

Effects of Counter Cations of Base Catalysts on Nitrosation Mechanisms

Hirohito IKEDA,* Miho YUKAWA, Tokihiro NIIYA, and Yoshinobu GOTO

Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan.

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Reaction of 2-butanone (**1**) with *tert*-butyl nitrite (*tert*-BuONO) was performed using base catalysts (RO^-M^+ ; $\text{R}=\text{CH}_3, \text{C}_2\text{H}_5$; $\text{M}^+=\text{Li}^+, \text{Na}^+, \text{K}^+$) in alcohols (CH_3OH or $\text{C}_2\text{H}_5\text{OH}$). In this report, the effects of M^+ of RO^-M^+ on the nitrosation mechanisms were investigated. The yield of *E*-hydroxyimino compound (**5E**) increases much better in the reaction using Na^+ or K^+ as M^+ compared with that using Li^+ . It is also observed that the yield of **5E** increases by addition of crown ether as a cation-capturing agent. The experimental results suggested that under the conditions lowering the effects of M^+ of RO^-M^+ on the nitrosation mechanisms, because the reactivity of naked enolate of **1** increases and the reaction in the C–N bond formation process tends to proceed *via* open-chain transition state without M^+ , the yield of **5E** tends to increase.

Key words nitrosation; counter cation; crown ether; open-chain transition state; hydroxyimino compound

It is well known that the nitrosation is one of the most significant synthetic methods of carbonyl derivatives. To study the reaction mechanisms is useful for not only understanding the reactivity of active alkyl groups with electrophiles but also the synthesis of medicines.¹⁾ The mechanisms of nitrosation of ketones are similar to those of aldol condensations. The aldol condensations are investigated in detail and the mechanisms have been made clear gradually accompanied by the progress of enolate chemistry. On the contrary, the study of the mechanisms of nitrosation has not been much developed. We tried to examine this reaction experimentally and theoretically in order to clarify the reaction mechanisms.^{2,3)}

The nitrosation of **1** with *tert*-butyl nitrite (*tert*-BuONO) using a base catalyst is shown in Chart 1. In our study, the nitrosation was divided into three steps, that is, the deprotonation process of **1** by a base catalyst, the C–N bond formation process involving enolate and *tert*-BuONO, and the elimination process that the proton and the *tert*-butoxyl group are eliminated from the complex of reactants with a base catalyst as described in the previous papers.²⁾ The rate determining step of this reaction is the C–N bond formation process. Though it can be considered that four kinds of hydroxyimino compounds (**3E**, **3Z**, **5E**, **5Z**) are formed simultaneously in the nitrosation of **1** shown in Chart 1, **5E** is obtained exclusively as a final product under these reaction conditions.⁴⁾ It is well known that there is an equilibrium between **2M** and **4M** in protic solvent.⁵⁾ Because **5E** is obtained as an only product, **4M** exists predominantly in this equilibrium before addition of *tert*-BuONO. It may be thought that the experi-

mental result described above is closely related to the reactivity and the thermodynamic stability of enolate produced by deprotonation with a base catalyst. The reactivity and thermodynamic stability of **2M** and **4M** were investigated using *ab initio* MO calculation performed with Gaussian 98 program.⁶⁾ The results of calculation showed that the eigenvalue of HOMO of **4M** is higher than that of **2M** and the electron density of C^3 in HOMO of **4M** is larger than that of C^1 of **2M**.⁷⁾ Therefore, the reactivity of **4M** is relatively higher than that of **2M**. Compound **4M** is more stable than **2M** thermodynamically.⁸⁾

The experimental results of the nitrosation of **1** with *tert*-BuONO using RO^-M^+ in an alcohol are shown in Table 1. The yield of **5E** was determined by gas chromatography.

The yield of **5E** given by the reaction in $\text{C}_2\text{H}_5\text{O}^- - \text{C}_2\text{H}_5\text{OH}$ was obviously better than that in $\text{CH}_3\text{O}^- - \text{CH}_3\text{OH}$. Because the electron density of oxygen atom of $\text{C}_2\text{H}_5\text{O}^-$ is larger than that of CH_3O^- , the yield of **4M** increases in the deprotonation step using $\text{C}_2\text{H}_5\text{O}^-\text{M}^+$. And the yield of **5E** increased much better in the reaction using Na^+ or K^+ as M^+ compared with that using Li^+ . It is considered that these results were caused by high eigenvalues of HOMO and large electron densities of C^3 in HOMO in the case of using Na^+ or K^+ as M^+ (Table 2).⁹⁾

It may be assumed that M^+ of RO^-M^+ plays an important role in the transition state, *i.e.* metal-chelated pericyclic transition state in the C–N bond formation process of the nitrosation.²⁾ This concept is similar to that of the illustration of the reaction mechanism in the aldol condensation.¹⁰⁾ On the

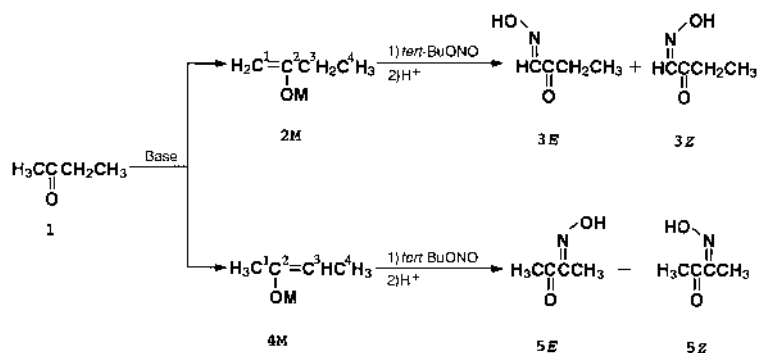


Chart 1

* To whom correspondence should be addressed. e-mail: ikeda@fukuoka-u.ac.jp

Table 1. The Product Yields of Nitrosation of **1**

Entry	Base	Solvent	Yield of 5E (%)
1	CH ₃ OLi	CH ₃ OH	12
2	CH ₃ ONa	CH ₃ OH	17
3	CH ₃ OK	CH ₃ OH	16
4	C ₂ H ₅ OLi	C ₂ H ₅ OH	20
5	C ₂ H ₅ ONa	C ₂ H ₅ OH	39
6	C ₂ H ₅ OK	C ₂ H ₅ OH	32

Table 2. The Eigenvalues of HOMO and Electron Densities of C³ in HOMO of **4M**

Entry	M ⁺	Eigenvalue/a.u.	Electron density
1	Li ⁺	-0.25643	0.68
2	Na ⁺	-0.23242	0.72
3	K ⁺	-0.22654	0.74

Table 3. The Product Yields of Nitrosation of **1** Using Crown Ether in Ethanol

Entry	Base	Crown ether	Yield of 5E (%)
1	C ₂ H ₅ OLi	15C5	32
2	C ₂ H ₅ ONa	15C5	46
3	C ₂ H ₅ OK	15C5	44
4	C ₂ H ₅ ONa	DC18C6	61
5	C ₂ H ₅ OK	DC18C6	59

other hand, there is another report on the mechanism of aldol condensation reaction which proceeds *via* open-chain transition state.¹¹⁾ Thus in the C–N bond formation process also, it is considered that there are possibilities of existence of two transition states, *i.e.* M⁺-chelated pericyclic transition state and open-chain transition state without M⁺. But it is difficult to clarify the transition structure experimentally. As an experimental attempt to explore the role of M⁺, the nitrosation in the presence of crown ether was examined. When 15-crown-5 (15C5) or dicyclohexyl-18-crown-6 (DC18C6) was added to the reaction mixture before addition of *tert*-BuONO, the yield of **5E** increased remarkably (Table 3).

When DC18C6 was added to the reaction mixture in C₂H₅OLi–C₂H₅OH, the solution was solidified and the reaction did not proceed. On the basis of these experimental results, it is assumed that the coordination of M⁺ of RO⁻M⁺ to naked enolate **4** is inhibited in the reaction using crown ether and the reaction in the C–N bond formation process tends to proceed *via* open-chain transition state without M⁺. The MO calculation of **4** was also performed,⁹⁾ and the eigenvalue of HOMO and electron density of C³ in HOMO of **4** are -0.06490 a.u. and 0.90, respectively. This calculation result indicates that the reactivity of **4** is relatively higher than that of **4M** (see Table 2) and supports the experimental results in the presence of crown ethers.

It can be concluded that when the reaction proceeds under

the conditions lowering the effects of M⁺ of RO⁻M⁺ on the nitrosation mechanisms, the *E*-hydroxyimino compound is liable to be obtained. This result supports our theoretical investigation by *ab initio* MO calculations in the previous paper.^{2b)}

Experimental

To a solution of alkoxide (2.0×10⁻³ mol) in alcohol or alkoxide (2.0×10⁻³ mol) and crown ether (2.1×10⁻³ mol) in alcohol, **1** (5.0×10⁻⁴ mol) was added. After stirring for 1 h, *tert*-BuONO (7.5×10⁻⁴ mol) was added dropwise with stirring. The temperature of the solution was kept at 0 °C during carrying out this reaction. The reaction mixture was allowed to stand for 18 h in a refrigerator. Afterward the reaction mixture was acidified with dilute H₃PO₄, and then **5E** was obtained. The yield of **5E** was determined by gas chromatography (GC). GC analysis was performed on a Shimadzu GC-6AM connected to a System Instruments Chromatocorder 11 integrator. Triton X-305 (5%) (2 mm×0.5 m, packed glass) column was used.

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References and Notes

- 1) For example; a) Rice W. G., Hillyer C. D., Harten B., Schaeffer C. A., Dorminity M., Lackey III D. A., Kirsten E., Mendeleyev J., Buki K. G., Hakam A., Kun E., *Proc. Natl., Acad. Sci. U.S.A.*, **89**, 7703–7707 (1992); b) Degorre F., Kiffer D., Terrier F., *J. Med. Chem.*, **31**, 757–763 (1988).
- 2) a) Niiya T., Ikeda H., Yukawa M., Goto Y., *Chem. Pharm. Bull.*, **45**, 1387–1392 (1997); b) *Idem, ibid.*, **49**, 473–475 (2001).
- 3) Ikeda H., Haraguchi T., Yukawa M., Niiya T., Goto Y., *Chem. Pharm. Bull.*, **43**, 526–528 (1995).
- 4) a) Bartnik R., Orłowska B., *Polish J. Chem.*, **62**, 427–431 (1988); b) Baas P., Cerfontain H., *J. Chem. Soc., Perkin Trans. II*, **1979**, 156–162; c) Semon W. L., Damerell V. R., "Org. Syntheses," Coll. Vol. II, ed. by Blatt A. H., John Wiley & Sons, Inc., New York, 1943, pp. 204–208; d) Williams D. L. H., "Nitrosation," Cambridge University Press, New York, 1988, pp. 36–42.
- 5) d'Angelo J., *Tetrahedron*, **32**, 2979–2990 (1976).
- 6) Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A., Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Baboul A. G., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E. S., Pople J. A., "Gaussian 98," Revision A.9; Gaussian, Inc., Pittsburgh, PA, 1998.
- 7) The eigenvalues and coefficients of molecular orbitals of sodium enolate are calculated with the HF/6-31+G(d).
- 8) The energy difference of sodium enolate between **2M** and **4M** calculated at the MP3/6-31+G(d)/HF/6-31+G(d) level is 0.0028 a.u. (1.76 kcal·mol⁻¹).
- 9) The eigenvalues and electron densities of molecular orbitals are calculated with the HF/LANLIDZ.
- 10) a) Zimmerman H. E., Traxler M. D., *J. Am. Chem. Soc.*, **79**, 1920–1923 (1957); b) Dubois J. E., Dubois M., *Tetrahedron Lett.*, **1967**, 4215–4219; c) House H. O., Crumrine D. S., Teranishi A. Y., Olmsted H. D., *J. Am. Chem. Soc.*, **95**, 3310–3325 (1973).
- 11) a) Noyori R., Nishida I., Sakata J., *J. Am. Chem. Soc.*, **103**, 2106–2108 (1981); b) *Idem, ibid.*, **105**, 1598–1608 (1983).