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A nonplanar porphyrin-based receptor molecule for chiral amine ligands

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A novel porphyrin-based receptor molecule for chiral amine ligands is described in which nonplanarity of the porphyrin macrocycle is used to orient the ligand and to enhance porphyrin-ligand interactions.

The porphyrin macrocycle provides a versatile platform upon which to build elaborate superstructures, and this feature coupled with a rich and well-developed synthetic chemistry has led to the synthesis of many elegant models of heme protein active sites[1,2] and numerous porphyrin-based receptor molecules.[3] One design feature which is not usually considered in the design of porphyrin-based receptor molecules is nonplanarity of the porphyrin ring, although there are a few systems such as the pyridine sensitive Venus Flytrap[4] and the chirality-memory

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molecule[5] which illustrate that nonplanar porphyrin-based receptors can display unique and interesting behavior. Given the novel properties of these receptors and the continuing interest in the effects of nonplanarity on the properties of porphyrins[6,7] we decided to investigate in more detail the potential applications of nonplanarity in the design of porphyrin-based receptors. Herein, we describe the design, synthesis, and characterization of a new kind of nonplanar porphyrin-based receptor molecule for chiral amines.

The last decade has seen a greatly increased understanding of the effects of nonplanar distortions on the properties of porphyrins.[6,7] It is now known that the nonplanar distortions can be represented in terms of linear combinations of distortions along the lowest energy normal coordinates of the macrocycle, and that only the lowest energy distortions (the ruffle, saddle, dome and wave) are usually significant.[8] Evidence from spectroscopic[9,10] and molecular modelling studies[11,12] suggests that two of the deformations, the ruffle and saddle, can be engineered in solution, making porphyrins which exhibit these distortions good starting points when designing nonplanar porphyrin-based systems. The ruffle conformation, in which the pyrrole ring are twisted alternately clockwise and anticlockwise and the meso positions are moved out of the porphyrin plane, is conserved for porphyrins with bulky meso alkyl groups such as **1**.[12] The saddle conformation, in which pyrrole rings are tilted alternately up or down and the pyrrole substituents are moved out of the porphyrin plane, is conserved in dodecasubstituted porphyrins such as **2**[13] and **3**.[11] There are two features of the ruffle and saddle conformations which seem to offer an advantage over planar porphyrins. Firstly, the surface of the macrocycle is curved to form cavities which might be used to orient substrate molecules.[14] Secondly, the out-of-plane movement of the meso substituents in ruffled porphyrins and the β substituents in saddle porphyrins forces the substituents closer to the center of the porphyrin ring potentially increasing porphyrin-substrate interactions.

To evaluate the usefulness of these features we designed a new type of nonplanar porphyrin-based receptor molecule for chiral amine ligands (**4**). Porphyrin **4** is expected to be saddle-shaped by analogy with the structures observed for porphyrin **2**[13] and should also display

a planar chirality (see Figure 1) analogous to that seen in ortho substituted biphenyls. These features were confirmed by molecular modelling studies[11] which showed a saddle structure with a very high rotational barrier for the 2-methoxyphenyl group (>146 kJ mol^{-1}). Additional calculations suggested that porphyrin **4** was capable of discriminating chiral amine ligands such as 2-pyrrolidinemethanol (**5**) because the nonplanar conformation oriented the plane of the amine ligand along a cavity in the saddle structure such that the 'axial' methoxy group of one porphyrin enantiomer (see Figure 1) was in close proximity to the hydroxyl group of one enantiomer of 2-pyrrolidinemethanol. For example, the hydroxyl group of the S form of 2-pyrrolidinemethanol interacted more closely with with the methoxy group of porphyrin enantiomer 2 than with the methoxy group of enantiomer 1. Note that the enantiomers with 'axial' methoxy substituents (1 and 2 in Figure 1) were calculated to be favored by aproximately 8 kJ mol^{-1} over the enantiomers with non-interacting 'equatorial' methoxy substituents (3 and 4 in Figure 1), suggesting that the solution behavior of 4 could be viewed largely in terms of enantiomers 1 and 2.

The free base of porphyrin **4** was synthesized using the Suzuki reaction for porphyrins recently described by Chan and co-workers,[15] with the conditions modified so as to favor formation of the product with one rather than eight β aryl substituents. This involved heating **2** (M = 2H) (1 equivalents), 2-methoxyphenylboronic acid (5 equivalents), $Pd[(PPh_3)]_4$ (0.15 equivalents), K_2CO_3 (20 equivalents) in toluene under argon at 90-100°C for two days using a Schlenk apparatus. The free base of porphyrin **4** was then isolated using column chromatography with silica gel and 60:40 chloroform/hexane, and its structure confirmed by MALDI mass spectrometry.[16] Zinc was inserted by adding zinc acetate in methanol to the free base porphyrin in chloroform, and the enantiomers of **4** separated by chiral chromatography using a Chiralcel OD column eluted with 89:10:1 hexanes, chloroform, and isopropanol. The CD spectra of the two components (elution times of 12 and 28 minutes) showed the expected mirror images. Passing each enantiomer through the hplc column 24 hours after separation revealed only a trace of racemization, so the rotational barrier of the 2-methoxyphenyl substituent in **4** is very high (•113 kJ mol^{-1}) as expected for an ortho substituted phenyl ring on a porphyrin.[17] ^1H NMR

studies of **4** in toluene-d_8 at 295 K showed a single broad methoxyl signal at δ 2.77 which at 193 K split into two peaks at δ 3.61 (ratio 1, equatorial OMe) and 2.30 (ratio 11.5, axial OMe). The observed energy difference (4 kJ mol^{-1}) is in qualitative agreement with the modeling studies described earlier. The activation energy for the macrocyclic inversion process which averaged out the methoxy signals in **4** was calculated to be 51 kJ mol^{-1} at the coalescence temperature of 273 K. This is reasonably close to the an energy of approximately 40 kJ mol^{-1} obtained from the modelling studies when the porphyrin inverted during rotation of the 2-methoxyphenyl substituent. For comparison, the activation energy for macrocyclic inversion of the **3** (M = Zn) in pyridine-d_5 was 66 kJ mol^{-1} at 323 K.[18]

Figure 2 shows portions of the NMR spectra obtained when (S)-2-pyrrolidinemethanol was added to the racemic mixture or to the separated enantiomers of **4** and to the achiral reference porphyrin **2** (M = Zn). Note that the spectra were recorded at 193 K with 0.8 equivalents of (S)-2-pyrrolidinemethanol, under which conditions amine exchange, inversion of the porphyrin macrocycle, and rotation of the 2-methoxyphenyl group are all slow on the NMR timescale. The region shown includes some of the signals for the amine ligand, with those marked 'NH' being definitively assigned to the NH protons of the pyrrolidine ring by deuteration with D_2O. Interestingly, the number of NH signals in the two fractions reveal a significant difference in how (S)-2-pyrrolidinemethanol complexes to the enantiomers of **4**. The spectrum of the 28 minute fraction shows three proton signals of which one can be assigned to the NH protons, and is similar to that seen for **2** (M = Zn). In contrast, the spectrum of the 12 minute fraction shows additional peaks and no fewer than four NH signals. This indicates a specific binding mode for the 28 minute fraction but not for the 12 minute fraction. To date, we have been unable to determine the structures of the complexes formed by these enantiomers with (S)-2-pyrrolidinemethanol using X-ray crystallography. Molecular modelling studies suggest that the 28 minute fraction is enantiomer 2, because the porphyrin methoxy group in this enantiomer is positioned to interact with the hydroxyl group of (S)-2-pyrrolidinemethanol to form a weak hydrogen bond. If this is indeed the driving force for the specific binding observed in the case of

the 28 minute fraction, then it seems likely that the four NH signals seen for the 12 minute fraction, in which this hydrogen-bonding interaction should be weaker, signify binding of the ligand on both faces of the porphyrin and in both possible orientations in the porphyrin cavity. Note that observation of signals for both orientations in the cavity is consistent with the high barrier (42 kJ mol^{-1}) calculated for rotation of (S)-2-pyrrolidinemethanol complexed to enantiomer 1.

The results reported here suggest that certain features of nonplanar porphyrins such as the presence of cavities for orienting substrates and the out-of-plane movements of substituents which increase porphyrin-substrate interactions may be useful in the design of porphyrin-based receptor molecules. It will be interesting to see if nonplanarity can be more widely exploited in the design of porphyrin-based receptor molecules, and additional studies in this area are currently in progress in our laboratories.

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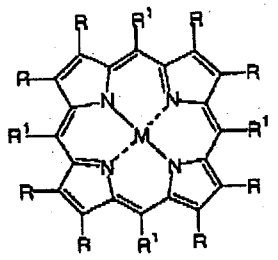
Structures



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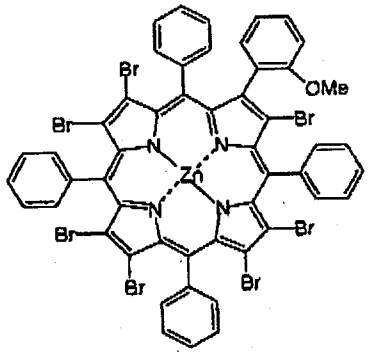
2	Br	phenyl
3	Ethyl	phenyl



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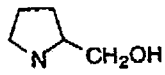

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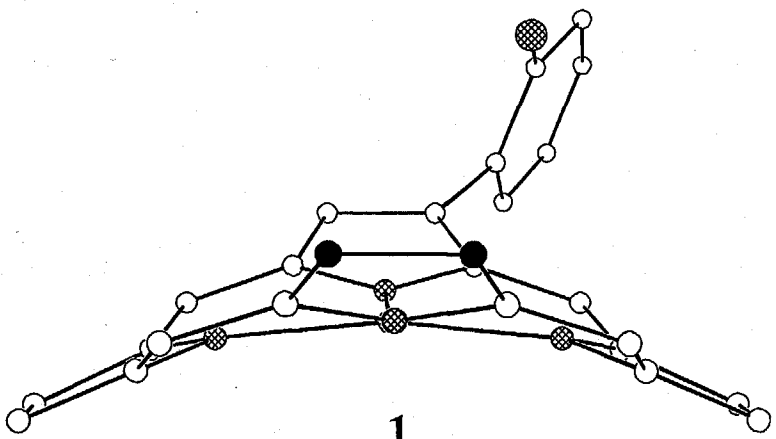
Figure Captions

Figure 1 Representations of the enantiomers of **4** with axial methoxy groups (1 and 2) and with equatorial methoxy groups (3 and 4).

Figure 2 Selected portions of 300 MHz ^{1}H NMR spectra measured at 193K in toluene-d_8 containing 0.8 equivalents of (S)-2-pyrrolidinemethanol: (a) the racemic mixture of **4**, (b) the fraction of **4** with a 28 minute hplc retention time, (c) the fraction of **4** with a 12 minute hplc retention time, and (d) the achiral reference complex **2** (M = Zn)



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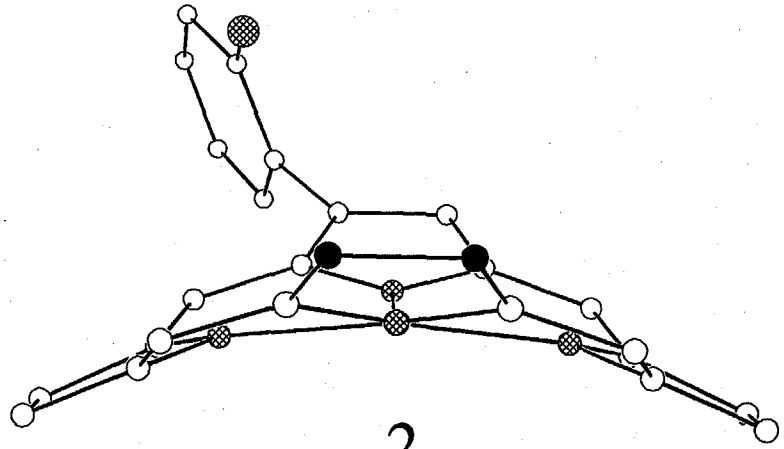

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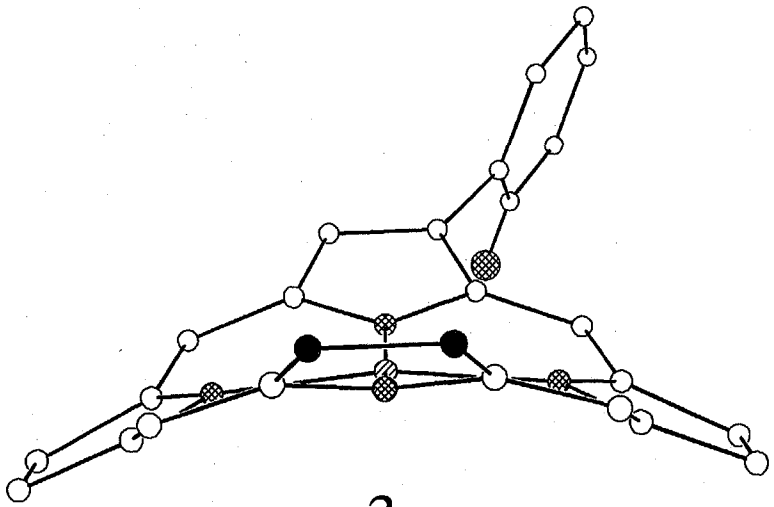

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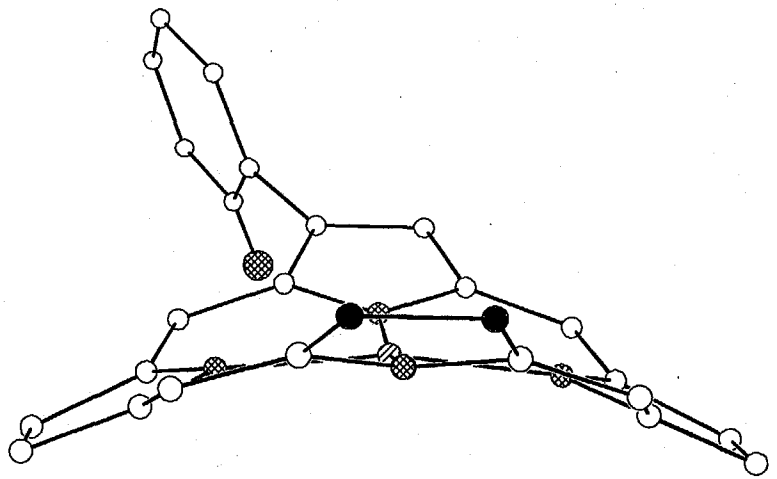
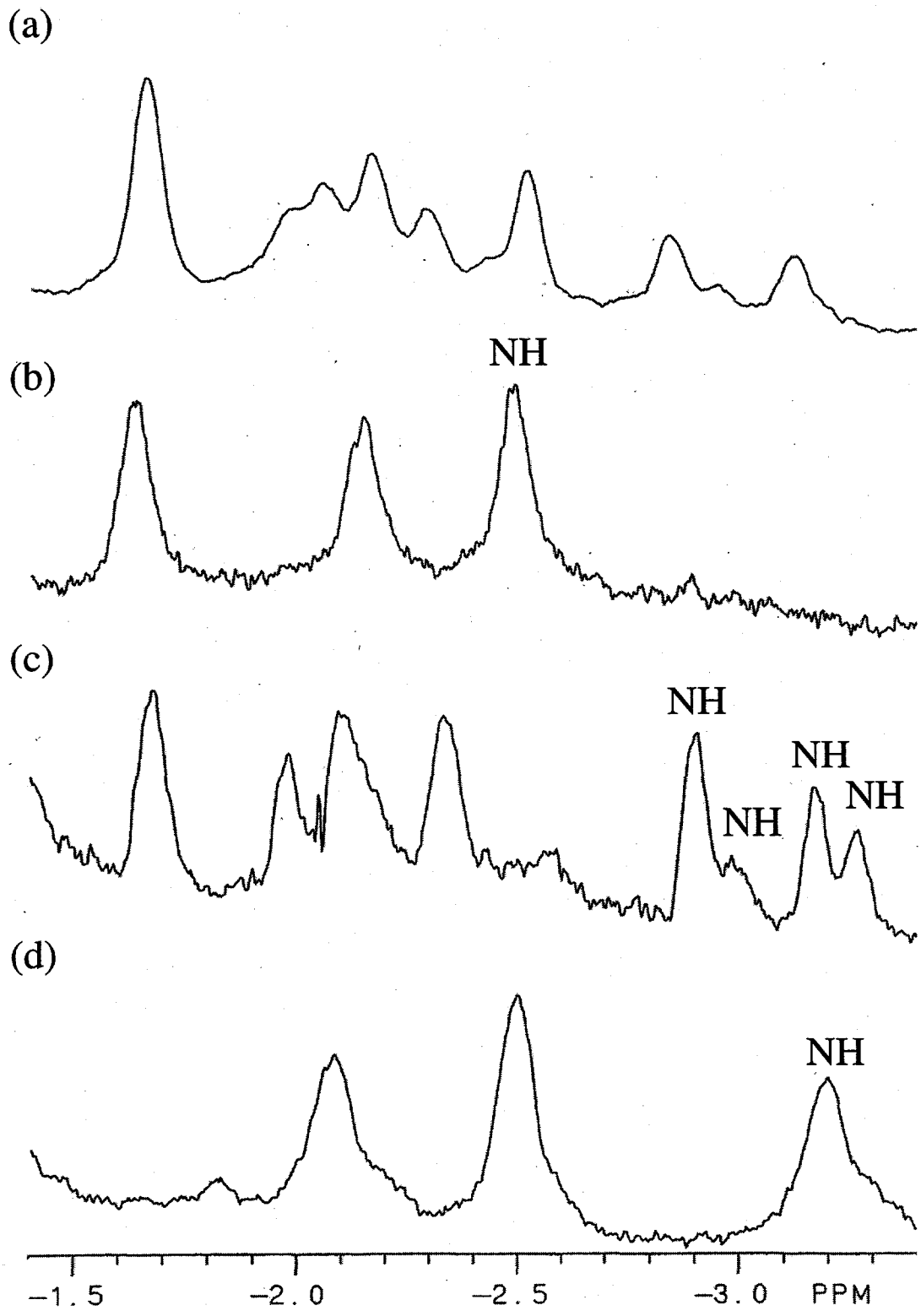


4

MIRROR PLANE


(a)
(b)
NH
(c)
NH
NH
NH
NH
(d)
NH
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−2.0
−2.5
−3.0
PPM