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STEREOCHEMISTRY OF REACTION PRODUCTS OF 1,3-DIMETHYLTHYMINE EPOXIDE WITH AMINES

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Abstract : Reaction of 1,3-dimethylthymine epoxide with amines afforded *cis* and *trans* adducts, stereostructures of which were elucidated and treatment of *trans* adduct with boron trifluoride etherate afforded *cis* adduct; mechanism for the isomerization is presented.

Much attention has focused on the oxidations of nucleic acids and their components with active oxygens and on the formation of nucleic acid-protein cross-linkages in relation to the study of mutagenesis and carcinogenesis.[1,2] Recently, we reported the oxidation of some pyrimidine bases with *m*-chloroperbenzoic acid as a representative of acylperoxide.[3,4] In this oxidation we supposed the epoxide (1)[5] as the reaction intermediate which was subjected to nucleophiles to afford products.[4] Then, we have envisaged the reaction of (1) with amine or amino acid as a model reaction for nucleic acid-protein interactions. In the present communication we describe the stereochemistry of the reaction products of (1) with several amines containing achiral amino acid derivatives and the isomerization of *trans* adduct to *cis* adduct with boron trifluoride etherate.

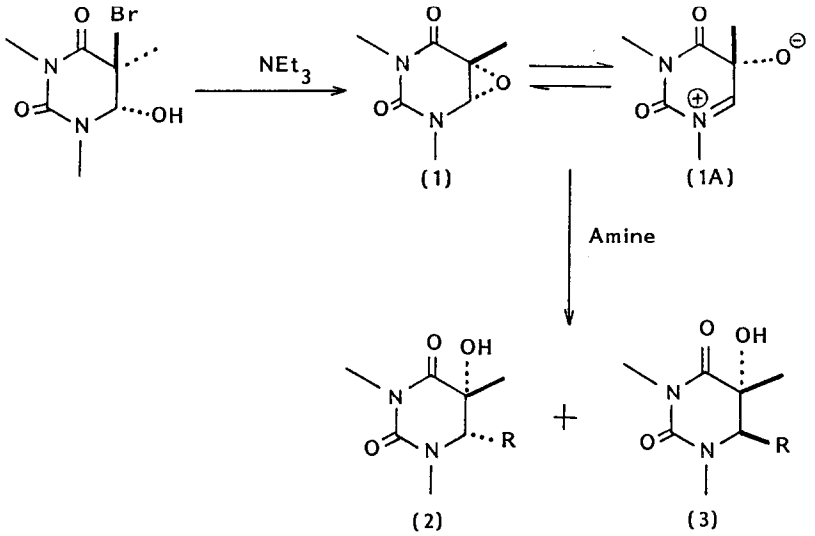
Treatment of (1) prepared *in situ* from *trans*-5-bromo-6-hydroxy-1,3-dimethyl-5,6-dihydrothymine and triethylamine[1] with amine in tetrahydrofuran (THF) under reflux gave two products, *cis* adduct (minor product) (2)[6] and *trans* adduct (major product) (3)[6], except the case of ethylamine. The results were summarized in Table 1. Among those products, the stereostructures of (2d), (2f), and (3a) were determined as shown in Scheme 1 by X-ray analyses.[7] Therefore, it is clear that the major products (3d) and (3f) are *trans* adducts. On treatment with boron trifluoride etherate in THF, (3a), (3d), and (3f) isomerized completely to *cis* adducts, (2a), (2d), and (2f), respectively, suggesting that *trans* adduct is prone to isomerize to *cis* adduct. Other major products (*trans* adducts) also isomerized to the corresponding minor products (*cis* adducts) as summarized in Table 2. Therefore, it can be concluded that all the major products are *trans* adducts and all the minor products *cis* adducts.

No isomerization of (3) to (2) occurs during the addition reaction, because (2) was not obtained on treatment of (3) with equimolar triethylamine hydrobromide and 0.5 equivalent of triethylamine in THF under reflux for 24-48 h. Therefore, it would be reasonable to assume that the addition reaction proceeds *via* both an epoxide (1) which gives *trans* adduct[8] and an iminium intermediate (1A) which gives *cis* adduct selectively[2,9] by nucleophilic attack of amine. Assuming two routes,

Table 1. The Results of Addition Reactions[a]

Amine	Products	Ratio of 2 : 3	Total yield (%)[b]	Reflux time
Ethylamine	3a		80.7	24 h
Tryptamine	2b, 3b	1 : 5.6	95.0	24 h
βAla-OEt	2c, 3c	1 : 3.9	89.7	24 h
Benzylamine	2d, 3d	1 : 3.7	74.5	24 h
Gly-OEt	2e, 3e	1 : 2.8	71.7	24 h
Morpholine	2f, 3f	1 : 2.6	62.3[c]	24 h
Neopentylamine	2g, 3g	1 : 2.4	quantitative	48 h

[a] Reactions were carried out with *trans*-5-bromo-6-hydroxy-1,3-dimethyl-5,6-dihydrothymine, 1.5 eq. of NEt_3, and 2 eq. of amine in THF under reflux. [b] Products were isolated by preparative t.l.c.. [c] 1,3-Dimethylthymine was obtained in *ca.* 20 % yield.



a) R=NHC$_2$H$_5$

b) R=NHCH$_2$CH$_2$-indole

c) R=NHCH$_2$CH$_2$CO$_2$Et

d) R=NHCH$_2$C$_6$H$_5$

e) R=NHCH$_2$CO$_2$Et

f) R=morpholine

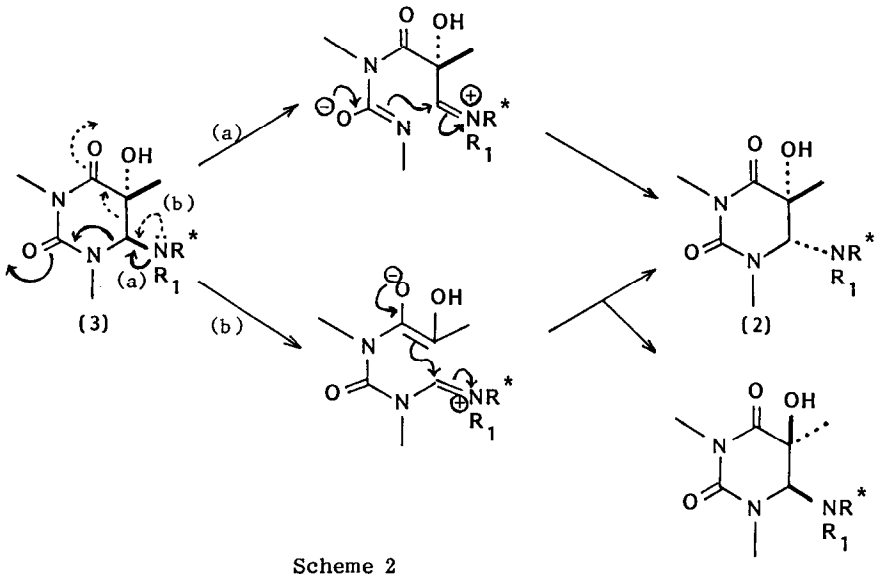
g) R=NHCH$_2$C(CH$_3$)$_3$

Scheme 1

Table 2. Isomerization of *Trans* Adduct (3) to *Cis* Adduct (2)[a]

	Product	Yield (%)	$BF_3 \cdot Et_2O$	Reaction condition
3a	2a	quantitative	1 eq.	20 h at 50° C
3b	2b	79.4	2 eq.	20 h at r.t.
3c	2c	83.3	1 eq.	20 h at r.t.
3d	2d	88.8	1 eq.	20 h at r.t.
3e	2e	64.0	1 eq.	20 h at r.t.
3f	2f	87.8	2 eq.	40 h at 60° C
3g	2g	quantitative	1 eq.	20 h at r.t.

[a] Reactions were carried out with *trans* adduct and $BF_3 \cdot Et_2O$ in THF under indicated reaction condition.



Scheme 2

route a and route b, shown in Scheme 2 as mechanism of the isomerization, route b may lead to two optically active *cis* adducts (a mixture of diastereomers) in the case of isomerization of an optically active *trans* adduct prepared from a chiral amino acid. Since an optically active *trans* adduct isomerized to one optically active *cis* adduct under a similar reaction condition,[10] we suggest that the isomerization reaction proceeds *via* route a.

The present stereostructure establishment of the reaction products and the isomerization procedure of *trans* adduct to *cis* adduct would be very useful for chemistry of the cross-linkage of nucleic acid with protein or chiral amino acid.

References and Footnotes

1) H.-S.Ryang and S.Y.Wang, *J. Org. Chem.*, 44, 1191 (1979) and references cited therein.
2) H.-S.Ryang and S.Y.Wang, *J. Am. Chem. Soc.*, 100, 1302 (1978) and references cited therein.
3) T.Harayama, K.Kotoji, F.Yoneda, T.Taga, K.Osaki, and T.Nagamatsu, *Chem. Pharm. Bull.*, 32, 2056 (1984).
4) T.Harayama, R.Yanada, K.Kotoji, F.Yoneda, T.Taga, K.Osaki, and T.Nagamatsu, *Nucleic Acids Res. Symposium Series*, No. 15, 1 (1984).
5) Ryang and Wang also suggested the formation of the thymine epoxides when thymines were photochemically oxidized[2] or when *trans*-5-bromo-6-hydroxydihydrothymines were treated with bases.[1]
6) All new compounds in this communication gave satisfactory elemental analyses and/or mass spectra, and other spectral data (200 MHz NMR and IR).
7) *X-ray analysis* : The reflection data were collected on a Rigaku AFC-5 diffractometer for $0<\Theta<60°$ using monochromated Cu$K\alpha$ radiation and ω-2Θ scan technique. The structures were solved by direct methods and refined by full-matrix least-squares method. *Crystal data* : (2d) $C_{14}H_{19}N_3O_3$, monoclinic, space group $P2_1/a$, a=8.546(1), b=14.988(1), c=11.255(2) Å, β=98.90(1)°, D_c=1.293 g/cm^3, Z=4, R=0.048 for 1901 unique reflections [$F>3\sigma(F)$]. (2f) $C_{11}H_{19}N_3O_4$, monoclinic, space group $C2/c$, a=23.488(3), b=6.644(1), c=18.445(3) Å, β=119.13(1)°, D_c=1.359 g/cm^3, Z=8, R=0.058 for 1738 unique reflections [$F>3\sigma(F)$]. (3a) $C_9H_{17}N_3O_3$, orthorombic, space group $P2_12_12_1$, a=6.754(2), b=9.620(1), c=17.586(1) Å, D_c=1.251 g/cm^3, Z=4, R=0.053 for 887 unique reflections [$F>3\sigma(F)$]. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.
8) O.Hernandez and M.B.Gopinathan, *J. Chem. Soc., Chem. Commun.*, 1491 (1984).
9) E.P.Burrows, H.-S.Ryang, S.Y.Wang, and J.L.Flippen-Anderson, *J. Org. Chem.*, 44, 3736 (1979).
10) Reaction of (1) with L-Met-OEt gave four products, the compound (A) $[\alpha]_D^{18}$ -119.0°, (B) $[\alpha]_D^{18}$ +26.4°, (C) $[\alpha]_D^{18}$ +41.2°, and (D) $[\alpha]_D^{18}$ -120.2°, in 17.9, 22.9, 31.1. and 21.4 % yields, respectively. Isomerization of the compound (C) and (D) with boron trifluoride etherate afforded the compound (A) $[\alpha]_D^{18}$ -121.8° and (B) $[\alpha]_D^{18}$ +26.2° in 94.5 and 81.5 % yields, respectively.

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