The influence of sterics on the formation of polar 1-D hydrogen-bonded networks†

Adam J. Preston, Judith C. Gallucci and Jon R. Parquette*

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Polar, noncentrosymmetric packing of directional, 1-D hydrogen-bonded networks of chiral, 4-amino-2,6-bis(oxazolinyl)pyridines (ampybox) occurs for isopropyl-substituted ampybox 2; in contrast, 1-D networks of methyl-substituted ampybox 1 pack in an antiparallel arrangement.

The design of supramolecular synthons that direct intermolecular interactions in the solid state represents an important strategy to control lattice architecture in the field of crystal engineering.[1] Many potential applications such as electro-optic modulation and second harmonic generation require noncentrosymmetric lattices having polar order.[2] One strategy for the design of 1-D acentric chains relies on the development of specific intermolecular interactions that link molecules into an infinite chain.[3] However, the assembly of polar, noncentrosymmetric crystals composed of directional networks remains a significant challenge due to the tendency of such networks to align in an antiparallel manner to minimize dipolar interactions. Chiral molecules must crystallize in chiral, noncentrosymmetric space groups and, hence, may have some directions that are polar. However, the use of chirality to avoid centrosymmetric packing creates networks that may pack in either parallel (polar)[4] or antiparallel (nonpolar) arrays.[5] The relative alignment of adjacent networks depends on many subtle interactions and crystal engineering has not yet advanced to the point where these interactions can be easily predicted. We report in this communication the effect of chiral substituents in determining the packing alignment of hydrogen-bonded chains of 4-amino-2,6-bis(oxazolinyl)pyridines **1** and **2**.

According to Etter's rules, the most acidic hydrogens will hydrogen bond with the best acceptors in the crystal lattice.[6] Therefore, self-assembly of 4-amino-2,6-bis(oxazolinyl)pyridine into a 1-D directional network was envisaged to occur *via* the accumulation of intermolecular hydrogen-bonding interactions of both 4-amino N^1–Hs with the oxazolinyl nitrogens[7] (N^2), which represent the best acceptors of the ampybox, of an adjacent 4-ampybox in the network (Fig. 1a). Ampyboxs, **1** and **2**, both possessing C_2 chirality but differing in the steric bulk of the substituents at the stereogenic centers, were studied in order to induce a parallel packing arrangement of adjacent networks in the crystal lattice (Fig. 1b).[8]

Accordingly, enantiomerically pure 4-ampybox derivatives were prepared having either a methyl or isopropyl substituent at the 4′-position of the oxazoline moieties as shown in Scheme 1. Ampyboxes **1** and **2** were only sparingly soluble in all organic solvents that were used (CH_2Cl_2, $CHCl_3$, acetone, EtOAc, THF, CH_3CN, DMSO); however, adding 5% methanol, which presumably disrupted intermolecular H-bonding interactions, to any of these solvents resulted in complete dissolution. These solubility characteristics contrasted with the 4-chloropybox derivative that

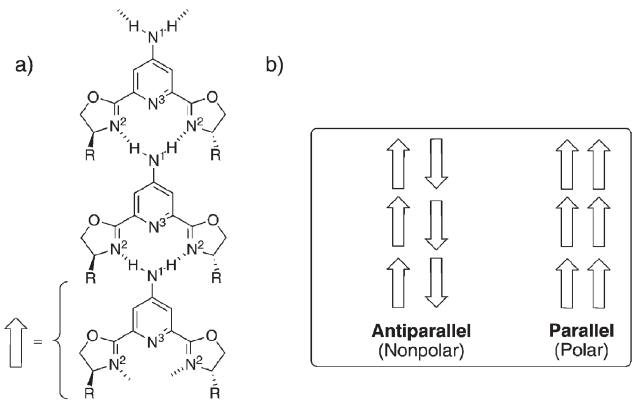
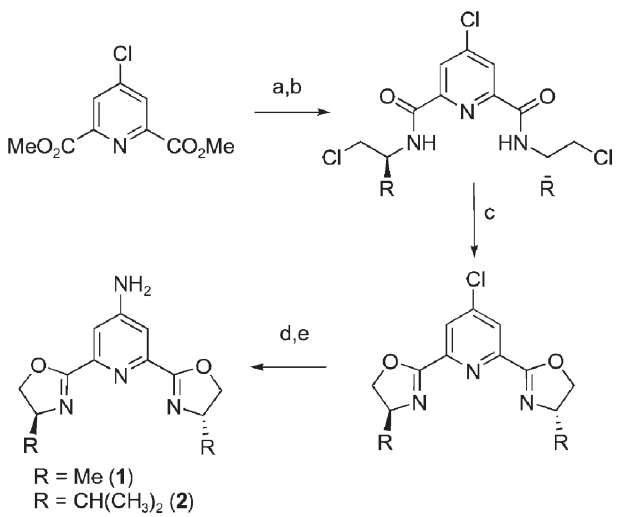


Fig. 1 (a) Formation of a 1-D network *via* intermolecular hydrogen-bonding between adjacent ampybox molecules. (b) Antiparallel and parallel packing of adjacent 1-D networks.



Scheme 1 (a) (*S*)-(+)-2-amino-1-propanol or (*S*)-(+)-2-amino-3-methyl-1-butanol, 100 °C, neat 2 h; (b) $CHCl_3$, $SOCl_2$, reflux, 1 h (87%, R = Me; 96%, R = *i*-Pr, 2 steps); (c) NaH, THF (71%, R = Me; 86%, R = *i*-Pr); (d) NaN_3, DMF, 65 °C, 3 h; (e) $NaBH_4$, *i*-PrOH, reflux, 1 h (99%, R = Me; 87%, R = *i*-Pr, 2 steps).

† Electronic supplementary information (ESI) available: Full synthetic experimental details for compounds depicted in Scheme 1 and X-ray data tables for compounds **1** and **2**. See http://www.rsc.org/suppdata/cc/b4/b414470h/index.sht

*parquett@chemistry.ohio-state.edu.

displayed high solubility in all of these solvents. In contrast to the 4-chloropybox derivatives that exhibited relatively low melting points (mp 112–114 °C (R = Me); 55–57 °C (R = *i*-Pr)), crystals of **1** and **2** were stable up to 250 °C and 230 °C, respectively, at which point discoloration occurred without melting.

A clear, colorless crystal (orthorhombic, space group $P2_12_12$) of ampybox **1** was obtained by slow evaporation of a mixture of 5% CH_3OH–CH_2Cl_2.‡ X-Ray diffraction revealed the presence of 2.5 molecules in the asymmetric unit, which, upon translation along the crystallographic *c* axis, afforded a directional, 1-D network of molecules aligned in a perfectly coplanar assembly. Intermolecular hydrogen-bonds between the amino N–Hs and oxazoline Ns of adjacent molecules stabilize the network affording N^1–H···N^2 distances of 2.996(3) to 3.044(3) Å, and N^1···N^3 distances ranging from 3.009(3) to 3.019(3) Å, consistent with a strong H-bonding interaction (Fig. 2a). The planar 1-D networks were stacked along the crystallographic *a* axis and the stacked assemblies were further organized in a herringbone arrangement,[9] viewing along the *c* axis (Fig. 2b). Although the $P2_12_12$ space group is noncentrosymmetric and chiral, it is not a polar space group. The 1-D networks are packed in a centric mode whereby adjacent networks align in an antiparallel arrangement. This network organization affords a nonpolar crystal lacking polarity in any of the three major crystallographic axes.

Ampybox **2**, having sterically larger isopropyl substituents at the stereogenic centers, crystallized in the polar, noncentrosymmetric space group $P2_1$, with two molecules in the asymmetric unit, upon slow evaporation from 5% MeOH–CH_2Cl_2.‡ In constrast to the $P2_12_12$ space group observed for **1**, the space group $P2_1$ exhibits polarity along the crystallographic *b* axis. The polarity along this axis evolves from the development of a 1-D directional network that is stabilized by intermolecular hydrogen-bonds between the amine NHs and the oxazoline Ns (Fig. 3), as was also observed in the crystal structure of **1**. However, in contrast to **1**, the directional, hydrogen-bonded columns are packed in an acentric, parallel arrangement, giving rise to polarity along the *b* axis. To accommodate the parallel packing, the hydrogen-bonded networks orient adjacent pybox molecules in a noncoplanar, zig-zag arrangement exhibiting angles of 32.3° and 45.8° relative to the planes of adjacent ampyboxes for each of the two crystallographically unique networks.

In conclusion, the ability to form directional, 1-D networks in the solid state *via* intermolecular hydrogen-bonding interactions of 4-amino-2,6-bis(oxazolinyl)pyridines has been demonstrated. The subtle factors responsible for the polar packing of **2** are not fully understood at this point. However, increasing the steric influence of the substituents at the stereogenic centers appears to be an important determinant of the relative ordering of adjacent hydrogen-bonded networks. Accordingly, the generality of this observation remains as a current topic of investigation. Although the ability of these networks to exhibit significant nonlinear optical properties is likely to be minimal due to the intrinsically weak dipolar nature of **1** and **2**, this design strategy should be useful in the development of new systems having NLO responses. It is noteworthy that **1** and **2** exhibit high melting points and high thermal stabilities, both of which are essential properties for organic NLO materials. The NLO properties of these systems and more dipolar analogs will be explored in future studies. This work was supported by the National Science Foundation (CHE-0239871).

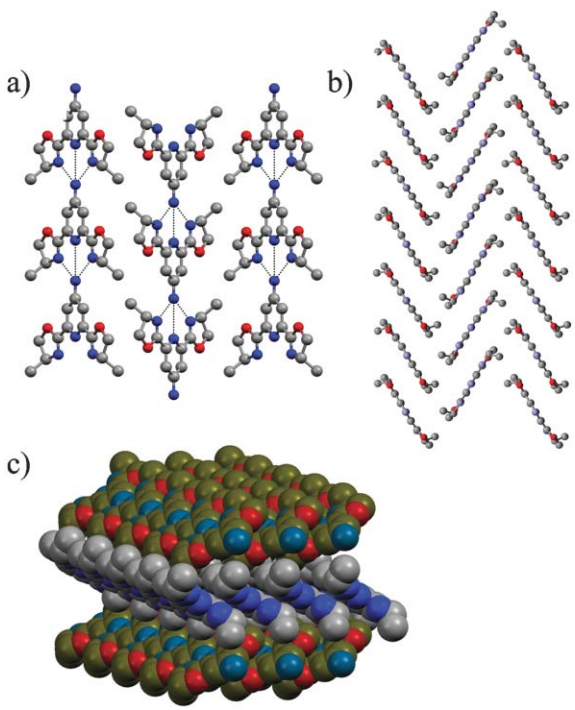


Fig. 2 (a) A portion of the crystal structure of **1** showing the antiparallel packing of the hydrogen-bonded 1-D networks. (b) Herringbone-type packing of 1-D networks. (c) Space-filling representation showing layer-to-layer organization.

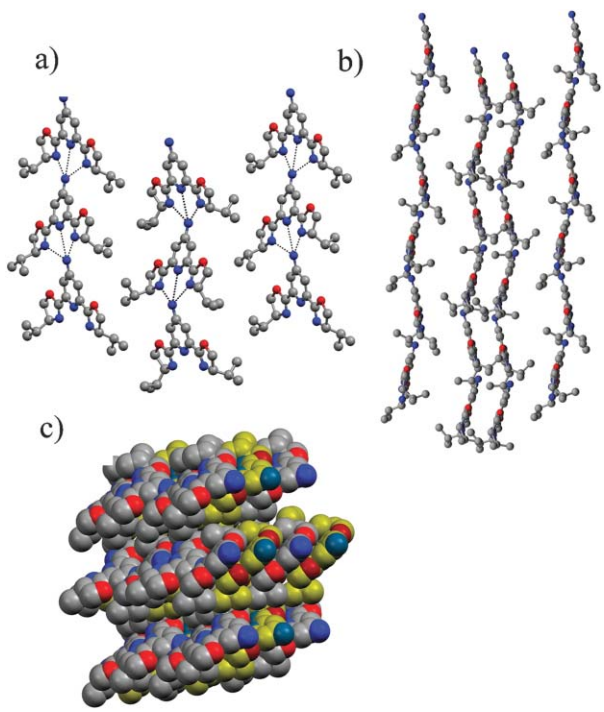


Fig. 3 (a) A portion of the crystal structure of **2** showing the parallel packing of the hydrogen-bonded 1-D networks. (b) Side-on view of 1-D networks showing the zig-zag alignment of adjacent ampyboxes. (c) Space-filling representation showing layer-to-layer organization.

Adam J. Preston, Judith C. Gallucci and Jon R. Parquette*
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA. E-mail: parquett@chemistry.ohio-state.edu.; Fax: +1 (614) 292-1685; Tel: +1 (614) 292-5886

Notes and references

‡ Crystallographic data for **1** (clear, colorless rectangular rod, 200 K): $C_{13}H_{16}N_4O_2$, M = 260.30, orthorhombic, a = 32.0792(5), b = 14.4080(2), c = 7.20350(10) Å, μ = 0.091 mm^{-1}, U = 3329.44(8) $Å^3$, space group $P2_12_12$, Z = 10, D_c = 1.298 Mg m^{-3}, Kappa CCD, 3345 data, R = 0.0380, Rw = 0.0877. Crystallographic data for **2** (colorless rectangular block, 150 K): $C_{17}H_{24}N_4O_2$, M = 316.40, monoclinic, a = 6.131(1), b = 13.950(2), c = 20.220(3) Å, β = 91.021(4)°, μ = 0.082 mm^{-1}, U = 1729.1(5) $Å^3$, space group $P2_1$, Z = 4, D_c = 1.215 Mg m^{-3}, Kappa CCD, 4105, data, R = 0.0339, Rw = 0.079. CCDC 252731 and 252732. See http://www.rsc.org/suppdata/cc/b4/b414470h/index.sht for crystallographic data in CIF or other electronic format.

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