ARTICLE

OBC
www.rsc.org/obc

Polycyclic compounds from aminopolyols and α-dicarbonyls: structure and application in the synthesis of exoditopic ligands

Giovanni B. Giovenzana,*[a] Giovanni Palmisano,*[b] Erika Del Grosso,[a] Lorella Giovannelli,[a] Andrea Penoni[b] and Tullio Pilati[c]

[a] *Dipartimento di Scienze Chimiche Alimentari Farmaceutiche Farmacologiche, Via Bovio 6, 28100, Novara, Italy. E-mail: giovenza@pharm.unipmn.it*

[b] *Dipartimento di Scienze Chimiche e Ambientali, Via Valleggio 11, 22100, Como, Italy*

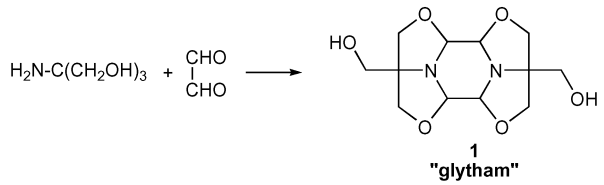
[c] *CNR-Istituto di Scienze e Tecnologie Molecolari, Via Golgi 19, 20133, Milano, Italy*

Received 13th January 2005, Accepted 18th February 2005
First published as an Advance Article on the web 15th March 2005

The structure and stereochemistry of the crystalline 2 : 2 condensation product ("glytham") of glyoxal and tris(hydroxymethyl)aminomethane was conclusively determined by X-ray diffractometric analysis. The singular disposition of the heteroatoms suggests the employment of glytham as starting material for the synthesis of ditopic ligands for metal ions. Some derivatives of glytham were prepared and their binding properties towards alkaline metal ions were preliminarily investigated by ESI-MS and NMR.

Introduction

In 1976, a German patent[1] described the synthesis of several condensation products from aldehydes and tris(hydroxymethyl)-aminomethane ("Tris" or "THAM") to be used as lubricant and fuel additives. Among them, particularly intriguing was the reaction of "Tris" with glyoxal, claimed to give a novel pentacyclic structure (**1**, Scheme 1) christened glytham.



Scheme 1

Nevertheless, this interesting structure was not unequivocally corroborated by spectroscopic data; the patent reported elemental analysis and IR spectrum only, with no NMR or crystallographic data, except for a ^{1}H-NMR spectrum of a *O*,*O*-diacetyl derivative, the latter revealing an highly symmetric structure. Following our interest in processes of covalent self assembly to give heterocyclic compounds able to complex metal ions,[2] we were prompted to determine the real structure; apart from the connectivity of the polycyclic compound, particularly impelling was the determination of the relative (and eventually, absolute) stereochemistry of the several stereogenic atoms involved, being essential for the molecule morphology and behaviour towards metal ions. In addition, we were interested in assessing the extendibility of this transformation to substrates other than Tris or glyoxal.

The synthesis of glytham was then repeated, following the reported procedure. Dissolution of a stoichiometric amount of Tris in 40% aqueous glyoxal resulted in an exothermic reaction affording a clear yellow solution which, upon standing, left a white crystalline precipitate of glytham. The solid, recrystallized from boiling water, gave long colourless needles, with physical properties identical to literature.[1] Mass spectrometric analysis (ESI) gave a protonated molecular ion at 287 amu, corresponding to $[(2\ \text{glyoxal} + 2\ \text{Tris}) - 2\ H_2O]\cdot H^+$ equivalent to the formula $C_{12}H_{18}N_2O_6$ with five rings or double bonds. ^{1}H-NMR analysis in D_2O showed 3 resonances in the ratio 1 : 2 : 1. In the ^{13}C-NMR spectrum four resonances were present, confirming high symmetry of the molecule. APT-^{13}C-NMR revealed these signals corresponding to two methylenes, one methine and one quaternary carbon atom. All chemical shifts corresponded to saturated carbons, excluding structure with multiple bonds and assigning the five unsaturations entirely to rings; furthermore, the chemical shifts were compatible with the glytham structure, containing two different N–CH_2–O moieties, one N–CH(–C)–O and a quaternary carbon atom. HSQC-NMR experiments supported these assignments. The absence of evident couplings in ^{1}H-NMR spectrum offers no further help for the elucidation of stereochemistry.

A single-crystal X-ray diffractometric analysis was then performed on glytham, to conclusively resolve the quest for the relative stereochemistry of the stereogenic centers. The ORTEP plot of the molecule definitely confirmed the pentacyclic structure proposed for glytham (Fig. 1) and showed an unusual all-axial arrangement for the four exocyclic oxygen atoms

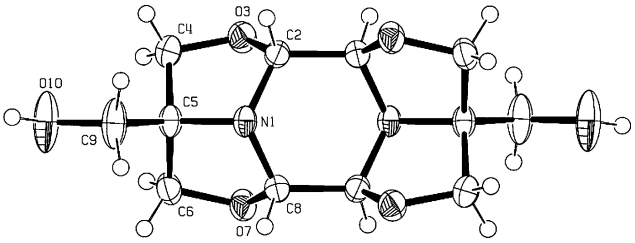


Fig. 1 Glytham: ORTEP plot. Atomic displacement parameters at 50% probability level. H atoms not to scale.

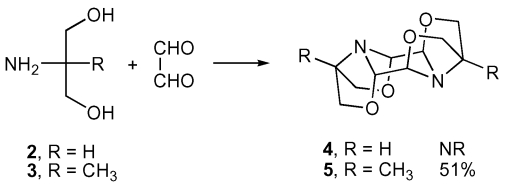
The formation of the glytham molecule appears as a genuine covalent self-assembly process, in which two substrates react in a 2 : 2 ratio in a high-yielding and completely stereoselective transformation. The latter is extremely remarkable, as in a single step four C–O bonds, four C–N bonds, five rings and four stereocentres are efficiently formed, representing one of the reactions with a very high intricacy quotient.[3]

To test the generality of this reaction other commercially available aminopolyols (*i.e.*, serinol **2**, 2-amino-2-methyl-1,2-propanediol **3**) were subjected to the optimized reaction with glyoxal.

As shown in Scheme 2, the substitution of a hydroxymethyl moiety should lead to the modification of the pendant arms of the molecule.

Reaction of **3** with glyoxal gave a product in the usual way, although slower. However, reaction of glyoxal with **2**

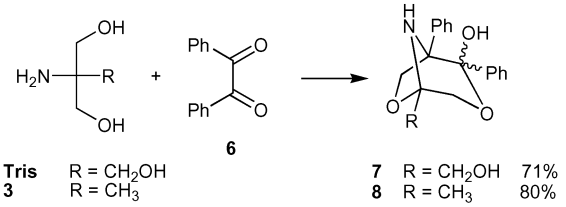
DOI: 10.1039/b500580a



Scheme 2 Variation of aminopolyol reactant.

afforded only complex mixtures, containing polymeric products as did reaction of **1** and **3** with enolizable α-diketones (*e.g.* 2,3-butanedione, 1,2-cyclohexanedione).

The behaviour of non-enolizable α-diketones such as 1,2-diphenyl-1,2-ethanedione (benzil) **6** and acenaphthenequinone was next investigated. The latter was extremely insoluble in polar solvents, thereby thwarting successful reaction with aminopolyols. On the other hand, an equimolar mixture of benzil and Tris was found to be quite soluble in MeOH–H_2O mixtures, yielding after 1 day colourless needles. MS analysis ruled out the expected 2 : 2 condensation, indicating a molecular formula compatible with a 1 : 1 condensation product with elimination of 1 H_2O. ^{1}H-NMR spectra evidenced a rigid structure, devoid of symmetry elements, confirmed by ^{13}C-NMR spectrum. COSY and HETCOR experiments allowed the assignment of the 3,6-dioxa-8-azabicyclic structure **7** (Scheme 3). This ring system has few examples in the literature,[4] the more comparable being unexpectedly formed in a similar reaction between Tris and pyruvaldehyde.[5]



Scheme 3 Condensation of aminopolyols with benzyl.

Unfortunately, it was impossible to establish the relative stereochemistry of the carbon atom bearing the tertiary alcohol by spectrometric analysis. A single crystal X-ray diffractometric analysis was then performed on the needles of **7** obtained in the reaction, and the result is depicted in Fig. 2, showing the *exo* configuration of the tertiary hydroxyl group on C(2).

As shown in Scheme 3, 2-amino-2-methyl-1,3-propanediol **3** and benzil **6** afforded in good yield the corresponding bicyclic adduct as a single product **8**. As previously noted, serinol failed to give a clean reaction with benzil, too; once again, no crystalline product was obtained from the complex (as ascertained by HPLC) mixture.

The preliminary investigations on the condensation reaction of aminopolyols and α-dicarbonyls show a marked influence of the substituents on the products obtained. The pentacyclic adducts are obtained only when glyoxal is the α-dicarbonyl component, while less complex bicyclic structures were obtained when the steric hindrance of the α-dicarbonyl was increased.

The structure of glytham and its dideoxyderivative **5** appeared to be a promising building block for the synthesis of ligands. In particular, the symmetric disposition of the donor atoms, organized in two distinct N–O_3 sets with electron pairs directed towards the outer surface, suggests its employment in the synthesis of exoditopic ligands. The latter are attracting increasing attention in view of their potential in metallosupramolecular chemistry,[6] but the scarce reports about them reflect the difficult task of their lengthy syntheses.[7]

We were then prompted to convert the glytham molecule (and its dideoxyderivative **5**) into exoditopic ligands. When one or two donor atoms are appended to the hydroxymethyl arms of glytham scaffold, polydentate coordination would be accessed

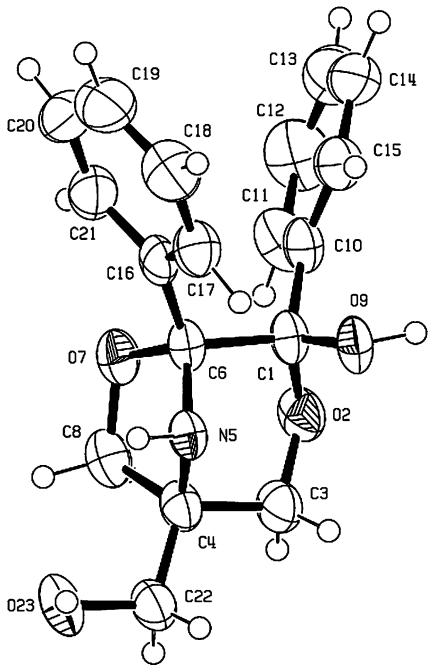
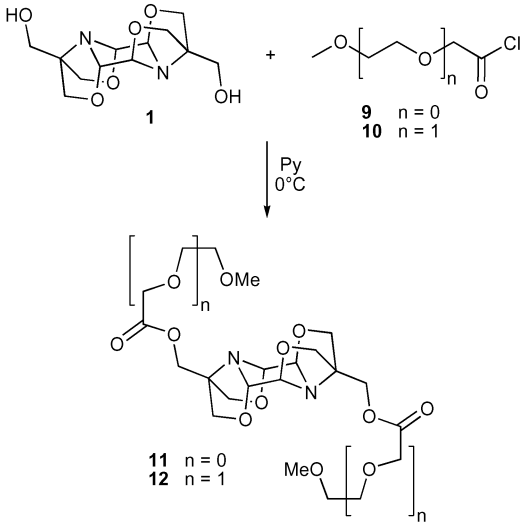


Fig. 2 ORTEP plot of compound **7**. Atomic displacement parameters at 50% probability level. H atoms not to scale.

with a trigonal bipyramidal and ψ-octahedral geometries, respectively (Fig. 3).

Our initial efforts on the functionalization of glytham proved less trivial than its structure would suggest. Attempts to alkylate **1** with either 2-methoxyethyl tosylate or 2-(2-methoxyethoxy)ethyl tosylate under different reaction conditions (*i.e.*, NaH–THF, NaH–DMF, KOH–THF, KOH–$Bu_4N^+HSO_4^-$–PhMe), yielded intractable mixtures showing little or no evidence of containing the desired alkylated derivatives. The failure of this approach was almost certainly due to the modest solubility of **1** (slightly soluble in cold water; readily soluble only in boiling water or hot pyridine).

The introduction of side chains bearing the oxygen-donor groups was then attempted through acylation of the hydroxyl groups.[1] Gratifyingly, treating a solution of glytham in pyridine at 0 °C and then at room temperature overnight with 2.2 equiv. of methoxyacetyl chloride **9** (prepared by reacting methoxyacetic acid with thionyl chloride) resulted in an exothermic reaction and usual workup led to the isolation (56% overall yield) of the desired *O*,*O*-diacylglytham **11** (Scheme 4).



Scheme 4 *O*,*O*-Diacyl glytham-based exoditopic ligands.

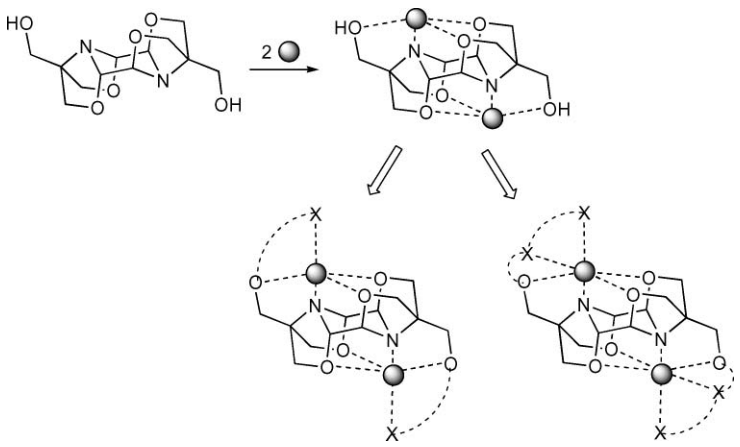
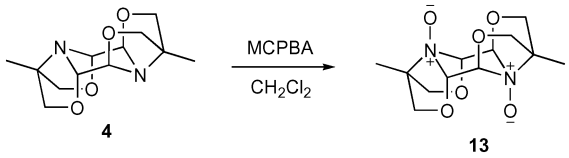


Fig. 3 Putative coordination modes for glytham and its derivatives.

Similarly, **1** also gave the corresponding exoditopic ligand **12** (44% overall yield) in the presence of the higher homolog 2-(2-methoxyethoxy)acetyl chloride **10** (from 2-(2-methoxyethoxy)acetic acid and thionyl chloride).

The functionalization of compound **4** appeared more difficult, lacking the primary alcoholic groups. Nevertheless, the tertiary amino groups offer a chance for linking further donor atoms, through their oxidation to *N*-oxide. *N*-Oxides are known to act efficiently as coordinating groups, binding metal ions through their anionic oxygen atom.[8] Reaction of **4** with hydrogen peroxide in water solution produced a complex mixture of partially oxidized and decomposed **4**. However, oxidation of **4** with 2 equiv. of *m*-chloroperbenzoic acid in dichloromethane at room temperature, resulted in clean conversion to *N*,*N*′-dioxide **13** (75%)(Scheme 5).



Scheme 5 Exoditopic ligand from oxidation of **4**.

Compound **13** embodies two O_3-subsets, suited to bind two metal ions. The number of donor atoms and the opposite orientation of the two subsets provide a rare example of linear multidentate exoditopic ligand, suitable for the preparation of infinite chain monodimensional polymer.

In order to exploit optimally their task, preliminary experiments were performed, using electrospray ionization mass spectrometry (ESI-MS) for obtaining an initial assessment of the metal binding affinities of new ligands. ESI-MS has proved invaluable for qualitative and quantitative evaluation of host binding selectivities in weakly bound noncovalent host–guest complexes, requiring only negligible amounts of material.[9,10] In view of the denticity and nature of donor atoms, binding experiments for **11, 12** and **13** were limited to alkali metal ions. ESI-MS spectra were acquired for MeOH solutions containing the ligand (10 μM), LiCl, NaCl, and KCl. Even if the concentration of metal ions is in 1 : 1 ratio, the protonated molecular peak is hardly detected (<0.8%), indicating an overwhelming affinity for alkali ions. At higher metal : ligand ratio (5 : 1), it is possible to discern a significant selectivity in the order $Li^+ > Na^+ > K^+$ (Fig. 4) for both **11** and **12**, in excellent agreement with MM predictions performed on similar structures.[11]

Although the complexes probably possess limited stability and the concentration involved in these ESI-MS experiments are too low to appreciate higher adducts, it is possible to detect small signals of 1 : 2 adducts $[\mathbf{11}\cdot Li_2]^{2+}$ and $[\mathbf{12}\cdot Li_2]^{2+}$.

Affinity determination was not possible for **4**: although solutions of the ligand are indefinitely stable, the addition of trace metal ions catalyzes its rapid decomposition. However, from ESI-MS infusion experiments, it is possible to assess that:

decomposition takes place within seconds at μM concentration;

decomposition involves a rapid deoxygenation to give a mono *N*-oxide, fairly stable in methanol–water solution;

the mass spectra of solutions of **13** in the presence of alkaline metal ions prior to decomposition show a marked affinity for lithium rather than sodium or potassium ions.

NMR spectra of **13** in the presence of alkaline metal ions, run in D_2O solution, confirm the rapid decomposition of the molecule.

The decomposition of **13** to monoxide may also be induced thermally, as ascertained by TGA-DSC (Fig. 5).

From thermogravimetric run it can be observed that the degradation of **13** is a two-step process, the first (onset at about 140 °C) corresponding to the loss of one oxygen atom (5.02% of the total weight) and the second to the incoherent decomposition of the molecule starting from about 170.0 °C. These reactions are confirmed by exothermic peaks shown by the DSC thermograms.

In conclusion, the compounds **11, 12** and **13** synthesized are rare examples of multidentate exoditopic ligands, whose preparation is short, simple and cheap, involving a self-assembly key step from readily available starting materials; their coordination behaviour will be analyzed in more detail further. The easily obtained pentacyclic structure of glytham and its dideoxyderivative **5** represent rigid polyfunctional scaffolds with a virtually unexplored chemistry; moreover, the noteworthy covalent self-assembly process leading to the construction of the pentacyclic structure need to be investigated further to exploit its potential *en route* to novel complex polycyclic molecules.

Experimental

Reagents were obtained from Aldrich and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were registered on a Jeol Eclipse ECP300 spectrometer at 300 MHz and 75.4 MHz, respectively. ESI-MS were recorded on a Finnigan Mat spectrometer. DSC analysis of **13** was performed on a Perkin-Elmer Pyris 1 DSC, while thermogravimetric study (TGA) was carried out on a Perkin-Elmer Pyris 1 TGA. The sample (3–5 mg), subjected to a scanning rate of 20 °C min^{-1} under a 20 ml min^{-1} nitrogen purge, was heated in vented aluminium pan between 25 and 250 °C (DSC) or in open platinum pan up to 700 °C (TGA).

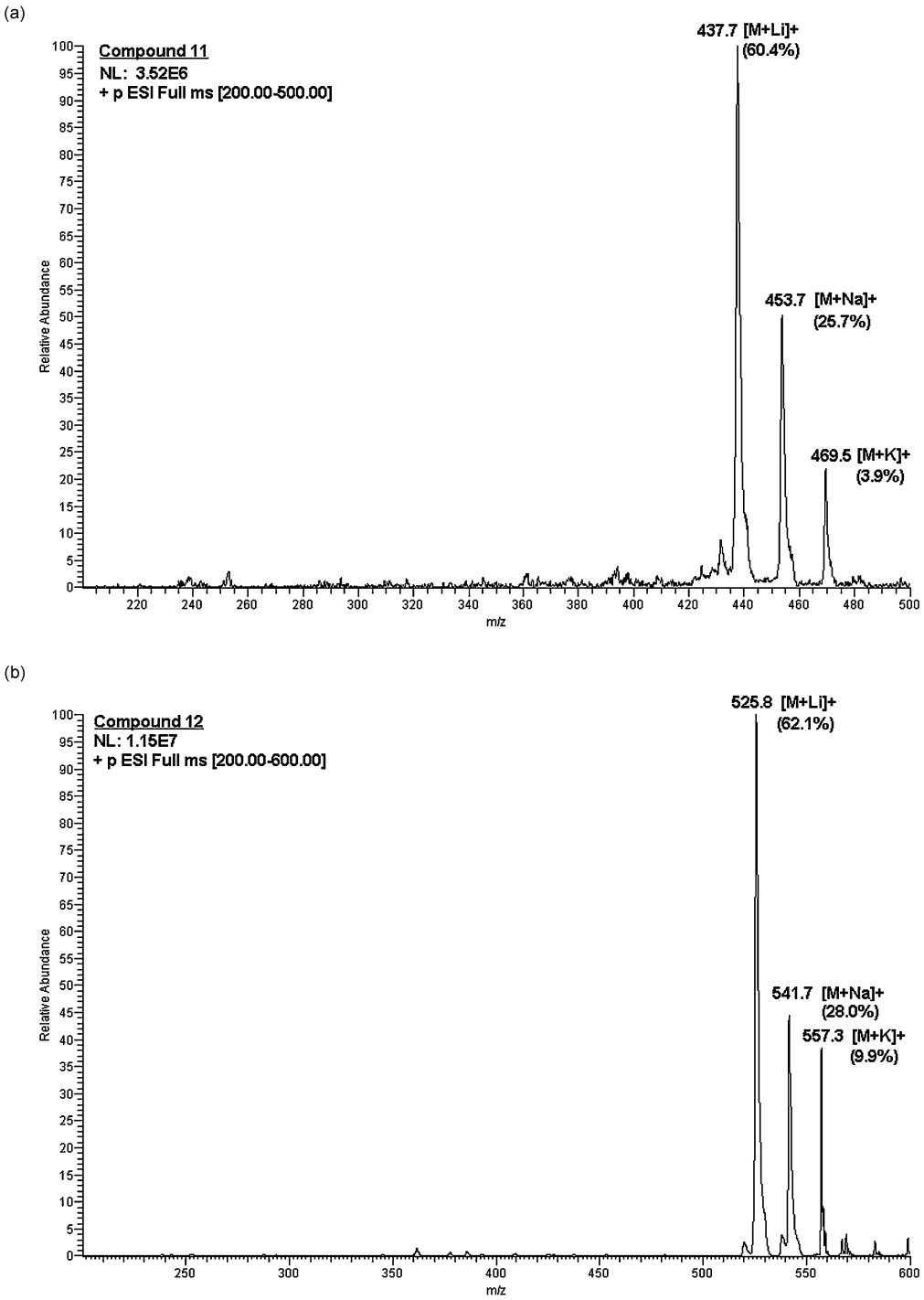


Fig. 4 **a** ESI-MS determination of relative binding affinities—compound **11**. **b** ESI-MS determination of relative binding affinities—compound **12**.

Elemental analyses were carried out with a Perkin Elmer Serie II CHNS/O 2400 analyzer.

(4a*R**,4b*R**,8a*S**,8b*S**)-[6a-(Hydroxymethyl)hexahydro-2*H*,6*H*-1,4,5,8-tetraoxa-6b,8c-diazadicyclopent[*cd*,*ij*]-*s*-indacene-2(3*H*)-yl]methanol ("glytham") (1)

Tris(hydroxymethyl)aminomethane (50.0 g, 0.413 mol) was dissolved in water (150 mL) and 50% aqueous glyoxal (24.0 g, 0.414 mol) was added dropwise in 5 min; a mild exothermic reaction ensued. The yellow solution was stirred for 1 h, during which colourless crystals separated out. The solid was filtered, washed twice with cold water, recrystallized from water and dried *in vacuo*. Yield 53.8 g (91%). Mp 356–358 °C (dec.). Found: C, 50.25; H, 6.51, N, 9.62. Calc. for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34, N, 9.79%. Mass spectrum (ESI): *m*/*z* 287 (MH^+), 257 ($MH^+ - CH_2O$). Calc. for $C_{12}H_{18}N_2O_6$: 286 amu. ^{1}H-NMR (D_2O) 3.65 (s, 4H), 3.90 (bs, 8H), 4.74 (s, 4H). ^{13}C-NMR (DMSO-d_6) 64.3, 72.6, 74.1, 88.4.

2a,6a-Dimethyloctahydro-2*H*,6*H*-1,4,5,8-tetraoxa-6b,8c-diazadicyclopenta[*cd*,*ij*]-*s*-indacene (5)

2-Amino-2-methyl-1,3-propanediol (9.04 g, 0.086 mol) was dissolved in water (20.0 mL). Glyoxal (50% aqueous solution, 10.0 g, 0.086 mol) was added in one portion. The solution was left standing for 10 days; the crystalline precipitate was filtered, washed twice with cold water and dried *in vacuo*. Yield 5.58 g (51%). Mp 290–294 °C (dec.). Found: C, 56.47; H, 7.31, N, 10.87. Calc. for $C_{12}H_{18}N_2O_6$: C, 56.68; H, 7.13, N, 11.02%. Mass

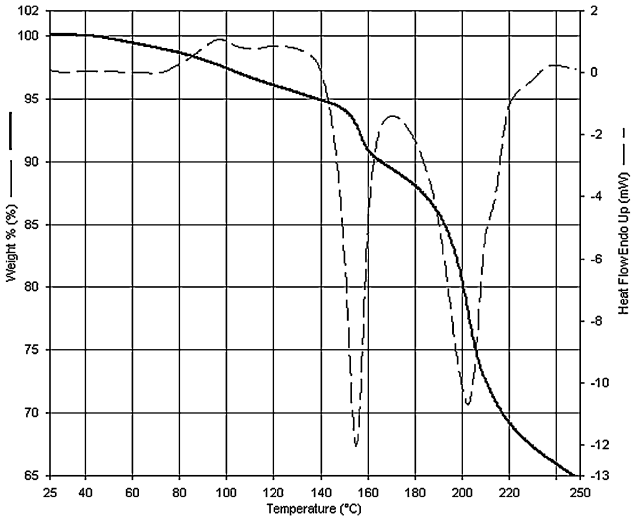


Fig. 5 Simultaneous TG-DSC trace of **13** (solid line, TG; dashed line, DSC signal).

spectrum (ESI): *m/z* 255 (MH^+), 225 ($MH^+ - CH_2O$). Calc. for $C_{12}H_{18}N_2O_4$: 254 amu. ^{1}H-NMR (DMSO-d_6) 1.26 (s, 6H), 3.47 (d, 4H, $J = 8.5$ Hz), 3.78 (d, 4H, $J = 8.5$ Hz), 4.58 (s, 4H). ^{13}C-NMR (DMSO-d_6) 23.0, 70.2, 75.5, 88.4.

(1*R**,2*R**,5*S**)-1-Hydroxymethyl-4,5-diphenyl-3,6-dioxa-8-azabicyclo[3.2.1]octan-4-ol (7)

Tris(hydroxymethyl)aminomethane (5.0 g, 41 mmol) was dissolved in water (20 mL) and benzil (8.6 g, 41 mmol) was added in a single portion. Methanol (100 ml) was added and the suspension was heated to 40 °C to give a clear yellow solution. After 2 h heating, the reaction mixture was left standing overnight, obtaining crude **7** as colourless needles. The product was filtered, washed thoroughly with water, recrystallized from water–acetone and finally dried *in vacuo*. Yield 9.1 g (71%). Mp 189–191 °C (dec.). Found: C, 68.93; H, 6.29, N, 4.37. Calc. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11, N, 4.47%. Mass spectrum (ESI): *m/z* 314 (MH^+), 296 ($MH^+ - H_2O$). Calc. for $C_{18}H_{19}NO_4$: 313 amu. ^{1}H-NMR (CD_3OD) 3.65–3.87 (m, 4H), 4.24 (dd, 1H, $J_1 = 10.3$ Hz, $J_2 = 1.5$ Hz), 4.37 (d, 1H, $J = 6.9$ Hz), 7.03–7.21 (m, 10H). ^{13}C-NMR (CD_3OD) 61.6, 66.4, 69.0, 71.4, 99.8, 100.9, 127.2, 127.7, 128.4, 128.6, 129.2, 129.4, 139.6, 140.8.

1-Methyl-4,5-diphenyl-3,6-dioxa-8-azabicyclo[3.2.1]octan-4-ol (8)

The procedure employed for **7** was adopted for this preparation, starting from 2-amino-2-methyl-1,3-propanediol (5.0 g, 48 mmol) and benzil (10.1 g, 48 mmol) in water–methanol (20 mL–130 mL). Recrystallization of the precipitated product from water–acetone gave pure **8**. Yield 11.30 g (80%). Mp 176–178 °C (dec.). Found: C, 72.82; H, 6.45, N, 4.57. Calc. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44, N, 4.71%. Mass spectrum (ESI): *m/z* 298 (MH^+). Calc. for $C_{18}H_{19}NO_3$: 297 amu. ^{1}H-NMR ($CDCl_3$) 1.26 (s, 3H), 2.54 (bs, 1H), 3.50 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 1.9$ Hz), 3.72 (d, 1H, $J = 10.7$ Hz), 4.12 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 2.0$ Hz), 4.45 (d, 1H, $J = 7.1$ Hz), 4.99 (bs, 1H), 7.03–7.28 (m, 10H). ^{13}C-NMR ($CDCl_3$) 17.5, 61.6, 71.1, 74.5, 97.9, 100.5, 126.8, 126.9, 127.2, 127.8, 128.0, 128.1, 137.7, 137.8.

General procedure for the preparation of acyl chlorides

The acid (50 mmol) was slowly dropped in a round bottomed flask containing thionyl chloride (150 mmol). The resulting clear solution was stirred at room temperature for 15 min, then refluxed for 1 h. Thionyl chloride and volatiles are removed by distillation obtaining the crude acyl chloride.

2-Methoxyacetyl chloride (9)

The crude chloride was purified by distillation, obtaining a clear colourless liquid. Yield 69%. Bp 98 °C. ^{1}H-NMR ($CDCl_3$) 3.47 (s, 3H), 4.34 (s, 2H). ^{13}C-NMR ($CDCl_3$) 59.7, 77.7, 172.0.

2-(2-Methoxyethoxy)acetyl chloride (10)

The crude chloride was used as such in the next step. Yield 51%. ^{1}H-NMR ($CDCl_3$) 3.28 (s, 3H), 3.49 (m, 2H), 3.68 (m, 2H), 4.42 (s, 2H). ^{13}C-NMR ($CDCl_3$) 58.9, 71.7, 71.8, 76.7, 172.0.

{6a-[(2-Methoxyacetoxy)methyl]hexahydro-2*H*,6*H*-1,4,5,8-tetraoxa-6b,8c-diazadicyclopenta[*cd*,*ij*]*s*-indacen-2(3*H*)-yl}methyl 2-methoxyacetate (11)

Glytham (**1**, 5.00 g, 17 mmol) was suspended in anhydrous pyridine (20 mL). 2-Methoxyacetyl chloride (**9**, 4.2 g, 38 mmol) was slowly added dropwise, maintaining the reaction mixture at 0–5 °C with a ice–water bath. The whole was kept 30 min at 0–5 °C and then stirred overnight at room temperature. The orange reaction mixture was filtered and the filtrate poured into a 10% aqueous citric acid solution (150 ml) and extracted with dichloromethane (4 × 15 mL). The organic extracts were washed in the order with 5% aqueous ammonia and water, then dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude light-brown solid was recrystallized from ethyl acetate, obtaining **11** as colourless crystals. Yield 4.1 g (56%). Mp 119–121 °C. Found: C, 49.99; H, 6.22, N, 6.51. Calc. for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09, N, 6.51%. Mass spectrum (ESI): *m/z* 453 (MNa^+), 431 (MH^+). Calc. for $C_{18}H_{26}N_2O_{10}$: 430 amu. ^{1}H-NMR ($CDCl_3$) 3.43 (m, 8H), 3.84 (s, 6H), 4.04 (s, 4H), 4.25 (s, 4H), 4.75 (s, 4H). ^{13}C-NMR ($CDCl_3$) 58.5, 66.8, 69.6, 72.0, 72.6, 88.5, 170.1.

{6a-{[2-(2-Methoxyethoxy)acetoxy]methyl}hexahydro-2*H*,6*H*-1,4,5,8-tetraoxa-6b,8c-diazadicyclopenta[*cd*,*ij*]*s*-indacen-2(3*H*)-yl}methyl 2-(2-methoxyethoxy)acetate (12)

Glytham (**1**, 5.00 g, 17 mmol) was suspended in anhydrous pyridine (20 mL). 2-(2-Methoxyethoxy)acetyl chloride (**10**, 5.9 g, 38 mmol) was slowly added dropwise, maintaining the reaction mixture at 0–5 °C with an ice–water bath. The whole was kept 30 min at 0–5 °C and then stirred overnight at room temperature. The orange reaction mixture was filtered and the filtrate poured into a 10% aqueous citric acid solution (150 ml) and extracted with dichloromethane (4 × 15 mL). The organic extracts were washed in the order with 5% aqueous ammonia and water, then dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude reddish oily product was purified by flash chromatography (SiO_2, eluant ethyl acetate–hexane–2-propanol 8 : 1 : 1) and finally recrystallized from ethyl acetate, obtaining **12** as colourless crystals. Yield 3.9 g (44%). Mp 89–92 °C. Found: C, 50.91; H, 6.79, N, 5.35. Calc. for $C_{22}H_{34}N_2O_{12}$: C, 50.96; H, 6.61, N, 5.40%. Mass spectrum (ESI): *m/z* 541.7 (MNa^+), 519.4 (MH^+). Calc. for $C_{22}H_{34}N_2O_{12}$: 518 amu. ^{1}H-NMR ($CDCl_3$) 3.38 (m, 6H), 3.58 (m, 4H), 3.71 (m, 4H), 3.86 (m, 8H), 4.05 (s, 4H), 4.18 (s, 4H), 4.26 (s, 4H). ^{13}C-NMR ($CDCl_3$) 58.6, 67.0, 70.0, 71.6, 71.9, 72.1, 72.5, 88.4, 170.2.

2a,6a-Dimethyloctahydro-2*H*,6*H*-1,4,5,8-tetraoxa-6b,8c-diazoniadicyclopenta[*cd*,*ij*]*s*-indacene-6b,8c-diolate (13)

Compound **4** (0.257 g, 1.01 mmol) was dissolved in dichloromethane (30 mL). *m*-Chloroperoxybenzoic acid (0.800 g, 4.34 mmol) was added in four portions during 30 min with vigorous stirring. After the addition a voluminous white precipitate separated out and the reaction mixture was stirred at room temperature for 3 h. The precipitate was then filtered out and the filtrate was evaporated *in vacuo*. The solid residue was purified by column chromatography (SiO_2, eluant methanol–28% aqueous ammonia 9 : 1 → 8 : 2). The purified product was redissolved in water, washed twice with dichloromethane to

remove the last traces of *m*-chlorobenzoic acid and the aqueous layer was then evaporated to give pure **13** as amorphous off-white solid (0.217 g, 75%). Mp 120 °C (sint) 150 °C (dec). Mass spectrum (ESI): *m/z* 287 (MH^+), 271 ($MH^+ - O$). Calc. for $C_{12}H_{18}N_2O_6$: 286 amu. ^{1}H-NMR (D_2O) 5.14 (s, 4H), 4.56 (d, 4H, $J = 9.9$ Hz), 4.01 (d, 4H, $J = 9.9$ Hz). ^{13}C-NMR (D_2O) 96.8, 82.8, 77.9, 20.6.

Crystal structure analysis

Crystal data of compounds **1** and **7** were collected at room temperature on a Bruker SMART-APEX diffractometer equipped with CCDC device. The structures were solved by direct methods using the *SIR*-92[12] program and refined by *SHELX*-97 full-matrix least-squares.[13]

Crystal data of compound 1. $C_{12}H_{18}N_2O_6$, $M = 286.28$, $a = 6.2236(12)$, $b = 9.575(2)$, $c = 10.455(2)$ Å, $\beta = 92.630(10)°$, $V = 622.4(2)$ Å^3, space group $P2_1/n$ (no. 14), $Z = 2$, μ(Mo-Kα) = 0.123 mm^{-1}, 11124 measured reflections, 2200 unique ($R_{int} = 0.0210$) which were used in all calculations. The final $wR(F^2)$ was 0.0967 (all data). The molecule lies on a crystallographic centre of symmetry, but its symmetry is near to C_{2h}, being 0.0307 the molecular RMS[14], including the H atoms. Molecular geometry does not show any particular feature, with the exclusion of the quite strained N1–C5 bond [1.506(1) Å]. The central six-membered ring has pressed chair conformation, being the angle between the planes through N1,C2,C8 and C2,C8,C2′,C8′ 147.93(5)° to be compared with 120° for ideal cyclohexane ring. The five membered rings show envelope conformation with the oxygen atom out of plane by 0.589 and 0.544 Å for O3 and O7, respectively. The molecular packing is characterized by a medium nearly linear H bond [2.07(2) and 2.945(1) Å for N1 ··· H10^i and N1 ··· O10^i, respectively ($i = 3/2 - x, -1/2 + y, 3/2 - z$)] that is the main responsible for the high crystal density, $\rho = 1.528$ g cm^{-3}.†

Crystal data of compound 7. $C_{18}H_{19}NO_4$, $M = 313.34$, $a = 15.6300(19)$, $b = 12.6665(15)$, $c = 7.9832(10)$ Å, $\beta = 93.946(3)°$, $V = 1576.7(3)$ Å^3, space group Cc (no. 9), $Z = 4$, μ(Mo-Kα) = 0.093 mm^{-1}, 27040 measured reflections, 1826 unique ($R_{int} = 0.0237$) which were calculated in all calculations. The final $wR(F^2)$ was 0.0845 (all data). The only unusual bond distance is C1–C6 [1.574(2) Å]. The six-membered hetero-ring has chair conformation, while the five-membered one shows an envelope conformation with N5 out of plane of about 0.60 Å. The crystal density, $\rho = 1.320$ g cm^{-3}, is lower than in **1**, despite the O9–H9 ··· O23^{ii} H bond [O9 ··· O23^{ii} 2.780(2), H9 ··· O23^{ii} 1.93(3) Å, $ii = x, y, 1 - z$] and the bifurcated H bond N5^{iii} ··· H23 ··· O9^{iv} [N5^{iii} ··· H23 2.24(2), H23 ··· O9^{iv} 2.29(2), N5^{iii} ··· O23 2.927(2), O23 ··· O9^{iii} 2.982(2) Å, $iii = x, 1 - y, 1/2 - z$]; this is probably due to the two phenyl rings that show very weak packing interaction.†

† CCDC reference numbers 260606 (**1**) and 260607 (**7**). See http://www.rsc.org/suppdata/ob/b5/b500580a/ for crystallographic data in .cif or other electronic format.

Acknowledgements

Two of us (G.P., A.P.) are grateful for the financial support (Progetto d'Eccellenza per la Ricerca d'Ateneo 2002) by the Università dell'Insubria. We thank the reviewers for fruitful suggestions and for ref. 11.

References

1 S. J. Brois, J. Ryer and E. Winans, (Exxon Research and Engineering), *Ger. Offen.*, DE 2617680, 1976 (*Chem. Abstr.*, 1977, **87**, 455620).
2 S. Aime, C. Cavallotti, E. Gianolio, G. B. Giovenzana, G. Palmisano and M. Sisti, *Tetrahedron Lett.*, 2002, **43**, 8387–8389.
3 (*a*) P. L. Fuchs, *Tetrahedron*, 2001, **57**, 6855–6875; (*b*) W. H. Whitlock, *J. Org. Chem.*, 1998, **63**, 7982–7989.
4 (*a*) G. Gaudiano, E. Frank, M. S. Wysor, D. Averbuch and T. H. Koch, *J. Org. Chem.*, 1993, **58**, 7355–7363; (*b*) G. Just and W. Zehetner, *J. Chem. Soc., Chem. Commun.*, 1971, 81–82; (*c*) G. Gaudiano and T. H. Koch, *J. Org. Chem.*, 1993, **52**, 3073–3081.
5 W. A. Bubb, *Magn. Reson. Chem.*, 1997, **35**, 191–198.
6 S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853–908.
7 L. A. Paquette, J. Tae and J. C. Gallucci, *Org. Lett.*, 2000, **2**, 143–146 and references cited therein.
8 D. Bayot, B. Tinant, B. Mathieu, J.-P. Declercq and M. Devillers, *Eur. J. Inorg. Chem.*, 2003, 737–743.
9 (*a*) S. Inokuma, T. Sakaizawa, T. Funaki, T. Yonekura, H. Satoh, S.-I. Kondo, Y. Nakamura and J. Nishimura, *Tetrahedron*, 2003, **59**, 8183–8190; (*b*) A. Szczepánska, P. Sałański and J. Jurczak, *Tetrahedron*, 2003, **59**, 4775–4783.
10 D.-S. Young, H.-Y. Hung and L. K. Liu, *Rapid Commun. Mass Spectrom.*, 1997, **11**, 769–773.
11 (*a*) R. D. Hancock and K. Hegetschweiler, *J. Chem. Soc., Dalton Trans.*, 1993, **14**, 2137–2140; (*b*) K. Hegetschweiler, R. D. Hancock, M. Ghisletta, T. Kradolfer, V. Gramlich and H. W. Schmalle, *Inorg. Chem.*, 1993, **32**, 5273–5284.
12 G. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
13 G. M. Sheldrick, 1997. *SHELX 97*. University of Göttingen, Germany.
14 T. Pilati and A. Forni, *J. Appl. Crystallogr.*, 1998, **31**, 503–504.