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SYNTHESIS AND STRUCTURE OF TRIPLY BRIDGED PURINOPHANES[1]

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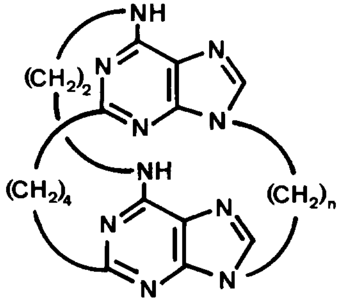
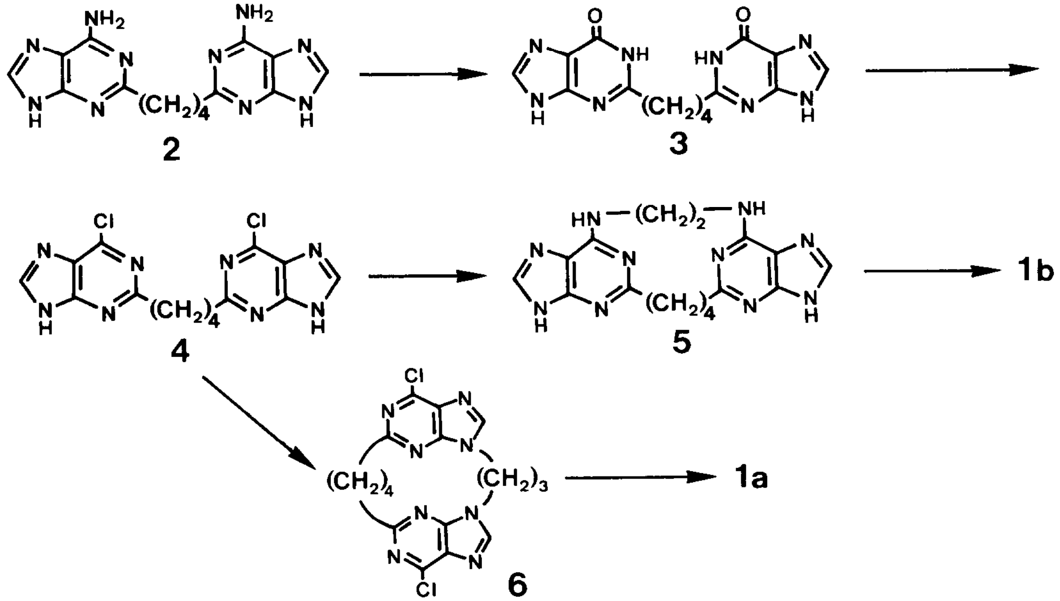
Summary: The title compounds were synthesized as a model for studying the relationship between the hypochromism and the stacking mode of two purine rings. By comparing **1** with other purinophanes it was concluded that the fully overlapped orientation of two purine rings gives the largest hypochromicity.

As a conformationally frozen model to study the stacking interaction of nucleic acid bases in DNA, we have prepared so far various doubly bridged purinophanes having different stacking mode.[2] However, there has been no report on the synthesis of purinophanes with fully overlapped orientation in contrast to polynuclear carbophanes such as naphthalenophanes,[3] owing presumably to an increase in the dipole-dipole repulsion between the two heterorings. We now report on the first example of triply bridged purinophanes **1a,b** where two stacked purine rings are forced to take an eclipsed conformation by the additional third bridging chain.

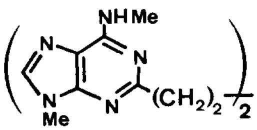


1 a: n = 3
b: n = 4

1,4-Di(2-adenyl)butane **2**,[2e] prepared via three steps from phenylazomalononitrile and adipodiamidine, was converted to **3** in 88% yield by using the similar method of Todd et al.[4] [**3**[5]: white solid from aqueous ammonia, dec > 329 °C; NMR (100 MHz, DMSO-d_6) δ 1.70-1.81 (4H, m, $\mathrm{ArCH_2\underline{CH_2}}$), 2.58-2.72 (4H, m, $\mathrm{Ar\underline{CH_2}}$), 8.00 (2H, s, ArH); Mass 325 (M^+-1)]. Chlorination of **3** with thionyl chloride in DMF gave **4** in 80% yield [**4**[5]: colorless fine needles from DMSO-H_2O, dec > 285 °C; NMR (100 MHz, DMSO-d_6) δ 1.79-1.88 (4H, m, $\mathrm{ArCH_2\underline{CH_2}}$), 2.90-3.02 (4H, m, $\mathrm{Ar\underline{CH_2}}$), 8.56 (2H, s, ArH); M^+ 364]. Doubly bridged compound **5** was prepared by treatment of **4** with ethylenediamine in DMSO-H_2O (2:1) under high dilution conditions to give **5** in 25% yield after purification by column chromatography on silica gel with methanol-chloroform (1:3) [**5**[5]: fine colorless needles from acetic acid, dec > 327 °C; NMR (100 MHz, DMSO-d_6) δ 1.78-1.88 (4H, m, $\mathrm{ArCH_2\underline{CH_2}}$), 2.64-2.78 (4H, m, $\mathrm{ArCH_2}$), 3.62-3.74 (4H, m, $\mathrm{NH\underline{CH_2}}$), 7.64 (2H, br.s, $\mathrm{N\underline{H}CH_2}$), 7.99 (2H, s, ArH), 12.6 (2H, br.s, NH); M^+ 350]. Coupling reaction of **5** with 1,4-dibromobutane was carried out in DMSO in the presence of anhyd potassium carbonate under high dilution conditions



to yield the desired compound **1b** in 26% yield. The crude product was separated by column (silica gel) and liquid chromatography, and purified by recrystallization and sublimation [**1b**[5)]: colorless microcrystals, dec > 315 °C; NMR (100 MHz, $CDCl_3$) δ 1.84-2.28 (8H, m, CH_2), 2.68 (4H, br.s, CH_2), 3.64-3.81 (4H, m, CH_2), 4.23-4.45 (4H, m, CH_2), 5.91 (2H, br.s, NH), 7.34 (2H, s, ArH); UV (EtOH) λ_{max} 266 nm (ε=21,800); M^+ 404]. Under the same reaction conditions as for **1b**, however, **1a** was obtained in extremely low yield (less than 1%). After several examinations **1a** was obtained via another synthetic route. Thus, the reaction of **4** with 1,3-dibromopropane was carried out in a manner similar to that for **1b** to give **6** in 28% yield [**6**[5)]: colorless prisms from EtOH, dec > 243 °C; NMR (100 MHz, $CDCl_3$) δ 1.72-1.99 (4H, m, $ArCH_2\underline{CH_2}$), 2.93 (2H, quint J=7 Hz, $NCH_2\underline{CH_2}$), 3.05-3.13 (4H, m, $ArCH_2$), 4.25 (4H, t, NCH_2), 8.03 (2H, s, ArH); Mass 402, 404, 406]. Introduction of the third bridge was achieved by treatment of **6** with ethylenediamine in butanol under high dilution conditions. After separation and purification procedures similar to **1b**, **1a** was obtained in 8% yield [**1a**[5)]: colorless microcrystals from 2-PrOH, mp 303-305 °C; NMR (100 MHz, $CDCl_3$) δ 1.88-2.67 (10H, m, CH_2), 3.67-4.71 (8H, m, CH_2), 5.47-5.59 (2H, m, NH), 7.28 (2H, s, ArH); UV (EtOH) λ_{max} 264 nm (ε= 20,700); M^+ 390]. Reference compounds, **7** and **8** were prepared from **4** and **5**, respectively [**7**[5)]: colorless microcrystals from BuOH, mp 262-265 °C. **8**[5)]: colorless microcrystals by sublimation, mp 317-319 °C].



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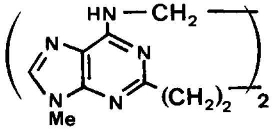

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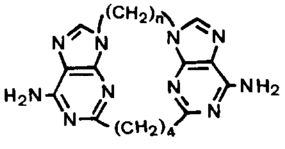

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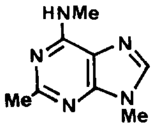

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In ^1H NMR spectra, aromatic protons of **1**a and **1**b show upfield shifts (0.35 ppm for **1**a; 0.29 ppm for **1**b) as compared with that of **10**, while the corresponding protons of **7** and **8** remain unchanged, suggesting the face-to-face structure for **1** and non-stacked structure for **7** and **8**. In order to get more detailed information about the structure of **1**, we carried out X-ray analysis of **1**b.[6)] The resulting ORTEP drawing is shown in Fig. 1. The figure shows clearly the fully overlapped orientation of two purine rings. The bond lengths and angles as well as the planarity of the purine rings of **1**b are comparable to common purines.[7)] The two purine rings are stacked with a dihedral angle of 13.9° and with an averaged interplanar distance of 3.7 Å. The electronic spectra of **1**a,b and **10** are very similar in shape, while the intensity of the longest absorption band is much decreased in **1**a,b. The hypochromicities (H%) of **1**a,b and the related compounds **7**-**9**[2e)] in two solvents are summarized in Table 1. The striking difference of H% is observed between **1**a,b and the others. In Table 2, the hypochromicities of all appreciably overlapped purinophanes, whose molecular structures are reported, are summarized together with stacking mode and interplanar distance. The values of **1**a,b are the largest as compared with purinophanes having the same interplanar distance. Consequently, it is concluded at the present stage that the hypochromism is highly dependent upon the overlapping of two stacked purine rings and is increased with the increase of overlapping extent.

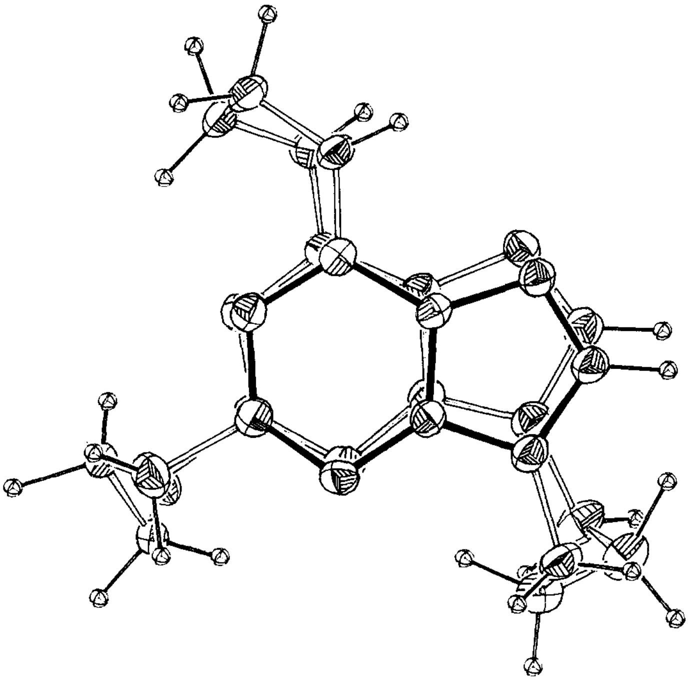


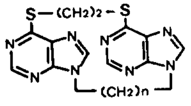
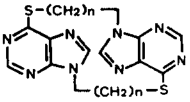
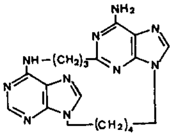
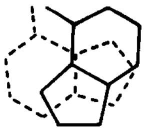
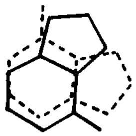
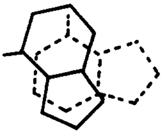
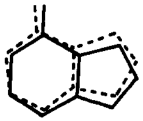
Fig. 1. View of **1**b on the least-squares plane defined with a purine ring.

Table 1. Hypochromicity (%) of **1**a,b and related compounds.

	1a	**1**b	**7**	**8**	**9**(n=3)	**9**(n=4)
0.5N HCl	30.1	30.6	0.5	-0.3	-2.8	3.9
EtOH	29.9	26.1	1.9	-3.0	2.8*	3.8*

*in MeOH

Table 2. Hypochromicity, Interplanar Distance, and Stacking Mode of **1** and Related Compounds.

Compound						**1**	
	n=3	n=4	n=2	n=3		n=3	n=4
Hypochromicity (%)	32.4	24.1	47.3	22.4	13.9	29.9	26.1
Interplanar Distance (Å)	3.4^a	3.6^a	3.3^a	3.7^b	3.5^a	3.6^b	3.7^a
Stacking Mode							
Reference	2b		2d		8	this work	

^{a} determined by X-ray analysis. ^{b} estimated from molecular model.

References and Notes

1) Layered Compounds LXXVI. Part LXXV: K. Doyama, F. Hama, Y. Sakata, and S. Misumi, Tetrahedron Lett., 24, 5253 (1983).

2) a) F. Hama, Y. Sakata, and S. Misumi, Nucleic Acids Res. Symp. Ser. No.8, 131 (1980); b) idem., Tetrahedron Lett., 22, 1123 (1981); c) idem., Nucleic Acids Res. Symp. Ser. No.10, 73 (1981); d) F. Hama, Y. Sakata, S. Misumi, M. Aida, and C. Nagata, Tetrahedron Lett., 23, 3061 (1982); e) K. Akahori, F. Hama, Y. Sakata, and S. Misumi, Nucleic Acids Res. Symp. Ser., No. 11, 265 (1982).

3) a) H. H. Wasserman and P. M. Keehn, J. Am. Chem. Soc., 91, 2374 (1969); b) M. W. Haenel, Tetrahedron Lett., 1974, 3053; c) M. Yoshinaga, T. Otsubo, Y. Sakata, and S. Misumi, Bull. Chem. Soc. Jpn., 52, 3759 (1979); d) T. Kawabata, T. Shinmyozu, T. Inazu, and T. Yoshino, Chem. Lett., 1979, 315; e) N. E. Blank and M. W. Haenel, Chem. Ber., 114, 1520 (1981); f) idem., ibid., 116, 827 (1983).

4) J. Baddiley , B. Lythgoe, and A. R. Todd, J. Chem. Soc., 1944, 318.

5) Satisfactory elemental analyses were obtained.

6) Crystal data: $C_{20}H_{24}H_{10}\cdot 3/4\ H_2O$, Mw=417.99, monoclinic, space group $P2_1/n$, a=13.428(1), b=15.578(1), c=9.509(1) Å, β=95.15(1)°, V=1981.1(2) Å^3, Z=4, Ni-filtered Cu-Kα radiation, 2942 independent reflections with 2839 observed (I ≥ 3σ(I)), final R value 0.058. The other crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.

7) W. J. Cook and C. E. Buff, J. Pharm. Sci., 64, 221 (1975).

8) F. Hama, Y. Sakata, and S. Misumi, unpublished result.

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