Conformationally defined piperazine bis(*N*-oxides) bearing amino acid derived side chains

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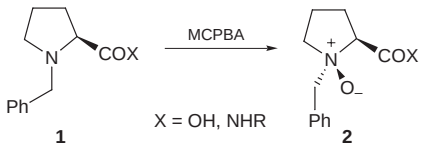
The preparation of a number of piperazine derivatives bearing amino acid substituents on the nitrogen is described; these compounds undergo oxidation with MCPBA to yield bis(*N*-oxides) in which both oxygen atoms are axially orientated and hydrogen bonded to the amide NHs, giving highly defined conformations to the molecules; the structure of the valine derivative (8c) was confirmed by X-ray analysis.

Biological systems rely on polymers, proteins and RNA to carry out the chemical transformations necessary for life. Both proteins and RNA fold into precisely ordered structures which provide a structural framework and the catalytic site for the particular transformation. In addition to their role as catalysts, biopolymers play a central role in the maintenance of structural integrity in living systems. There is great interest in the design and synthesis of polymeric molecules which possess the ability to fold in a discrete and predictable fashion and recently several groups have shown that poly-β-amino acids adopt a stable helical structure.[1] Indeed, Gellman has coined the term 'foldamer' to describe new types of polymeric backbones with well defined and predictable folding properties.

In previous studies we have shown that *N*-alkylated derivatives of proline and pipecolic acid undergo highly diastereoselective oxidations to give tertiary amine oxides that are stabilised by hydrogen bonding (Scheme 1).[2] In most cases these systems are stabilised by the presence of six membered hydrogen bonds between the *N*-oxide oxygen and the amide NH. In addition to their fascinating structural properties, the use of chiral amine oxides as catalysts in a number of synthetically useful transformations has been reported recently.[3]



Scheme 1

We considered that we could use this type of hydrogen bonding to enforce a conformational bias on otherwise flexible structures and give them a predictable and specific shape. We were particulary intrigued by the possibility of incorporating α-amino acid residues into the molecule since this would result in a peptide-like compound of defined structure. Earlier work from our group has shown that the oxidation of *N*-benzylpipecolic acid gave the *syn N*-oxide. Interestingly the *N*-oxide adopted an axial orientation in the crystal structure (Scheme 2).

We therefore postulated that attachment of a unit containing a peptide residue possessing an NH residue available for hydrogen bonding, followed by oxidation of both piperazine nitrogens, should yield a bis(*N*-oxide) in which both oxygens were axial and were stabilised by intramolecular hydrogen bonds to the NHs of the peptide chains. The synthesis of such compounds is show in Scheme 3.

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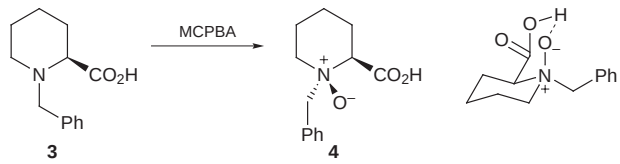
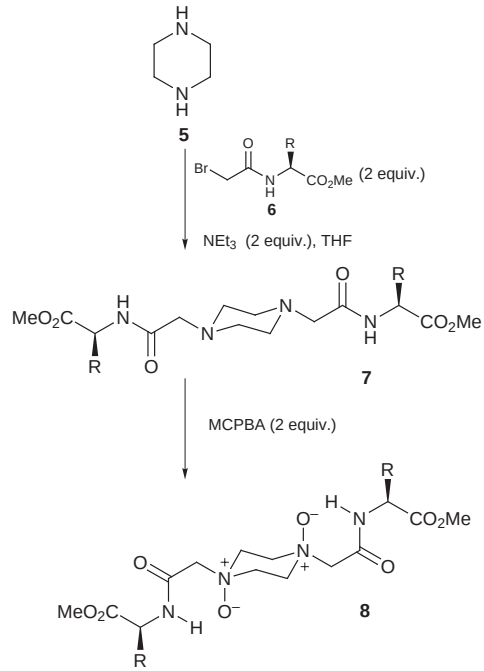


Scheme 2



Scheme 3

Piperazine was alkylated on both nitrogens with α-bromo amides derived from a range of α-amino acids using literature procedures.[4] The resulting tertiary amines were treated with 2 equiv. of MCPBA. Clean oxidation was observed and the resulting *N*-oxides were isolated as stable solids. A range of different amino acids was used and the results are summarised in Table 1.

The ^{1}H NMR spectra of the *N*-oxides were highly informative. They showed that the compounds were formed as

Table 1 Synthesis of piperazine bis(*N*-oxides)

		Yield (%)	
Bis(*N*-oxide)	R	*N*-alkylpiperazine	Bis(*N*-oxide)
8a	H	73	63
8b	Me	80	72
8c	Pr^i	67	77
8d	Bu^i	84	74
8e	Ph	79	75
8f	Bn	86	81

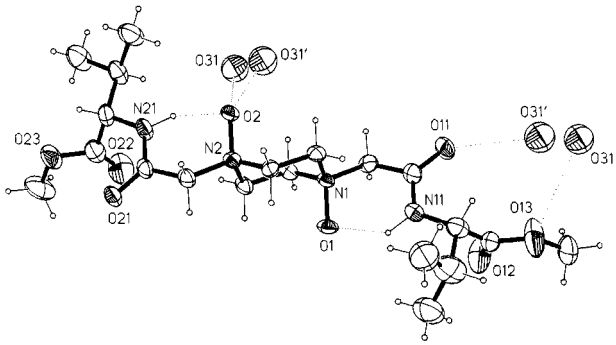


Fig. 1 Crystal structure of **8c** illustrating hydrogen bonding to the disordered water molecule. Thermal ellipsoids set at 50% probability.

single diastereoisomers; in addition the NH signals in $CDCl_3$ appeared as a singlet, which had been shifted downfield by approximately 3.5 ppm in all the compounds after *N*-oxide formation. For example, prior to oxidation, the valine derivative diamine NHs were at δ 7.63; after oxidation they had shifted to δ 11.12, and their chemical shift was found to be concentration independant in $CDCl_3$. The valine derivative gave crystals suitable for X-ray analysis‡ (Fig. 1).

The crystal structure clearly shows that both oxygen atoms are axial and are hydrogen bonded to the NH of the amides. The result is an almost linear molecule of highly defined conformation. N–O bond distances of both *N*-oxide moities are in the same range [N1–O1 1.398(5), N2–O2 1.399(5) Å]. Both hydrogen positions involved in intramolecular hydrogen bonding toward *N*-oxide moieties could be detected in difference Fourier maps and were refined freely. Both show comparable bonding distances [N11–H1 0.97(5), O1···H1 1.82(5), N21–H2 0.93(5), O2···H2 1.84(5) Å]. In addition, intermolecular interactions *via* hydrogen bonding are occuring across a water molecule which is disordered on two positions, resulting in infinite zig-zag-chains throughout the crystal lattice. One of the disordered positions (O31) bridges the amine oxide function O2 with an acyl–O (O13) [O2···O31 2.849(9), O13···O31 3.149(11) Å], while the other position forms a bridge between O2 and an amide–O (O11) [O2···O31′ 2.605(11), O11···O31′ 2.970(11) Å]. In contrast to the above described intramolecular H-bridges, hydrogen postions of the disordered water molecule could not be detected in difference Fourier maps.

In order to establish the range of the hydrogen bonding we prepared the piperazine derivative **10** which bears two amino acid substituents on each of the piperazine nitrogens (Scheme 4). Oxidation proceeded smoothly to give the bis (*N*-oxide) **11**.

NMR analysis of the product clearly showed that only the NHs of the alanine residues were hydrogen bonded to the amine oxide oxygens from their downfield chemical shift from δ 7.02 to 10.50. This specificity allows for fine-tuning of molecular shape.

We are currently examining the incorporation of these units into larger molecular structures and their use as chiral catalysts in a number of synthetic transformations.

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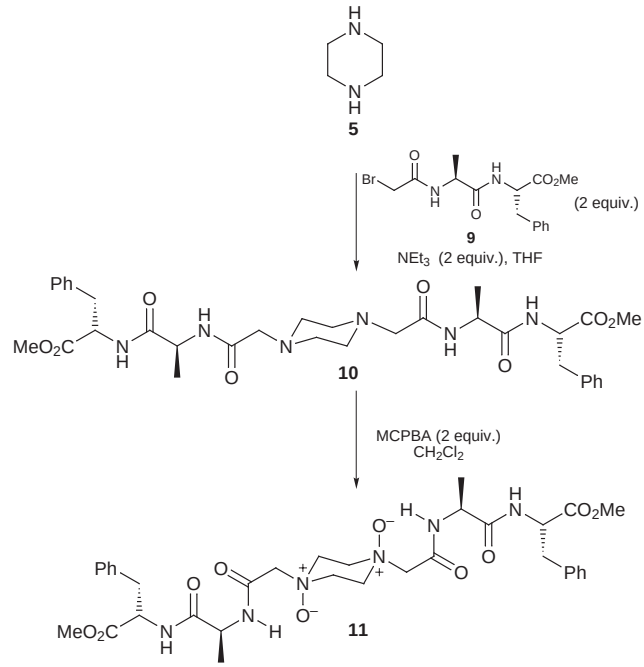

Scheme 4

Notes and references

‡ *Crystal data* for valine derivative: $C_{20}H_{38}N_4O_9$, M = 478.54, monoclinic space group $C2$, a = 25.424(6), b = 5.956(9), c = 16.654(5) Å, α = 100.28(2)°, U = 2481(4) Å^3, Z = 4, D_{calc} = 1.281 g cm^{-3}, μ(Mo-Kα) = 0.101 mm^{-1}. Data were recorded on a Rigaku-AFC6S diffractometer, Mo Kα radiation (λ = 0.71073 Å), T = 153 K, $2\theta_{max}$ = 45°. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 using all data (SHELX97, G. M. Sheldrick, Universität Göttingen, 1997). $R1$ [$I > 2\sigma(I)$] = 0.044, $wR2$ (1813 unique reflections) = 0.117. CCDC 182/1053. The CIF file for the crystal structure is available from the RSC web site: http://www.rsc.org/suppdata/cc/1998/2511

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