Chemistry & Biology Interface, 2014, 4, 5, 292-300

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Synthesis, ^{1}H NMR and X-ray crystallographic studies of three isomeric *butylidene* linker *protophanes*

Kamlakar Avasthi [a,*], Lakshmi Shukla[a] and Ruchir Kant[b]

[a]*Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow, 226031, India.*
[b]*Molecular and Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow, 226031, India.*
**E-mail: kavasthi@rediffmail.com*
Received 16 October 2014; Accepted 30 October 2014

Abstract: In this study, the synthesis of isomeric *butylidene* linker *protophanes* by the reaction of *butylidene* linker bis-lactam with n-propyl iodide in K_2CO_3/DMF is reported. All the three isomers showed folded (*syn*) conformation in solution based on ^{1}H NMR analysis. More importantly, this folding carries over to the solid state due to intramolecular π–π interactions as revealed by single crystal X-ray crystallography.

Keywords: Arene interaction, Butylidene linker, Protophanes, Pyrazolo[3,4-*d*]pyrimidine.

Introduction

Noncovalent interactions like π–π and C–H…π play a key role in controlling the conformation of flexible aromatic compounds both in solution as well as solid state. Generally, these interactions are weaker than H-bonding; therefore their understanding is quite difficult. Study of these interactions is facilitated by synthetic models as they are very important in controlling the shape of complex molecules like DNA/RNA and proteins. Arene interaction is one of the type of noncovalent interactions that participate prominently in chemistry [1-4], biology [5, 6], molecular recognition [7], DNA/RNA [8], protein structures [9-11], crystal engineering [12-14], and drug-receptor complexes [15]. In spite of their wide occurrence still they are not properly understood.

Pyrazolo[3,4-*d*]pyrimidine (PP) core is medicinally important [16] and it is isomeric of the purine. In our previous studies, we showed the use of PP core for the study of both inter- and intra-molecular arene interactions in fully flexible model, 1,3-bis(4,6-dimethylsulfanyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-1-yl)propane (**1**) in solution by ^{1}H NMR analysis [17] and in the solid state by single crystal X-ray crystallography [18]. The unusual *U motif* formed in **1** is robust enough as shown by many structurally different compounds (**3-5**, Fig. 1)

[19-21] derived from **1** *via* **2** [22]. During the synthesis of *propylene* linker compounds (**3-5**, Fig. 1) two more isomeric compounds (*O,O*- and *N,O*-) were isolated in small amounts, however, our all efforts were unsuccessful to crystallize all the three isomers in any case. Further studies on *propylene* linker compounds related to two parent compounds (**1** and **3**, Fig. 1) established that the unusual *U motif* is indeed robust for the study of arene interactions both at molecular and supramolecular levels [23, 24a]. The *propylene/ Leonard* linker has been also used to study the intramolecular cation–π interactions [24b] and anion–π interactions [24c].

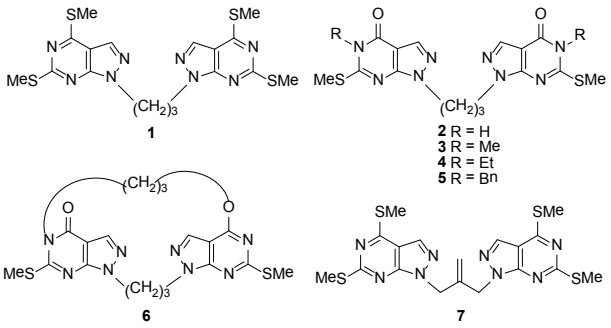


Figure 1. PP core based *propylene* (**1**, **3-5**) and *butylidene* (**7**) linker folded models

Interestingly, Vögtle refers to singly linked molecules that adopt π–stacked conformations as '*protophanes*' [25]. *Protophanes* have many properties similar to cyclophanes, especially as a model for understanding of arene interactions, the area, however, has not been developed much presumably due to paucity of general methods for their synthesis [26-28]. The major difference between cyclophane and *protophane* is that later has only one linker as compared to former which normally has two linkers. The main advantage offered by *protophanes* having one linker over cyclophanes is that they display natural folded conformation due to π–π interactions, while conformation of later is constrained by second linker. For example, *protophanes* (**1** and **3-5**, Fig. 1) showed unusual *U motif* in which only six member pyrimidine rings are partially overlapped while five member pyrazole rings are at maximum distance from each other. On the other hand conformation of cyclophane (**6**, Fig. 1) [29] showed normal *U motif* in which both five and six member rings were overlapped with similar five and six member rings of opposite face of cyclophane.

Previously, we have reported the use of *butylidene* as an alternative of *propylene* linker for studying arene interactions in symmetric and dissymmetric PP, purine, carbazole and 7-deazapurine core based flexible models. Six compounds were found to exist in folded conformation due to intramolecular π–π interactions as revealed by X-ray crystallography [30]. Herein, we report a method for the synthesis of variety of *protophanes* for studying of interesting properties of *protophanes*.

Materials and Methods

Experimental Section

General. Analytical grade reagents were used without any further purification. Melting points are uncorrected and were measured on a Buchi 530 melting point apparatus. Mass spectra were recorded on a Jeol-JMS D-300 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DRX-300 instrument at 300 MHz and 75 MHz, respectively, using TMS as an internal standard.

Synthesis of 1,3-bis(6-methylsulfanyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-methylene propane (8). Suspension of compound **7** [30a] (1.0 g, 2.10 mmol) in MeOH (45 mL) and THF (15 mL) was refluxed for 30 min and then 1N aq. NaOH (100 mL) was added drop wise over a period of 30 min. The resultant reaction mixture was refluxed for 10 h, and then it was cooled up to room temperature. All volatiles were removed under reduced pressure and the residue was neutralized with

acetic acid up to pH = 6 and kept as it is for 2 h. Then reaction mixture was filtered and the residue was washed with water, and dried to get crude product **8**. The crude product was boiled with $CHCl_3$ and filtered, and then the residue was obtained as a pure product **8**.

8: White solid; Yield 85%; mp 266−268 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 6H, 2 × SMe), 4.74 (s, 4H, 2 × NCH_2), 5.32 (s, 2H, CH_2), 8.05 (s, 2H, ArH), 12.39 (br s, 2H, 2 × NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 12.4, 48.1, 102.7, 118.2, 135.1, 139.3, 151.9, 157.4, 160.3; HRMS (ESI) calcd. for $C_{16}H_{17}N_8O_2S_2$ (M + H), 417.0916; found, 417.0895.

General procedure for the syntheses of *protophanes* (9-11) and monomers (13 and 14). To a stirred solution of compound **8** (0.80 g, 1.90 mmol) in DMF (30 mL) was added potassium carbonate (0.58 g, 4.20 mmol) and then after 20 minutes n-propyl iodide (0.79 mL, 8.06 mmol) was added. The resultant reaction solution was stirred at room temperature for 15 h. Then all volatiles were removed under reduced pressure and the residue was taken in a mixture of water:$CHCl_3$ (1:1, 200 mL). The organic layer was separated and the aqueous layer again extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15-50% EtOAc/ Hexane) to get the corresponding compounds.

1,1′-(2-Methylenepropane-1,3-diyl)bis(6-methylsulfanyl-4-propoxy-1*H*-pyrazolo[3,4-*d*]-pyrimidine) (9). White crystals; Yield: 16%; mp 113−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 6.0 Hz, 6H, 2 × CH_3), 1.79−1.91 (m, 4H, 2 × CH_2), 2.30 (s, 6H, 2 × SMe), 4.46 (t, J = 6.0 Hz, 4H, 2 × OCH_2), 4.81 (s, 4H, 2 × NCH_2), 5.40 (s, 2H, CH_2), 7.95 (s, 2 H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.7, 13.9, 22.2, 48.7, 68.9, 99.9, 118.5, 132.6, 139.5, 155.6, 162.6, 169.3; HRMS (ESI) calcd. for $C_{22}H_{29}N_8O_2S_2$, (M + H), 501.1855; found, 501.1821.

6-Methylsulfanyl-1-(2-(6-methylsulfanyl-4-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl) methyl)allyl)-5-propyl-1*H*-pyrazolo[3,4-*d*] pyrimidin-4(5*H*)-one (10). White crystals; Yield: 45%; mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3H, CH_3), 1.06 (t, J = 7.5 Hz, 3H, CH_3), 1.70–1.78 (m, 2H, CH_2), 1.79−1.89 (m, 2H, CH_2), 2.21 (s, 3H, SMe), 2.32 (s, 3H, SMe), 3.93 (t, J = 7.5 Hz, 2H, NCH_2), 4.45 (t, J = 7.5 Hz, 2H, OCH_2), 4.67 (s, 2H, NCH_2), 4.82 (s, 2H, NCH_2), 5.43 (s, 1H, CH_2), 5.46 (s, 1H, CH_2), 7.93 (s, 1H, ArH), 8.02 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.7, 11.4, 13.8, 14.8, 21.1, 22.2, 45.9, 48.7, 68.9, 99.7, 102.6, 103.0, 119.1, 132.4, 135.9, 139.1, 150.7, 155.7, 157.4, 161.0, 162.4, 169.8; HRMS (ESI) calcd. for $C_{22}H_{29}N_8O_2S_2$, (M + H), 501.1855; found, 501.1850.

1,1′-(2-Methylenepropane-1,3-diyl)bis(6-methylsulfanyl-5-propyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one) (11). White crystals; Yield: 30%; mp 172−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 6H, 2 × CH_3), 1.64−1.76 (m, 4H, 2 × CH_2), 2.29 (s, 6H, 2 × SMe), 3.94 (t, 4H, J = 7.5 Hz, 2 × NCH_2), 4.70 (s, 4H, 2 × NCH_2), 5.44 (s, 1H, CH_2), 8.02 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 14.9, 21.4, 45.8, 48.7, 102.5, 119.4, 135.9, 138.8, 150.9, 157.4, 161.5; HRMS (ESI) calcd. for $C_{22}H_{29}N_8O_2S_2$, (M + H), 501.1855; found, 501.1852.

1-Methyl-6-methylsulfanyl-4-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (13). White solid; Yield 19%; mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H, CH_3), 1.81−1.92 (m, 2H, CH_2), 2.62 (s, 3H, SCH_3), 4.00 (s, 3H, NCH_3), 4.49 (t, J = 7.5 Hz, 2H, OCH_2), 7.90 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 14.3, 22.1, 33.9, 68.6, 100.0, 131.3, 155.6, 162.7, 169.4; HRMS (ESI) calcd.

for $C_{22}H_{29}N_8O_2S_2$, (M + H), 239.0967; found, 239.0963.

1-Methyl-6-methylsulfanyl-5-propyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one (14). White solid; Yield 62%; mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3H, CH_3), 1.73−1.82 (m, 2H, CH_2), 2.64 (s, 3H, SCH_3), 3.93 (s, 3H, NCH_3), 4.06 (t, J = 7.5 Hz ,2H, NCH_2) 7.98 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 15.2, 21.3, 33.6, 45.3, 102.3, 134.7, 150.5, 157.5, 161.1; MS *m/z* 239 (M + H).

X-Ray crystallographic studies

Crystals of compounds **9-11** were obtained by recrystallization from ethyl acetate/hexane.

The crystal data of **9**: $C_{22}H_{28}N_8O_2S_2$, M = 500.64, triclinic, P-1, a = 9.599(4) Å, b = 10.228(5) Å, c = 25.479(12) Å, α = 94.941(10)°, β = 90.617(9)°, γ = 90.069(10)°, V = 2492(2) Å^3, Z = 4, D_c = 1.334 gcm^{-3}, μ (Mo-Kα) = 0.250 mm^{-1}, F(000) = 1056, rectangular block, colorless, size = 0.34 × 0.26 × 0.13 mm, 19556 reflections measured (R_{int} = 0.0741), 8947 unique, $wR_{2=}$ 0.2485 for all data, conventional R = 0.0651 [$(\Delta/\sigma)_{max}$ = 000)] on F-values of 3861 reflections with I>2σ(I), S = 0.948 for all data and 622 parameters.

The crystal data of **10**: $C_{22}H_{28}N_8O_2S_2$, M = 500.64, Monoclinic, $P$21/c, a = 12.906(5) Å, b = 14.084(5) Å, c = 14.223(5) Å, β = 102.863(7)°, V = 2520.4(16) Å^3, Z = 4, D_c = 1.319 gcm^{-3}, μ (Mo-Kα) = 0.247 mm^{-1}, F(000) = 1056, rectangular block, colorless, size = 0.51 × 0.15 × 0.10 mm, 19453 reflections measured (R_{int} = 0.0420), 4575 unique, $wR_{2=}$ 0.1549 for all data, conventional R = 0.0546 [$(\Delta/\sigma)_{max}$ = 000)] on F-values of 3584 reflections with I>2σ(I), S = 1.080 for all data and 308 parameters.

The crystal data of **11**: $C_{22}H_{28}N_8O_2S_2$, M = 500.64, Monoclinic, $C$2/c, a = 11.405(2) Å, b = 14.818(2) Å, c = 14.916(2) Å, β = 107.296(3)°, V = 2406.6(5) Å^3, Z = 4, D_c = 1.382 gcm^{-3}, μ (Mo-Kα) = 0.259 mm^{-1}, F(000) = 1056, rectangular block, colorless, size = 0.34 × 0.20 × 0.15 mm, 7653 reflections measured (R_{int} = 0.0590), 2896 unique, $wR_{2=}$ 0.2239 for all data, conventional R = 0.0687 [$(\Delta/\sigma)_{max}$ = 000)] on F-values of 2000 reflections with I>2σ(I), S = 1.129 for all data and 157 parameters.

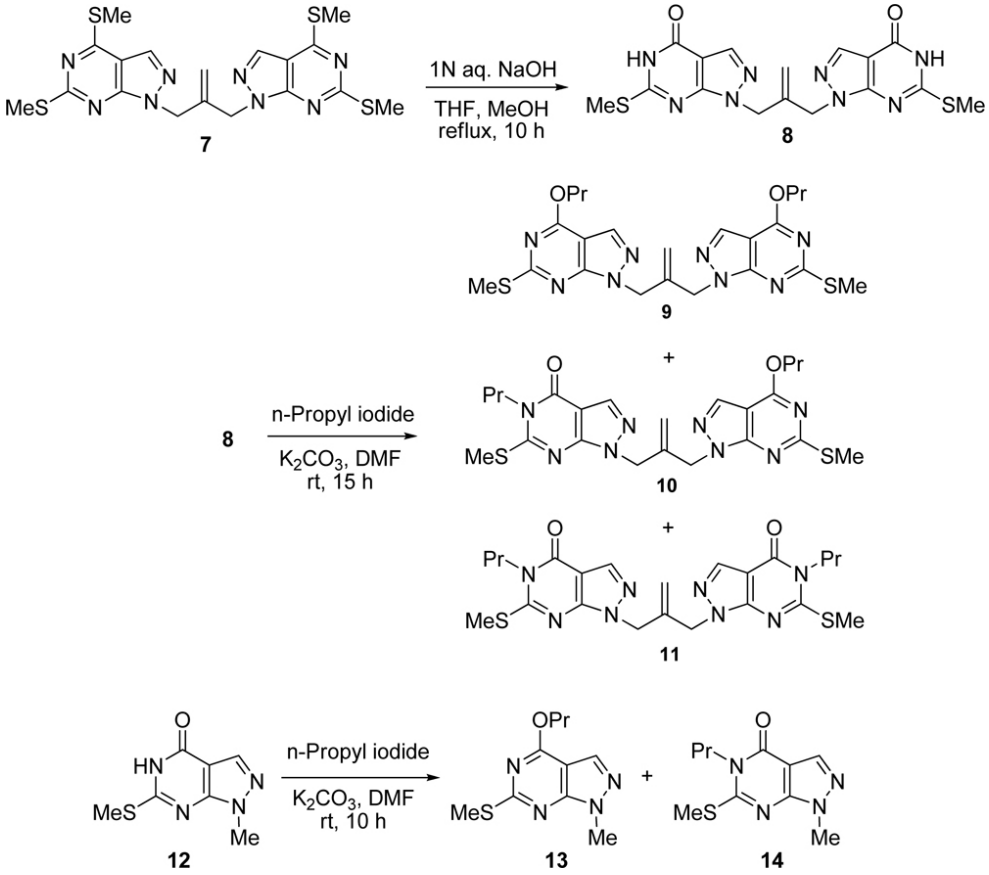
Unit cell determinations and intensity data collection of **11** were performed on Bruker SMART APEX CCD area-detector and of **9** and **10** were performed on Rigaku Kappa 3 circle diffractometer equipped with the AFC12 goniometer and enhanced sensitivity (HG) Saturn724+ CCD detector instruments, structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: SMART (Bruker, 2001) [31], SMART 32(Bruker) [32], SAINT (Bruker, 2001), Rigaku CrystalClear-SM Expert 2.1 b24 [33], SHELXTL-NT [32]. Crystallographic data for the structures **9**, **10** and **11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC No. 968936, 967777 and 967779, respectively.

Results and Discussion

Based on our initial experience with the *butylidene* linker that it helps in crystallization due to its reduced mobility in comparison to *propylene* linker [30], prompted us to study the propylation of *butylidene* linker analogue **8** [34] of compound **2**. Compound **8** was obtained from *butylidene* linker compound **7** under aqueous NaOH, THF/MeOH reflux condition (Scheme 1). The *butylidene* linker compound **8** on treatment with n-propyl iodide under K_2CO_3/ DMF condition at room temperature gave three expected products **9-11** (Scheme 1). The major product was *N,O*-dialkylated **10** (45%) followed by *N,N*-dialkylated **11** (30%) and *O,O*-

dialkylated **9** (16%). In case of the alkylation of compound **2** with methyl iodide, ethyl iodide or benzyl bromide, where size of methyl, ethyl or benzyl is not that much big, both the first and second alkylations are intermolecular which are governed only by the nucleophilicity of the nucleophile. As a result, we obtained *N*-, *N*- (major), *N*-, *O*- (intermediate) and *O*-, *O*- (minor) products, as the nucleophilicity of *N* is greater than *O*. Whereas in propylation of **8** second alkylation was not governed by nucleophilicity of the nucleophile alone. The bigger size of the n-propyl group prefers *O*-propylation as *O*- atom is sterically less congested in comparison to *N*- atom which is relatively hindered presumably due to stacked nature of mono *N*-alkylated intermediate. This resulted in the formation of *N,O*-dialkylated compound as major product. This assumption is supported by the fact that all the three isomers **9-11** are folded in solution as shown by up-field shift of the 6-methylsulfanyl protons in their ^{1}H NMR spectra (Table 1).

Careful analysis of ^{1}H NMR spectral data of compounds **10** and **11** showed that NCH_2 protons of *N*-propyl group are also up-field in comparison to the corresponding monomeric compounds (see Table 1) and it is indicating that this region is also close to the arene ring current. On the other hand no such up-field shift was seen in OCH_2 protons of *O*-propyl group in compounds **9** and **10**. For the comparison of ^{1}H NMR data with dimeric compounds, reference compounds 1-methyl-6-methylsulfanyl-4-propoxy-1*H*-pyrazolo[3,4-*d*] pyrimidine **13** (19%, *O*-product) and 1-methyl-6-methylsulfanyl-5-propyl-1*H*-pyrazolo[3,4-*d*] pyrimidin-4(5*H*)-one **14** (62%, *N*-product) [35], were prepared by reaction of 1-methyl-6-



Scheme 1. Synthesis of *butylidene* linker *protophanes* and monomers

Table 1. Chemical shift of 6-SCH_3 and 5-NCH_2 of various compounds in ^{1}H NMR

Entry	Compd. No.	Chemical shift of 6-SCH_3 δ (ppm)	Difference in chemical shift of 6-SCH_3 w.r.t. monomer reference $\Delta\delta$ (ppm)	Chemical shift of-5-NCH_2 δ (ppm)	Difference in chemical shift of -5-NCH_2 w.r.t. monomer reference $\Delta\delta$ (ppm)	Ref. No.
1	**3**	2.29	-0.37	-		[22]
2	**4**	2.33	-0.31	-		[36]
3	**5**	2.31	-0.30	-		[22]
4	**8**	2.31	-	-		[34]
5	**9**	2.30	-0.32	-	-	PW
6	**10**	2.21, 2.32	-0.41, -0.32	3.93	-0.13	PW
7	**11**	2.29	-0.35	3.94	-0.12	PW
8	**13**	2.62	-	-	-	[35]
9	**14**	2.64	-	4.06	-	[35]

PW = Present work

methysulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **12** [36] with n-propyl iodide under K_2CO_3/DMF condition at room temperature. The compound **14** has been reported in patent literature without yield; furthermore, *O*-isomer was not mentioned [37]. An up-field shift in ^{1}H NMR may indicate folding but does not always tell whether it is due to π–π or/and C−H…π interactions. Thus determination of the solid state structure by X-ray crystallography is important; not only to confirm the mode of interactions (π–π, C−H…π etc.) but also to understand the nature of arene interactions (e.g. how much overlapping of two arenes is present?). In case where no H atom is falling in the anisotropic region of arene system no proton will show up-field shift in ^{1}H NMR even when folding may be present.

Folding of three isomers **9-11** in solution also carries over to the solid state as shown in Figs. 2-4. Important distances describing the geometry of folded conformation along with the relevant literature compounds are depicted in Table 2. The observation of a folded conformation in solid state by X-ray crystallography is important as it gives the precise geometry as opposed to ^{1}H NMR data analysis which gives relatively approximate geometry about folded conformation.

The distances between two centroids of six member pyrimidine rings in compounds **9**, **10** and **11** are 3.60/3.68, 3.71 and 4.72 Å, respectively (Table 2). In fact in compound **11** the distance (4.72 Å, Table 2) between two centroids of six member pyrimidine rings is much more than any of other six known earlier reported *butylidene* linker compounds [30]. In case of closely related *propylene* linker ethyl analogue (**4**, Fig. 1), corresponding distance between two centroids of six member pyrimidine rings is 4.23 Å. Unusual large distance in compound **11** may be due to bulkiness of n-Pr group over Et group in compound **4**. In addition to the arene interactions weak C−H…O, C−H…S and S…S interactions are also present in X-ray structures of compounds **9-11**.

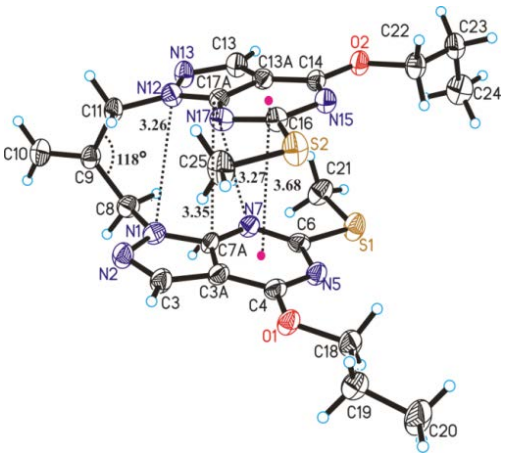


Figure 2. ORTEP diagram of **9** (at 30% probability level) showing π–π interactions with atomic labelling scheme

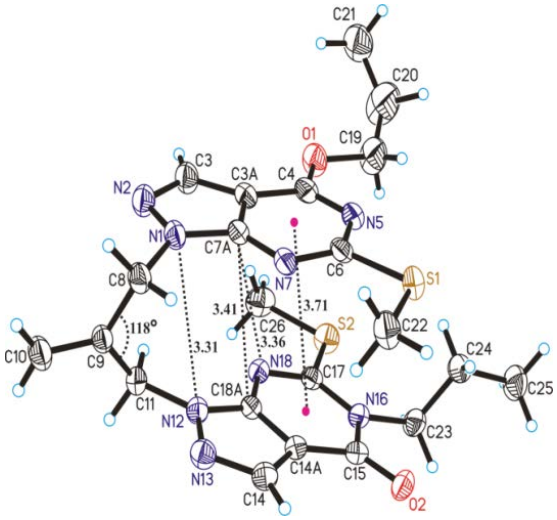


Figure 3. ORTEP diagram of **10** (at 30% probability level) showing π–π interactions with atomic labelling scheme

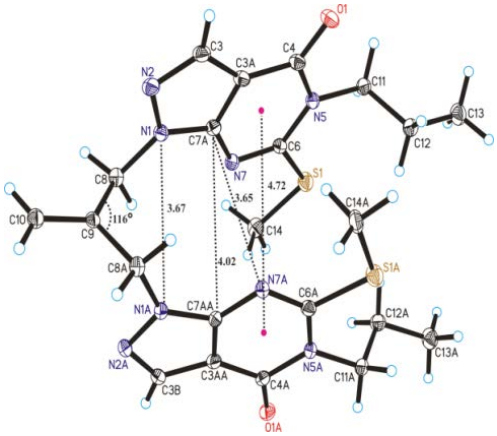


Figure 4. ORTEP diagram of **11** (at 30% probability level) showing π–π interactions with atomic labelling scheme

Table 2. Important geometrical data obtained from X-ray crystallographic studies

Entry	Compd. No.	Distance between two N atoms connecting linker (Å)	Intramolecular π–π stacking[a] distance (Å)	C…C distance (Å)	C…N distance (Å)	Angle between the least-squars planes (°)	Ref. No.
1	**1**	3.27	3.71[a]	3.40	3.37	13.17	[18]
2	**3**	3.35	3.77[a]	3.47	3.32	12.48	[19]
3	**4**	3.54	4.23[a]	3.81	3.34	10.90	[20]
4	**5**	3.33	3.86[a]	3.49	3.44	14.51	[21]
5	**7**	3.29	3.69[a]	3.41	3.30	13.83	[30a]
6	**9**	3.26 3.26	3.60[a] 3.68[a]	3.35 3.35	3.20 3.27	12.80(I), 15.96(II)	PW
7	**10**	3.31	3.71[a]	3.41	3.36	12.71	PW
8	**11**	3.67	4.72[a]	4.02	3.65	16.57	PW

[a]Distance between two centroids of six member rings. (For **9**, two molecules are in an asymmetric unit)

Conclusions

In summary, we have synthesized three isomeric *butylidene* linker *protophanes* from *butylidene* linker bis-lactam. All the three isomeric *protophanes* showed folded (*syn*) conformation both in solution and solid state due to intramolecular π–π interactions, to the best of our knowledge, this constitutes first such example. Earlier in *propylene* linker compounds (Me, Et and Bn) our efforts were unsuccessful in crystallizing all the three isomers confirming superiority of *butylidene* over *propylene* linker for crystallization. Formation of the major *N*,*O*- isomer has been rationalised on the basis of possible role of preorganization of starting material and intermediates- mono *N*/*O*-alkylation products.

Acknowledgements

K. Avasthi is grateful to DST, New Delhi, India for financial support (grant no. SR/S1/OC-14/2010). L. Shukla is thankful to CSIR, New Delhi, India for a fellowship (SRF). We are thankful to Dr. T. S. Thakur of Molecular and Structural Biology Division, for supervising the X-ray Data collection and structure determination of our compounds and SAIF, CSIR-CDRI, Lucknow, for providing spectral data. This paper has CDRI communication no. 8848.

References

1. C. Janiak, J. Chem. Soc. Dalton Trans., **2000**, 3885−3896.
2. C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, J. Chem. Soc., Perkin Trans. 2, **2001**, 651−669.
3. S. Grimme, C. M. Lichtenfeld, J. Antony, Phys. Chem. Chem. Phys., **2008**, 10, 3327−3334.
4. K. Mati, S. L. Cockroft, Chem. Soc. Rev., **2010**, 39, 4195−4205.
5. R. Bhattacharyya, U. Samanta, P. Chakrabarti, Protein Eng., Des. Sel., **2002**, 15, 91−100.
6. A. T. Krueger, E. T. Kool, Curr. Opin. Chem. Biol., **2007**, 11, 588−594.
7. C. A. Hunter, Chem. Soc. Rev., **1994**, 23, 101−109.
8. P. Hobza, J. Sponer, Chem. Rev., **1999**, 99, 3247−3276.

9. S. K. Burley, G. A. Petsko, Science, **1985**, 229, 23−28.
10. S. K. Burley, G. A. Petsko, Adv. Protein Chem., **1988**, 39, 125−189.
11. M. Brandl, M. S. Weiss, A. Jabs, J. Suhnel, R. Hilgenfeld, J. Mol. Biol., **2001**, 307, 357−377.
12. J.-M. Lehn; Supramolecular Chemistry. Concepts and Perspectives, Wiley-Vch, Weinheim, **1995**, 1.
13. G. R. Desiraju, Angew. Chem., Int. Ed. Engl., **1995**, 34, 2311−2327.
14. G. R. Desiraju, T. Steiner; The Weak Hydrogen Bond in Structural Chemistry and Biology, Oxford University Press, Oxford, **1999**.
15. L. M. Salonen, M. Ellermann, F. Diederich, Angew. Chem., Int. Ed., **2011**, 50, 4808−4842.
16. M. Chauhan, R. Kumar, Bioorg. Med. Chem., **2013**, 21, 5657−5668.
17. K. Avasthi, T. Chandra, D. S. Bhakuni, Indian J. Chem., **1995**, 34B, 944−949.
18. G. Biswas, T. Chandra, K. Avasthi, P. R. Maulik, Acta Crystallogr., **1995**, C51, 2453−2455.
19. P. R. Maulik, K. Avasthi, G. Biswas, S. Biswas, D. S. Rawat, S. Sarkhel, T. Chandra, D. S. Bhakuni, Acta Crystallogr., **1998**, C54, 275−277.
20. K. Avasthi, S. Aswal, P. R. Maulik, Acta Crystallogr., **2001**, C57, 1324−1325.
21. K. Avasthi, A. K. Tewari, D. S. Rawat, A. Sharon, P. R. Maulik, Acta Crystallogr., **2002**, C58, o494−o495.
22. K. Avasthi, D. S. Rawat, T. Chandra, D. S. Bhakuni, Indian J. Chem., **1998**, 37B, 754−759.
23. K. Avasthi, S. M. Farooq, R. Raghunandan, P. R. Maulik, J. Mol. Struct., **2009**, 927, 27−36.
24. (a) K. Avasthi, A. Kumar, Chemistry & Biology Interface, **2012**, 2, 258−295; (b) I. Richter, J. Minari, P. Axe, J. P. Lowe, T. D. James, K. Sakurai, S. D. Bull, J. S. Fossey, Chem. Commun., **2008**, 44, 1082−1084; (c) Y. Zhao, C. Beuchat, Y. Domoto, J. Gajewy, A. Wilson, J. Mareda, N. Sakai, S. Matile, **2014**, J. Am. Chem. Soc., 136, 2101−2111
25. F. Vögtle; Cyclophane Chemistry. Synthesis, Structures, and Reactions, J. Wiley, Chichester, New York, 1993.
26. F. D. Lewis, P. Daublain, F. B. D. Santos, W. Liu, A. M. Asatryan, S. A. Markarian, T. Fiebig, M. Raytchev, Q. Wang, J. Am. Chem. Soc., **2006**, 128, 4792−4801.
27. F. D. Lewis, G. B. D. Santos, W. Liu, J. Org. Chem., **2005**, 70, 2974−2979.
28. F. D. Lewis, T. L. Kurth, J. Am. Chem. Soc., **2003**, 125, 13760−13767.
29. K. Avasthi, A. Ansari, A. K. Tewari, R. Kant, P. R. Maulik, Org. Lett., **2009**, 11, 5290−5293.
30. (a) K. Avasthi, A. Ansari, R. Kant, P. R. Maulik, K. Ravikumar, P. Chattopadhyay, N. D. Adhikary, CrystEngComm, **2011**, 13, 2039−2046; (b) K. Avasthi, L. Shukla, R. Kant, K. Ravikumar, Acta Crystallogr., **2014**, C70, 555-561.
31. Bruker SMART and SAINT. Bruker AXS Inc., Madison, Wisconsin, U.S.A., **2001**.
32. Bruker SHELXTL-NT Version 5.10, Bruker AXS Inc., Madison, Wisconsin, U.S.A., **1997**.
33. Rigaku CrystalClear-SM Expert 2.1 b24. Rigaku Corporation, Tokyo, Japan, **2012**.
34. A. Ansari, "Design and Synthesis of Nitrogenous Heterocycles and Polymethylene Linker Based Flexible compounds for structural and biological Activity Studies," Ph.D. dissertation, Banaras Hindu University Varanasi, **2011**.
35. S. Aswal, "Synthesis of Flexible Bicyclic Nitrogenous Heterocycles, Their X-ray Crystallographic Studies and Biological Activities," Ph. D. dissertation, Jawaharlal Nehru University New Delhi, **2006**.
36. K. Avasthi, S. Aswal, R. Kumar. U. Yadav, D. S. Rawat, P. R. Maulik, J. Mol. Struct., **2005**, 750, 179−185.
37. H. Walter, Patent App. WO 97/33890 A1, **1997**.