Tetrahedron Letters,Vol.26,No.32,pp 3849-3852,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

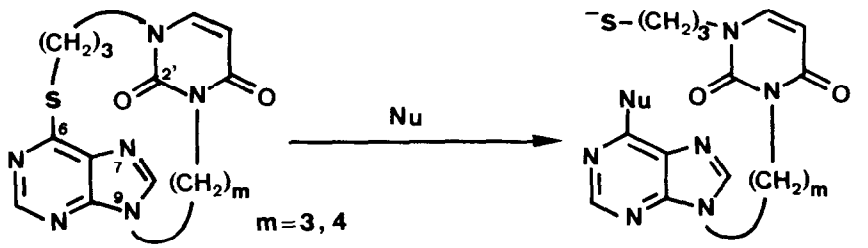
UNUSUAL REACTIVITY OF (6,9)PURINOPHANES DUE TO STEREOELECTRONIC EFFECT

Hiroyuki Higuchi, Miho Mitsuoka, Yoshiteru Sakata,* and Soichi Misumi

The Institute of Scientific and Industrial Research, Osaka University
Mihoga-oka 8-1, Ibaraki, Osaka 567, Japan

Abstract [n](6,9)Purinophanes **2a-c** were synthesized and their unusual reactivity toward nucleophiles was explained by the stereoelectronic effect in the fairly rigid tetrahedral intermediate.

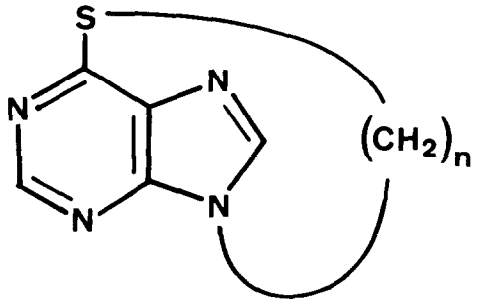
Previously, we reported[1] the unusually high reactivity of (1',3')-pyrimidino(6,9)purinophanes **1** at 6-position toward nucleophiles such as



(1)

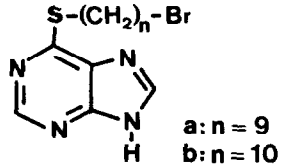
1

alkylamines or hydroxide anion (equation 1) and proposed a neighboring carbonyl-group assisted mechanism based on the result of X-ray analysis. In



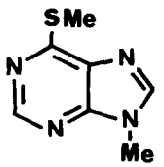
2

a: n = 9
b: n = 10
c: n = 11

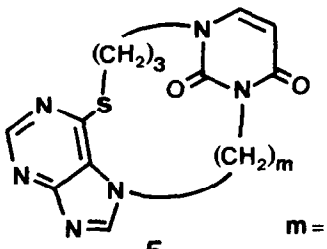


a: n = 9
b: n = 10
c: n = 11

3



4



m = 3, 4

5

order to confirm the mechanism, we planned to prepare [n](6,9)purinophanes **2**, where 6-thiopurine is bridged with a polymethylene chain at the same positions as **1** and hence there is no possibility of the participation of the carbonyl group in the transition state. Synthesis of **2** was performed as follows.

Reaction of 6-mercaptopurine and α,ω-dibromoalkane with sodium hydride in dry DMSO under an argon atmosphere gave **3**[2] (**3a**: 31%; **3b**: 16%; **3c**: 39% yield). Under the similar conditions intramolecular cyclization of **3** was carried out to give, after column chromatography on silica gel, the desired compounds **2**[2] [**2a**: 8.6% yield; colorless prisms from chloroform, mp 103-104 °C; MS 276 (M^+); ^1H NMR ($CDCl_3$ 360 MHz) δ 0.27-1.23(10H,m,CH_2), 1.49-2.14(4H,m,CH_2), 3.14-3.49(1H,m,SCH_2), 4.00-4.09(2H,m,SCH_2 and NCH_2), 4.61-4.70(1H,m,NCH_2), 8.11(1H,s,ArH), 8.73(1H,s,ArH). **2b**: 7.7% yield; colorless prisms from chloroform, mp 105-107 °C; MS 290(M^+); ^1H NMR ($CDCl_3$ 360 MHz) δ 0.33-1.22(12H,m,CH_2), 1.53-2.07(4H,m,CH_2), 3.28-3.56(1H,m,SCH_2), 4.02-4.10(2H,m,SCH_2 and NCH_2), 4.59-4.66(1H,m,NCH_2), 8.06(1H,s,ArH), 8.79(1H,s,ArH). **2c**: 13% yield; colorless prisms form chloroform, mp 99-102 °C; MS 304(M^+); ^1H NMR($CDCl_3$ 360 MHz) δ 0.36-1.35(14H,m,CH_2), 1.59-2.11(4H,m,CH_2), 3.26-3.61(1H,m,SCH_2), 4.06-4.19(2H,m,SCH_2 and NCH_2), 4.60-4.71(1H,m,NCH_2), 8.09(1H,s,ArH), 8.82(1H,s,ArH).].

When a large excess (1,000-5,000 eq) of monomethylamine was added to a dilute solution (10^{-6} mol/l) of **2** in ethanol at room temperature, time-dependent change in the absorption spectra, similar to that seen for **1**, was observed.[3] Under the same conditions, however, the spectrum of the corresponding acyclic compound **4** was virtually invariant. On the basis of the spectrophotometry, rate constants of **2** were obtained by analyzing the reaction

Table 1. Reaction Rate Constants of **2a-c** and Related Compounds with Monomethylamine in Ethanol at 25 ± 1 °C

Compd	k, $S^{-1}M^{-1}$
1 (m=3)	4.4×10^{-3}
2a	2.6×10^{-3}
2b	1.1×10^{-4}
2c	4.6×10^{-5}
4	$> 10^{-6}$

as pseudo first order and the results are summarized in Table 1. Unexpected high reactivity of **2** toward nucleophile has made it clear that the similar unusual reactivity of **1** is not attributable to the participation of the carbonyl group at 2'-position or to some electronic effect of the transannularly situated pyrimidine ring.

On the basis of X-ray analysis on **1**(m=4) and molecular model considerations on **2a-c**, there exists no strain even in **2a** with the shortest bridge among them. Therefore, the high reactivity of these compounds cannot be explained by molecular strain. Considering the extremely low reactivity of (1',3')-pyrimidino(6,7)purinophane **5**[4] toward the same nucleophile, the unusual behavior of **1** and **2** seems to be due to the molecular framework of 6-thiopurines bridged at S^6- and 9-positions. The only reasonable explanation for the high reactivity of **1** and **2** in contrast to the low reactivity of **4** and **5** is, at the

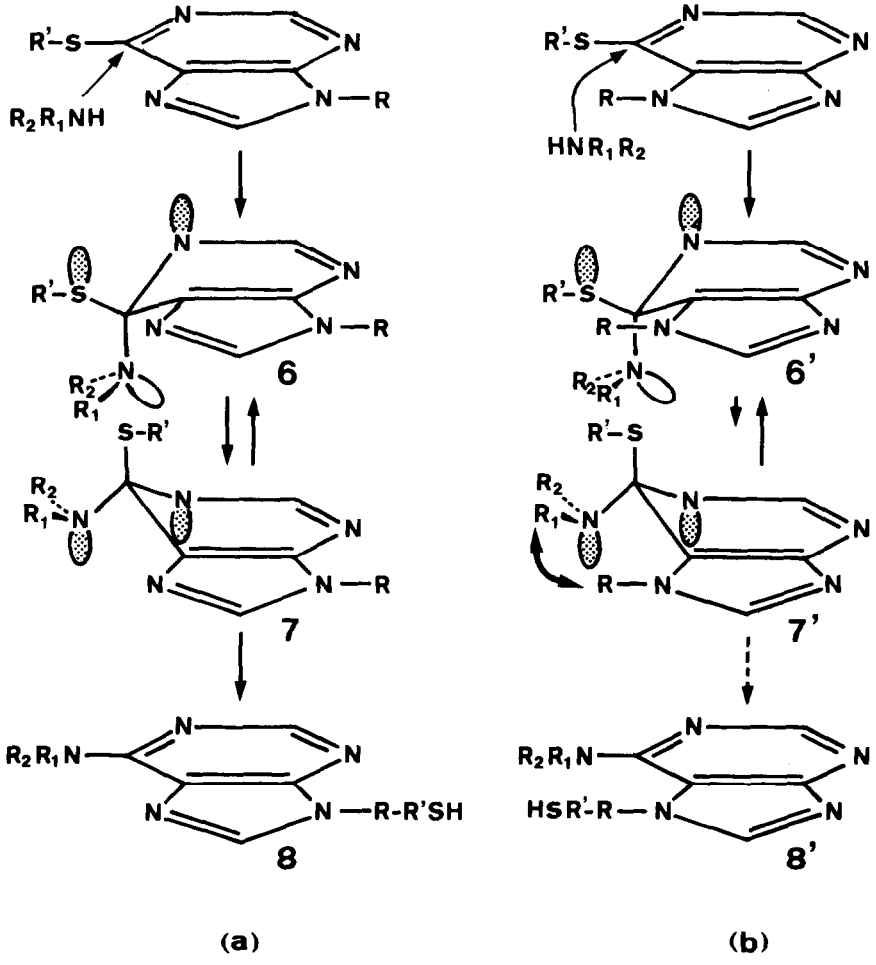


Fig. 1. Reaction course of (6,9)- and (6,7)-purinophanes with alkylamines.

present stage, given by the concept of "stereoelectronic effect" presented by Deslongchamps.[5] This concept states that in the hydrolysis of esters and amides the cleavage is stereoelectronically controlled only when two heteroatoms of the tetrahedral intermediate, each having one nonbonded electron pair, orient antiperiplanar to the departing X-alkyl (X=O,N,S) group. If we apply the theory to the present system (Fig. 1a), the tetrahedral intermediate **7**, which would easily be obtained from **6**, is expected to give smoothly **8**, because of its antiperiplanar orientation. On the other hand, as shown in Fig. 1b, the tetrahedral intermediate **6'** derived from (6,7)purinophanes would not pass into **7'** because of the steric hindrance between NR_1R_2 and R. This might be the reason for the unusual high reactivity of (6,9)purinophanes as against (6,7)-isomer. The stereoelectronic theory is applicable only when the structure of the tetrahedral intermediate or antiperiplanar arrangement is fairly rigid. This request is reflected to the order of the reaction rate constants of **2a-c** in Table 1. Thus, the rate increases with a decrease of the length of the polymethylene chain, i.e., **2a>2b>2c**. Similarly, the quite low reactivity of the reference compound **4** could be explained by the conformational flexibility of the antiperiplanar orientaion.

The present study is the first example, where the concept of the stereoelectronic effect is successfully applied to the field of purine ring. This suggests that the theory is widely applicable to the elucidation of the reaction course of nucleophilic substitution reactions which occur at various heteroaromatic rings including nucleic acid bases.

Acknowledgement Y.S. wishes to thank Prof. P. Deslongchamps for his helpful discussions.

References and Notes

1. K. Doyama, F. Hama, Y. Sakata, and S. Misumi, Tetrahedron Lett., **24**, 5253 (1983).
2. Satisfactory elemental analyses were obtained.
3. The structure of the reaction product was determined on the basis of spectral data.
4. K. Doyama, F. Hama, Y. Sakata, and S. Misumi, Tetrahedron Lett., **22**, 4101 (1981).
5. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, 1983; P. Deslongchamps, P. Atlani, D. Frêhel, and A. Maravel, Can. J. Chem., **50**, 3405 (1972).

(Received in Japan 23 May 1985)