

Intermolecular Phenolic Hydroxy Methylation Occurring between Chiral *N,N'*-Bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide and Co-crystallized Methanol under Electron Impact Ionization Conditions

XU, Jia-Xi*^a(许家喜) JIAO, Peng^a(焦鹏) HE, Zheng^b(何筝)
ZHANG, Qi-Han^a(张奇涵) YAN, Chun-Hua^b(严纯华)

^a Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

^b State Key Laboratory of Rare Earth, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

An intermolecular phenolic hydroxy methylation occurring between chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide and co-crystallized methanol under electron impact ionization conditions was observed. The result was confirmed by X-ray diffraction structural analysis of a co-crystalline of (*R,R*)-enantiomer and methanol.

Keywords mass spectrometry, methylation, phenolic hydroxy group, electron impact ionization

Introduction

Chiral C_2 -symmetric bisamides are an important and useful type of ligands, which have been widely used in asymmetric catalysis.¹⁻⁷ They were used successfully in asymmetric molybdenum (0)-catalyzed allylic substitution,²⁻⁵ palladium-catalyzed alkylation,^{1,6} and Lewis acid-catalyzed asymmetric nucleophilic ring opening of epoxides,⁷ etc. In addition, bisamides are useful ligands for coordination chemistry⁸ and are used as building blocks⁹ for the synthesis of dissymmetrical tetralactams involved as receptors for molecular recognition^{10,11} and for self-assembly in supermolecular chemical studies.^{12,13} Recently we synthesized a new type of bisamides, chiral *N,N'*-bis(2-hydroxyaryl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides, derived from chiral tartaric acids and aminophenol derivatives.¹⁴ In the characterization of them, we found an intermolecular phenolic hydroxy methylation occurred between chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide and co-crystallized methanol under electron impact ionization conditions. To our best knowledge, intermolecular methylation under EI ionization conditions has not been reported in the literature yet.

Experimental

All title bisamides were synthesized according to the

reported method elsewhere.¹⁴

Low-resolution 70 eV electron impact (EI) mass spectra of the title compounds were obtained using a double-focusing mass spectrometer (VG-ZAB-HS, Micromass, Manchester, UK) coupled with a MASPEC II data system, using a direct insertion probe. Source temperature was 200 °C and probe temperature was 280 °C.

Colorless and rod crystals suitable for X-ray analysis were obtained from methanol solution. A crystal with approximate dimensions of 0.9 mm × 0.11 mm × 0.06 mm was selected for X-ray diffraction. A total of 4506 independent reflections, of which 3211 with $I \geq 2\sigma(I)$ were employed for structure determination and refinement, were collected on a NONIUS KappaCCD diffractometer with Mo $K\alpha$ ($\lambda = 0.71073$ nm) radiation using CCD mode in the range of 3.395° to 27.103° at room temperature (293 K) and corrected for Lp and empirical absorption. All of the calculations were carried out with SHELXS-97 and SHELXL-97 programs. The structure was solved by direct methods and then difference Fourier syntheses. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and added to the structure factor calculation, but their positions were fixed isotropically during the refinement. The final cycle of refinement converged to the discrepancy factors $R_1 = 0.0651$, $wR_2 = 0.1665$ with $I > 2\sigma(I)$, $R_1 = 0.0921$, $wR_2 = 0.1854$ for all data, with $S = 1.056$, $(\Delta\rho)_{\max} = 0.494 \text{ e}\cdot\text{nm}^{-3}$, $(\Delta/\sigma)_{\max} = 0.001$,

* E-mail: jxxu@chem.pku.edu.cn

Received September 4, 2003; revised and accepted January 5, 2004.

Project supported by the National Natural Science Foundation of China (No. 20272002), Ministry of Education of China (SRF for ROCS and EYTP), and Peking University (Present grant).

absolute structure parameter 1.2 (15).

Results and discussion

The characteristic electron impact fragmentation mechanism of chiral *N,N'*-bis(2-hydroxyaryl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides was investigated

and reported previously by us.¹⁵ Although a pair of chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides crystallized from acetonitrile yielded normal molecular ions under electron impact ionization conditions, they showed obvious [M+14] and weak [M+28] ions (Figure 1) under the same ionization

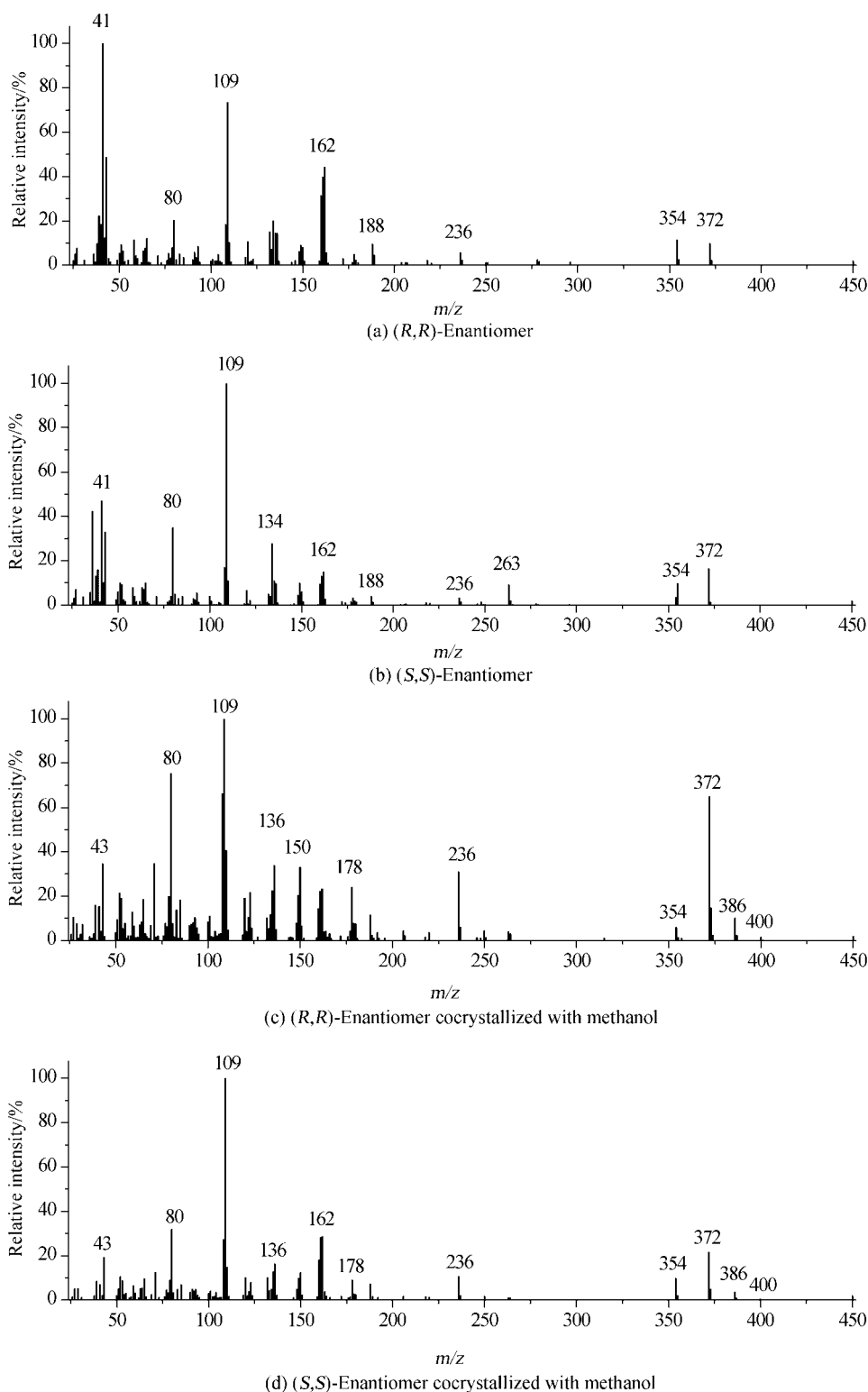


Figure 1 EI spectra of chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides and their co-crystallines with methanol. (a) (*R,R*)-Enantiomer, (b) (*S,S*)-enantiomer, (c) (*R,R*)-enantiomer co-crystallized with methanol and (d) (*S,S*)-enantiomer co-crystallized with methanol.

conditions when they were obtained by crystallization from methanol. ^1H NMR spectra also showed methoxyl signals. However, it is not possible that they are methylated under recrystallization conditions with methanol based on our organic chemistry knowledge. On the other hand, a few papers on intermolecular reactions under electron impact ionization conditions appeared in literature.^{16,17} It is not clear that in which step methylation occurs.

To give a clear elucidation to this phenomenon, a single crystal of (*R,R*)-*N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide was grown in methanol and analyzed to show that it is a co-crystalline with methanol (Figure 2). The crystal belongs to the orthorhombic system, space group *P2(1)2(1)2* with the following crystallographic parameters: $a = 15.3056(3)$ nm, $b = 17.7299(5)$ nm, $c = 7.59910(10)$ nm; $\alpha = \beta = \gamma = 90^\circ$, $V = 2062.14(8)$ nm³, $Z = 4$, $M = 404.16$, $D_c = 1.299$ g/cm³, $F(000) = 852$, $\mu(\text{Mo K}\alpha) = 0.099$ mm⁻¹.

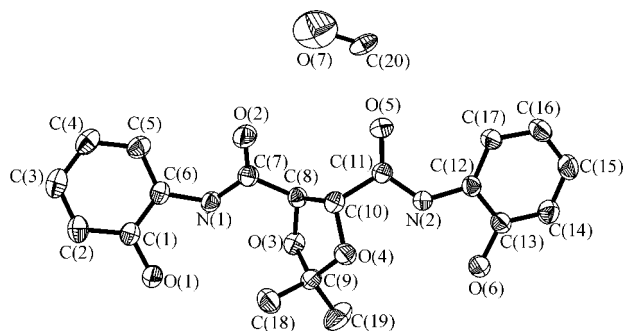
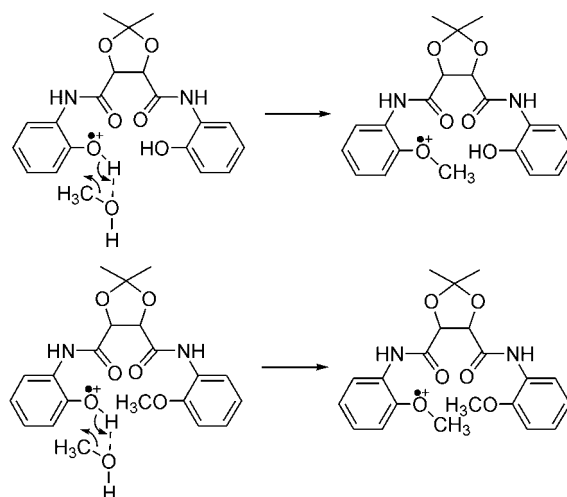


Figure 2 X-ray crystal structure of (*R,R*)-*N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide co-crystallized with methanol.

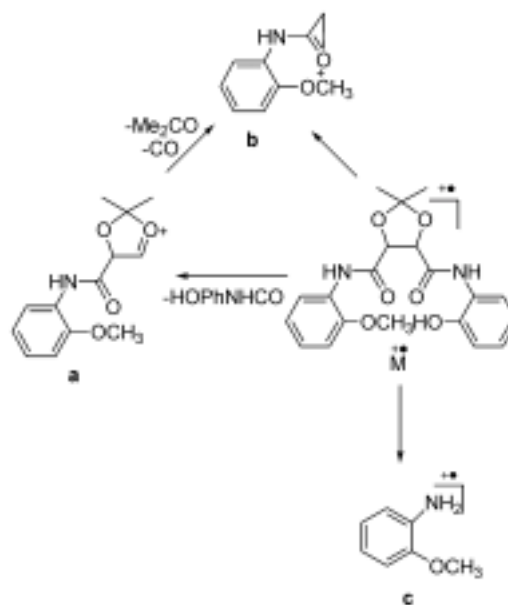
The X-ray analysis results indicate that *N,N'*-bis(2-hydroxyaryl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides cannot be methylated under recrystallization conditions with methanol. The methylation should occur under electron impact ionization conditions. The methylation mechanism could be assumed as follows. A hydrogen-bond is formed between *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides and methanol. A four-membered ring rearrangement could occur to yield methylated ions, *N*-(2-hydroxyphenyl)-*N'*-(2-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide ions at m/z 386, and very weak dimethylated ions, *N,N'*-bis(2-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide ions at m/z 400, under electron impact ionization conditions (Shown in Scheme 1). The four-membered ring rearrangement is one of important general rearrangements under electron impact ionization conditions.¹⁸⁻²⁰ Referring to their fragmentation mechanism reported previously,¹⁵ some methylated fragment ions, such as *N*-(2-methoxyphenyl)-2,2-dimethyl-1,3-dioxol-1-ium-4-carbamide ion (**a**) at m/z 250, 2-(2-methoxyphenylamino)-2*H*-oxirenum

Scheme 1



ion (**b**) at m/z 164, 2-aminoanisole ion (**c**) at m/z 123, produced from methylated molecular ions, were also observed in their spectra (Scheme 2).

Scheme 2



In order to investigate generality of the phenomenon, other chiral *N,N'*-bis(2-hydroxyaryl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides were recrystallized from methanol and determined. However, no methylated molecular ion was observed because no co-crystalline with methanol was formed according to their ^1H NMR analysis. For a pair of chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides, they were also refluxed and recrystallized from other alcohols, e.g. ethanol, isopropanol, or benzyl alcohol. However, ^1H NMR analysis showed that no co-crystalline with these alcohols was formed. And no alkylated product was found under electron impact ionization conditions when the dicarbamides obtained from these alcoholic solutions were determined.

X-ray diffraction analysis data for methanol-co-crystallized (*R,R*)-*N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide are tabulated in Tables 1—3.

Conclusion

An intermolecular phenolic hydroxy methylation

occurring between chiral *N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamides and co-crystallized methanol under electron impact ionization conditions was observed and the formation mechanism was suggested. The result was confirmed by X-ray diffraction structural analysis of a co-crystalline of (*R,R*)-*N,N'*-bis(2-hydroxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbamide and methanol.

Table 1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{nm}^2 \times 10^3$)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^a	Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^a
C(1)	7462(2)	4362(2)	8038(4)	55(1)	C(16)	7961(3)	711(2)	-4466(5)	76(1)
C(2)	7045(2)	4762(2)	9377(4)	69(1)	C(17)	7782(2)	1209(2)	-3118(4)	63(1)
C(3)	6212(3)	4576(2)	9871(5)	76(1)	C(18)	8786(3)	4318(2)	2967(5)	84(1)
C(4)	5783(2)	3988(2)	9023(5)	80(1)	C(19)	9992(3)	3420(3)	2053(6)	107(2)
C(5)	6193(2)	3582(2)	7712(4)	66(1)	N(1)	7514(2)	3391(1)	5883(3)	54(1)
C(6)	7034(2)	3771(2)	7209(3)	53(1)	N(2)	8342(2)	2191(1)	-1087(3)	53(1)
C(7)	7217(2)	3029(2)	4468(4)	55(1)	O(1)	8283(1)	4520(1)	7507(3)	68(1)
C(8)	7925(2)	2718(2)	3262(3)	51(1)	O(2)	6449(1)	2925(2)	4146(3)	87(1)
C(9)	9035(2)	3529(2)	2408(4)	57(1)	O(3)	8771(1)	2982(1)	3673(3)	60(1)
C(10)	7797(2)	2940(2)	1307(4)	52(1)	O(4)	8555(2)	3355(1)	870(2)	62(1)
C(11)	7698(2)	2271(2)	75(4)	54(1)	O(5)	7056(2)	1866(2)	163(3)	87(1)
C(12)	8447(2)	1647(2)	-2432(4)	51(1)	O(6)	9896(1)	2055(1)	-2390(3)	72(1)
C(13)	9290(2)	1587(2)	-3118(4)	57(1)	O(7)	5555(5)	1041(3)	2809(13)	223(3)
C(14)	9455(3)	1076(2)	-4452(5)	73(1)	C(20)	6054(2)	782(2)	1481(6)	69(1)
C(15)	8806(3)	639(2)	-5122(5)	83(1)					

^a U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2 Selected bond lengths (nm)

C(1)—O(1)	1.350(4)	C(8)—C(10)	1.550(4)	C(10)—C(11)	1.519(4)
C(6)—N(1)	1.417(4)	C(9)—O(4)	1.414(4)	C(11)—O(5)	1.218(3)
C(7)—O(2)	1.215(4)	C(9)—O(3)	1.424(4)	C(11)—N(2)	1.331(4)
C(7)—N(1)	1.332(4)	C(9)—C(19)	1.501(5)	C(12)—N(2)	1.415(4)
C(7)—C(8)	1.523(4)	C(9)—C(18)	1.511(5)	C(13)—O(6)	1.361(4)
C(8)—O(3)	1.413(4)	C(10)—O(4)	1.413(3)	O(7)—C(20)	1.346(9)

Table 3 Selected angles ($^\circ$)

C(7)-N(1)-C(6)	128.7(3)	O(4)-C(9)-C(19)	109.3(3)	O(5)-C(11)-N(2)	124.8(3)
O(2)-C(7)-N(1)	124.5(3)	O(3)-C(9)-C(19)	108.1(3)	O(5)-C(11)-C(10)	120.4(3)
O(2)-C(7)-C(8)	120.8(3)	O(4)-C(9)-C(18)	107.7(3)	N(2)-C(11)-C(10)	114.7(2)
N(1)-C(7)-C(8)	114.6(2)	O(3)-C(9)-C(18)	111.7(3)	C(11)-N(2)-C(12)	129.5(2)
O(3)-C(8)-C(7)	113.5(2)	C(19)-C(9)-C(18)	114.5(3)	C(8)-O(3)-C(9)	109.7(2)
O(3)-C(8)-C(10)	104.1(2)	O(4)-C(10)-C(11)	110.1(2)	C(10)-O(4)-C(9)	110.2(2)
C(7)-C(8)-C(10)	113.3(2)	O(4)-C(10)-C(8)	104.7(2)		
O(4)-C(9)-O(3)	105.2(2)	C(11)-C(10)-C(8)	113.9(2)		

References

- 1 Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. *W. Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
- 2 Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.
- 3 Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416.
- 4 Belda, O.; Kaiser, N. F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868.
- 5 Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* **2001**, *42*, 509.
- 6 Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057.
- 7 Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023.
- 8 Quirmback, M.; Holz, J.; Tararov, V. I.; Borner, A. *Tetrahedron* **2000**, *56*, 775.
- 9 Arnaud, N.; Cazaux, L.; Tisnes, P.; Picard, C. *Synlett* **1994**, 553.
- 10 Chang, S. K.; Engen, D. V.; Fan, E.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640.
- 11 Kluger, R.; Tsao, B. *J. Am. Chem. Soc.* **1993**, *115*, 2089.
- 12 Ma, G.; Jung, Y. S.; Chung, D. S.; Hong, J. I. *Tetrahedron Lett.* **1999**, *40*, 531.
- 13 Lessmann, J. J.; Horrocks, W. D. Jr. *Inorg. Chem.* **2000**, *39*, 3114.
- 14 Jiao, P.; Xu, J. X.; Zhang, Q. H.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 3081.
- 15 Xu, J. X.; Jiao, P.; Deng, D. Y.; Zhang, Q. H.; Tsang, C. W.; Chan, A. S. C. *Rapid Commun. Mass Spectrom.* **2002**, *16*, 1174.
- 16 Chen, Y. Z.; Li, H.; Hua, S. M.; Chen, N. Y.; Zhao, F. Z.; Li, H. Q. *J. Chin. Mass Spectrom. Soc.* **1988**, *9*, 7.
- 17 Li, H.; Chen, Y. Z.; Hua, S. M.; Chen, N. Y.; Chen, N.; Zhao, F. Z. *Org. Mass Spectrom.* **1986**, *21*, 726.
- 18 Xu, J. X.; Zuo, G. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1651.
- 19 Xu, J. X.; Zhang, X. Y.; Jin, S. *Chin. J. Chem.* **2000**, *18*, 368.
- 20 Xu, J. X.; Lan, R. X.; Jin, S. *Rapid Commun. Mass Spectrom.* **1999**, *13*, 1511.

(E0309042 ZHAO, X. J.)