking fragment, and 0.5 mol dm^{-3} in formaldehyde, was equally divided in 15 stoppered bottles. The bottles were put in a thermostat at 50.0 °C. They were taken at predetermined time intervals (3 h or more) and chilled in ice–water. Then, 3 mol dm^{-3} HCl (5 cm^3) was added, the solution vigorously shaken and its d–d spectrum recorded. It should be noted that, in the presence of acid, any non-cyclic metal complex [*i.e.* unreacted (1,9-diamino-3,7-diazanonane)copper(II), partially reacted, but not yet cyclised species] rapidly decompose, whereas the formed azacyclam complex remains intact and persists in solution. The spectrum of the more or less intense blue-violet acidified solution disclosed the typical absorption band of cyclam and cyclam-like copper(II) complexes, centred at *ca.* 520 nm. By dividing the measured absorbance at 520 nm by that of an equimolar solution of the pre-formed and analysed complex, the percentage yield of the macrocyclic complex is obtained. It should be noted that at the beginning of the experiment the solution when treated with the strong acid solution could become yellow or pink-yellow, due to the formation of large amounts of the $[Cu^{II}Cl_4]^{2-}$ chromophore. However, this species absorbs light in a completely different spectral range (*i.e.* below 480 nm) and does not affect the determination of the concentration of the macrocyclic complex. Percentage yield *vs.* time profiles obtained for the reactions involving some selected locking fragments are shown in Fig. 2. As a general behaviour, the percentage yield steadily increases to reach a plateau. Table 4 reports the significant parameters for each reaction profile: the slope of the initial linear portion, in percentage unit h^{-1}, and the percentage value of the plateau. Note that the values in Table 4 refer to reactions in which no precipitate formed during the reaction. For comparative purposes, reactions involving aliphatic and aromatic amines (propylamine and aniline) were also investigated. Moreover, two well known diprotic carbon acids, nitroethane[17] and diethyl malonate,[18] the efficiency of which as locking fragments in the template synthesis of copper(II) azacyclam complexes had previously been documented, were also considered. In the profiles in Fig. 2 the slope should have a kinetic meaning, being related to the initial reaction. On the other hand, the plateau value exactly indicates the yield in solution, in the absence of lattice effects. In particular, the value of the slope should be connected to the rate of the slowest step of the process and, in this sense, one would look to any correlation with the acidity of the diprotic acid used as a locking fragment. Unfortunately, only a few reliable and homogeneous pK_a values for the considered padlocks are available from the literature. A satisfactory linear correlation between the slope (in log units) and pK_a has been observed for all those systems for which the pK_a (in aqueous solution) was available, *i.e.* $EtNO_2$ ($pK_a = 8.6$),[19] $PhSO_2NH_2$ (10.1),[20] $CH_2(CO_2Et)_2$ (13.3),[19] and $MeCONH_2$ (15.1),[21] as shown in Fig. 3.

The stronger the acid, the faster is the template process. This behaviour is consistent with the hypothesis that process (i) in Scheme 2 is the rate-determining step of the overall template reaction. The rate of step (i) should depend linearly upon the concentration of the anion responsible for the nucleophilic attack, NRH^-, and this concentration is in turn linearly related to the acidity constant K_a. For the sake of clarity, Fig. 3 illustrates a linear correlation between the logarithms of the two envisaged quantities: slope and acidity constant. It should also be noted that template reactions involving amines are extremely rapid, considering the very low acidity exhibited by a primary amine group linked to an aliphatic or aromatic residue ($pK_a > 30$). It can be suggested that the amine group, in the transition state, is apically co-ordinated to the Cu^{II}. This should make the deprotonation process much easier and substantially reduce the pK_a value.

The interpretation of the trend of the plateau values, which are related to the stability of the formed polyaza ring, is less straightforward: yields in solution for the investigated systems range from 58 to 27% and decrease along the series $EtNO_2 >$ $NPrH_2 > PhSO_2NH_2 > PhCONH_2 > MeCONH_2 > PhNH_2$ $\approx CH_2(CO_2Et)_2$. In the case of the carbon acids $EtNO_2$ and $CH_2(CO_2Et)_2$ the yield of the cyclisation process parallels the K_a values, but a direct correlation between the acidity of the H_2A fragment, or its electron-withdrawing tendencies, and the stability of the macrocyclic ring cannot be predicted. In any case the azacyclam ring is much more fragile than that of cyclam. Attempts to demetallate $[Ni^{II}(azacyclam)]^{2+}$ complexes with sulfide or with boiling cyanide failed: demetallation was accompanied by macrocycle fragmentation.

Conclusion

This work has definitively demonstrated that diprotic acids of varying nature, of general formula H_2A, can act as efficient molecular padlocks, in the presence of formaldehyde, in closing open-chain tetramines around a labile metal centre, prone to tetragonal co-ordination (Cu^{II} and Ni^{II}). Metal complexes of cyclam-like macrocycles are thus synthesised in a very convenient way and using inexpensive reagents. However, the metal azacyclam complexes obtained cannot be considered as surrogates of the corresponding cyclam complexes. Template synthesis of cyclam remains the most convenient process to produce a tetraazamacrocyclic complex displaying genuine macrocyclic properties, with the additional advantage that the templating metal centre (Ni^{II}) can be extruded from the ring and the free macrocycle recovered. Interest in the template reactions described in this work rather lies in the possibility to use as a locking fragment a diprotic acid carrying a desirable functionality. In this sense, amides, in particular sulfonamides, seem very promising fragments to produce cyclam-like functionalised macrocycles through a one-pot procedure. For instance, as any substrate can be easily sulfonated, and the sulfonic group easily converted into the sulfonamide, it follows that a metalloazacyclam ring can be grown virtually on any aliphatic or aromatic substrate.

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