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^{1}H NMR and X-ray crystallographic analysis of 1,2-bis(4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethane and its 'propylene linker'-analog: molecular recognition versus crystal engineering†

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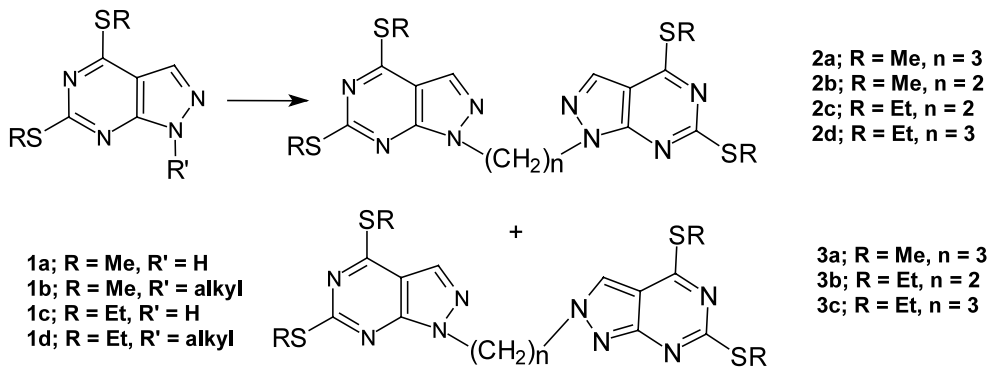
Abstract—Proton NMR analysis on newly synthesized 1,2-bis(4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethane, **2c**, and 1,2-bis(4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propane, **2d**, showed intramolecular stacking in solution. X-Ray crystallography on **2c** and **2d**, however, confirmed the presence of such intramolecular stacking only in case of the 'propylene linker' compound, **2d**, while the 'ethylene linker' compound, **2c**, was devoid of it.

Interactions between aromatic units play a significant role in chemistry,[1] biology and crystal engineering.[2] While π–π stacking is by consensus an important non-covalent interaction in DNA and proteins, the nature of this interaction remains under debate.[3] Recently, we have reported on the synthesis and X-ray structure of two isomeric 'trimethylene linker' compounds **2a** and **3a** (Scheme 1), based on the pyrazolo[3,4-*d*]pyrimidine core, which is isomeric with biologically important purines, as new flexible models for better understanding of aromatic π–π interactions (APPI).[4–6] One of the important findings of this study has been the unprecedented demonstration of a dramatic 'orientation effect' by X-ray crystallography. Thus, compound **2a** showed both intra- and intermolecular stacking[5] due to APPI, however, its positional isomer **3a** showed only intermolecular stacking.[6] Initial indications for intramolecular stacking in compound **2a** was provided by its ^{1}H



Scheme 1.

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NMR spectroscopic data.[4] In fact one set of the methylthio protons were found to move upfield compared to the corresponding signal in simple 1-alkyl-4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine[7] (**1b**). Leonard[8] in 1968 first introduced the use of polymethylene linkers, especially the 'trimethylene linker', for studying stacking interactions among nucleic acid bases. The use of the 'trimethylene linker' and closely related isobutyric acid linker, has been increasing ever since for such studies.[9–13] Even more interesting was the fact that compound **2b**, an 'ethylene linker' compound, also showed a comparable upfield shift for its methylthio group, thus indicating the presence of a '*syn*-conformation' in solution due to intramolecular stacking interactions.[4] However, in spite of our extensive efforts, we have not been able to obtain X-ray quality crystals of **2b**.

In this communication we present another strategy for the conformational analysis of compound **2b** in the solid state. In order to facilitate crystallization due to subtle 'packing forces', we simply replaced the methyl groups of compound **2b** by ethyl groups. This new compound 1,2-bis(4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethane (**2c**) was synthesized following the general methodology[4] described earlier for the synthesis of **2b**, except that 4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine[14] (**1c**) was used in place of **1a**. This compound **2c**[15] also showed an unusual upfield shift for the ethylthio group in its ^{1}H NMR spectrum as compared to the corresponding chemical shift in 1-alkyl-4,6-diethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1d**). These ^{1}H NMR spectroscopic data strongly indicated the presence of the '*syn*-conformation' in the solution state. Compound **2c** easily gave X-ray diffraction quality crystals (EtOAc–$CHCl_3$). The conformation of **2c** as determined by X-ray crystallography,[16] is shown in Fig. 1 with its atom-numbering scheme. The molecule does not show folding (N1–N1 = 3.702(5) Å) for intramolecular stacking. Interestingly, the crystal packing showed the presence of intermolecular stacking (average distance between the adjacent pyrimidine planes being 3.4 Å).

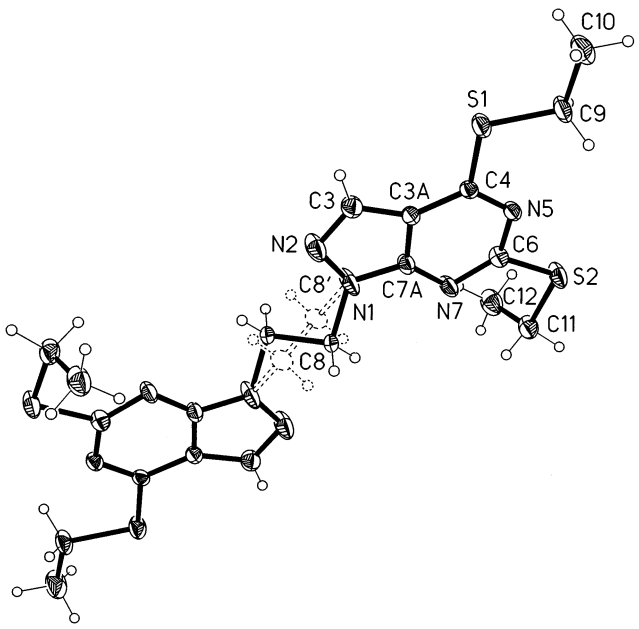

Figure 1. ORTEP diagram of **2c** showing the crystal structure. Only one half of the molecule has been labeled, the other half is related by symmetry transformation. The C8 atom has positional disorder as shown by the dotted representation.

The absence of intramolecular stacking in compound **2c**, as demonstrated by X-ray crystallography, was not in fact surprising as 'ethylene linker' (i.e. -CH_2-CH_2-) compounds having aromatic moieties at their termini are known normally to exist in the '*anti*-conformation' by X-ray crystallography.[17,18] This compound, however, in our opinion constitutes a very interesting example showing subtle differences of molecular recognition (in solution) and crystal engineering (in solid state), the two facets of supramolecular chemistry.[19] Apparently, the '*syn*-conformation' for compound **2c** due to APPI as shown by ^{1}H NMR analysis in the solution state did not survive the 'packing forces' present in the solid state. Furthermore, the dimethylene spacer can conveniently sit on an inversion center in the crystal. This would mandate a non-stacked conformation and could, in part, also account for the difference in behavior between the solution and solid state. Fig. 1 also shows that there is disorder at the C8 carbon and it can be resolved into two positions, C8 and C8′ (torsion angles: N1–C8–C8–N1 180.0°; N1–C8′–C8′–N1 138.6°).

In order to make sure that the introduction of an ethyl group in place of the methyl group has not produced any unexpected results apart from the expected steric increase, the 'propylene linker', compound **2d** was also synthesized. Compound **2d** was made following a similar method[4] to the described earlier for **2a**, except that ethylthio base (**1c**) was used in place of methylthio base (**1a**). The similarity of the ^{1}H NMR spectroscopic results of **2d**[15] with that of **2a**,[4] clearly indicated the presence of intramolecular stacking. X-Ray crystallographic structure,[16] as shown in Fig. 2 also confirmed the intramolecular stacking due to

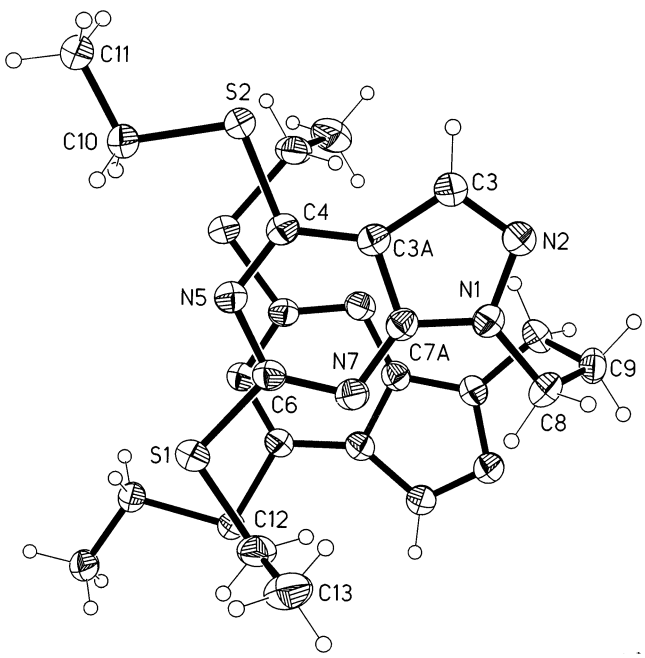

Figure 2. ORTEP diagram of **2d** showing the folded conformation of the molecule due to APPI.

APPI (average intraplanar distance between the overlapping pyrimidine rings is 3.37 Å). As the solid state conformation of **2d** was very similar to that of **2a**, it is reasonable to assume that ethyl and methyl groups have behaved quite similarly in solution also. In addition, the crystal packing of **2d** also showed intermolecular stacking (average spacing between pyrimidine rings is 3.44 Å).

In conclusion, it has been shown that the conformation observed for compounds **2a**–**d** in solution and largely directed by APPI carries over into the solid state only for **2a** and **2d**, the 'propylene linker' compounds.

References

1. Hunter, C. A. *Chem. Soc. Rev.* **1994**, 101–109.
2. Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311–2327.
3. Guckian, K. M.; Schweitzer, B. A.; Ren, R. X.-F.; Sheils, C. J.; Tahmassebi, D. C.; Kool, E. T. *J. Am. Chem. Soc.* **2000**, *122*, 2213–2222.
4. Avasthi, K.; Chandra, T.; Bhakuni, D. S. *Indian J. Chem.* **1995**, *B34*, 944–949.
5. Biswas, G.; Chandra, T.; Avasthi, K.; Maulik, P. R. *Acta Crystallogr.* **1995**, *C51*, 2453–2455.
6. Maulik, P. R.; Avasthi, K.; Sarkhel, S.; Chandra, T.; Rawat, D. S.; Logsdon, B.; Jacobson, R. A. *Acta Crystallogr.* **2000**, *C56*, 1361–1363.
7. Garg, N.; Avasthi, K.; Bhakuni, D. S. *Synthesis* **1989**, 876–878.
8. Browne, D. T.; Eisinger, J.; Leonard, N. J. *J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.
9. Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423–429.
10. Newcomb, L. F.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4993–4994.
11. Avasthi, K.; Rawat, D. S.; Chandra, T.; Bhakuni, D. S. *Indian J. Chem.* **1998**, *B37*, 754–759.
12. Maulik, P. R.; Avasthi, K.; Biswas, G.; Biswas, S.; Rawat, D. S.; Sarkhel, S.; Chandra, T.; Bhakuni, D. S. *Acta Crystallogr.* **1998**, *C54*, 275–277.
13. Pang, Y.-P.; Miller, J. L.; Kollman, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 1717–1725.
14. Brown, D. T.; Danckwerts, L.; Grigg, G. W.; Twai, Y. *Aust. J. Chem.* **1979**, *32*, 453–458.
15. Compound **2c**: mp 123°C (EtOAc–Hex); yield 43%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.365 (t, $J=7.4$ Hz, 6H, 2×Me), 1.41 (t, $J=7.3$ Hz, 6H, 2×CH_3), 2.60 (q, $J=6.7$ Hz, 2H, CH_2), 3.01 (q, $J=7.4$ Hz, 4H, 2×SCH_2), 3.30 (q, $J=7.4$ Hz, 4H, 2×SCH_2), 4.80 (s, 4H, 2×NCH_2), 7.78 (s, 2H, NH-3). Anal. calcd for $C_{20}H_{26}N_8S_4$: C, 47.40; H, 5.17; N, 22.21. Found: C, 47.60; H, 5.06; N, 22.16%.
Compound **2d**: mp 98°C (EtOAc–Hex); yield 49%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.37 (t, $J=7.3$ Hz, 6H, 2×CH_3), 1.43 (t, $J=7.3$ Hz, 6H, 2×CH_3), 2.60 (q, $J=6.7$ Hz, 2H, CH_2), 3.07 (q, $J=7.3$ Hz, 4H, 2×SCH_2), 3.34 (q, $J=7.3$ Hz, 4H, 2×SCH_2), 4.35 (t, $J=6.7$ Hz, 4H, 2×NCH_2), 7.87 (s, 2H, 2×H-3). Anal. calcd for $C_{21}H_{28}N_8S_4$: C, 48.53; H, 5.42; N, 21.52. Found: C, 48.73; H, 5.30; N, 21.80%.
16. Crystal data for **2c**: $C_{20}H_{26}N_8S_4$, $M=506.73$, triclinic, $P\bar{1}$, $a=8.2228(6)$, $b=8.5390(6)$, $c=9.2026(9)$ Å, $\alpha=64.526(3)$, $\beta=87.371(3)$, $\gamma=85.799(2)°$, $V=581.70(8)$ Å^3, $Z=1$, $D_{calcd}=1.447$ g cm^{-1}, μ(Mo Kα)$=0.435$ mm^{-1}, $F(000)=226.0$, colorless needle crystal, size 0.40×0.10×0.02 mm, 4909 reflections measured ($R_{int}=0.069$), 2606 unique, $R_w=0.094$ for all data, conventional $R=0.049$ on F values of 1202 reflections with $I>2\sigma(I)$, $S=0.814$ for all data and 156 parameters. Final difference map between 0.291 and −0.254 e Å^{-3}.
Crystal data for **2d**: $C_{21}H_{28}N_8S_4$, $M=520.75$, monoclinic, $C2/c$, $a=17.777(1)$, $b=9.3127(6)$, $c=15.239(1)$ Å, $\beta=98.388(1)°$, $V=2495.8(3)$ Å^3, $Z=4$, $D_{calcd}=1.386$ g cm^{-1}, μ(Mo Kα)$=0.408$ mm^{-1}, $F(000)=1096.0$, colorless block crystal, size 0.38×0.30×0.20 mm, 13623 reflections measured ($R_{int}=0.029$), 2874 unique, $R_w=0.084$ for all data, conventional $R=0.030$ on F values of 2565 reflections with $I>2\sigma(I)$, $S=1.067$ for all data and 150 parameters. Final difference map between 0.305 and 0.244 e Å^{-3}.
Unit cell determination and intensity data collection for both the compounds were performed on a Bruker SMARTCCD diffractometer at 150(2) K. Structure solutions were measured by direct methods and refinements by full-matrix least-squares methods on F^2 with absorption corrections. Programs: SMART and SAINT (Bruker AXS Inc.: Madison, WI, USA 1998), SHELXTL (Sheldrick, G. M. Siemens AXS Inc.: Madison, WI, USA, 1994), SHELXL-97 (Sheldrick, G. M. University of Göttingen: Germany, 1997), NRCVAX (Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384–387). Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC Deposition No. 162860 for **2c** and 162861 for **2d**, respectively).
17. Harada, J.; Ogawa, K.; Tomoda, S. *J. Am. Chem. Soc.* **1995**, *117*, 4476–4478.
18. Kahr, B.; Mitchell, C. A.; Chance, J. F.; Clark, R. V.; Gantzel, P.; Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 4479–4482.
19. Desiraju, G. R.; Sharma, C. V. K. In *The Crystal as a Supramolecular Entity*; Desiraju, G. R., Ed.; John Wiley & Sons: New York, 1996; pp. 31–61.