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Concentration-Dependent Thermal Isomerization of Nitrile N-Oxide

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Abstract: Kinetically stabilized nitrile *N*-oxides (**NO**s) have been regarded as viable tools for the postpolymerization functionalization of common polymers. However, thermal isomerization of **NO** to isocyanate restricts the applications of **NO** to industrial use. The reaction mechanism for the thermal isomerization has not been systematically evaluated. Herein, we report the concentration-dependent isomerization of **NO**s for the first time. The time-course plots suggest that the isomerization of **NO** would be driven by a very small amount of polymeric intermediate generated *in situ* in a substituent-dependent equilibrium. The substituent effects of **NO** on the isomerization have been clarified with the kinetic parameters and the reaction order. It is indicated that an electron-donating *para*substituent facilitates both the intermediate-forming reaction and the rearrangement reaction.

Introduction

Nitrile *N*-oxide (**NO**) is a highly reactive 1,3-dipole, which reacts to various unsaturated bonds via catalyst-free 1,3-dipolar cycloaddition reaction.^[1] Since **NO** is found to be highly reactive to alkenes and a nitrile group in common polymers, **NO**-containing molecules could have a potential usefulness for the postpolymerization functionalization of elastomers and resins.^[2] However, typical **NO**s are chemically unstable, easily leading to dimerization and polymerization.^[3]

On the other hand, **NO** bearing a steric barrier around the functionality kinetically suppresses the self-degradations, enabling the isolation of **NO**. According to the concept of kinetic stabilization, we have developed stable **NO**-based ligation tools such as homoditopic **NO**s to connect between unsaturated bonds,^[4] ambident molecules to connect an unsaturated bond with a nucleophile,^[5] and **NO**-terminated polymers as grafting agents.^[6] Although these ligation tools provide a viable mean for the catalyst-free postpolymerization functionalization, we have recently suffered from the unexpected side reaction of stable **NO**s during the practical use. It is indicated that the **NO**s thermally rearrange to the corresponding isocyanates (**Isoc**s) at high temperature, while neither the oligomerization nor the polymerization were detected due to the kinetic stability of **NO**.

As a result of literature survey, we found that the isomerization of **NO** to **Isoc** has been reported, however, three types of reaction mechanisms have been proposed to date, which has not been systematically evaluated (Scheme 1). The first mechanism is a unimolecular rearrangement via the intermediary formation of 1,2-oxazirene skeleton (Scheme 1A).^[7] The second is based on the skeletal rearrangement of 1,4,2,5-dioxadiazine as a bimolecular intermediate (Scheme 1B).^[8] The third is via the polymeric intermediate (Scheme 1C).^[9]

As an experimental effort to clarify the mechanism, we herein report the concentration-dependent thermal isomerization behaviors of NOs and the substituent effects on the isomerization for the first time. As the model compounds, we prepared four types of isolable NOs including three aromatic NOs with different para-substituents and an aliphatic NO. We investigated the thermal isomerization reactions of NOs in CDCl3 or in 1,2-dichlorobenzene-d4 as NMR solvents. The time-course plots of isomerization reactions indicate that (i) the isomerization rate of NO strongly depends on the concentration and (ii) the plots under diluted conditions include an induction period (τ') before the isomerization. Such results rule out the possibility of Scheme 1A, which are also supported by the analyses of reaction order. It turned out that an electron-donating para-substituent tends to facilitate not only the skeletal rearrangement but also the self-association reaction of NO to give the intermediate. Considering all the results, we concluded that the isomerization of NO would be driven by a very small amount of intermediate generated in situ from plural NOs in a substituentdependent equilibrium.

A)
$$R-C=N-O^{-}$$
 $\left[\begin{array}{c} O \\ R \end{array} \right] \xrightarrow{\Delta} R-N=C=O$
B) $R-C=N-O^{-}$ $\left[\begin{array}{c} O \\ R \end{array} \right] \xrightarrow{A} R-N=C=O$
C) $R-C=N-O^{-}$ $\left[\begin{array}{c} O \\ R \end{array} \right] \xrightarrow{A} R-N=C=O$

 $\label{eq:Scheme 1. Proposed mechanisms for the thermal isomerization of NO to Isoc via (A) monomeric, (B) dimeric, and (C) polymeric intermediates.$

Results and Discussion

Scheme 2 shows the synthesis and structures of **NOs**. Considering the structures of our previously developed **NO**-based ligation tools,^{4,6} we determined the structures of **NO-3** and **NO-4** as the unit models in order to make the discussion simplified. To know the electronic effects on the isomerization, we also designed **NO-1** and **NO-2** with different electron demands to that of **NO-3**. We used 3,5-dimethoxyaniline (1) as the starting compound for **NO-1** and **NO-2**. The acetylation of **1** was followed by methylation to give amide **2**. Rieche formylation of **2** proceeded regio-selectively to give **3**.^[10] Aldehyde **3** was converted to oxime **4**, which was further treated with *N*-chlorosuccinimide (NCS) to give amide-substituted **NO-1**. We found that **NO-1** was stable enough for the purification using silica gel column chromatography. On the

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other hand, the reduction of amide **2** with triethylsilane in the presence of $(C_6F_5)_3B$ gave *tert*-amine **5**. At the similar manner to the preparation of **NO-1**, we synthesized *tert*-amine-containing **NO-2** from **5**. We also prepared **NO-3** without a *para*-substituent and aliphatic **NO-4** according to the reported procedures.^[6a,11]

In the ¹H NMR spectra of three aromatic **NOs** (Figure 1),^[12] the chemical shifts of aromatic proton signals are 6.37 ppm for **NO-1**, 5.75 ppm for **NO-2**, and 6.53 ppm for **NO-3**, implying that the electron-donating capacity of *para*-substituents to the aromatic ring is in the order EtMeN- in **NO-2** > AcMeN- in **NO-1** > H- in **NO-3**.







Figure 2. Time-course plots for the thermal isomerization of (A) NO-1, (B) NO-2, (C) NO-3, and (D) NO-4 (blue circle: 10 mM, red triangle: 30 mM, orange square: 90 mM, and green rhombus: 270 mM).

Table 1. Dependences of concentration and substituent on the induction periods (τ '), half-lives ($\tau_{1/2}$), and kinetic constant (*k*) of thermal isomerization under the conditions of Scheme 3.

		10 mM	30 mM	90 mM	270 mM
	τ'	1.6 h	0.46 h	-	-
NO-1	τ _{1/2} a	150 h	108 h	90 h	40 h
	kª	4.6 × 10 ⁻³ h ⁻¹	6.4 × 10 ⁻³ h ⁻¹	7.7 × 10 ⁻³ h ⁻¹	17 × 10 ⁻³ h ⁻¹
	τ'	_	_	_	-
NO-2	τ _{1/2} a	5.5 h	5.5 h	3.9 h	2.9 h
	kª	126 × 10 ⁻³ h ⁻¹	126 × 10 ⁻³ h ⁻¹	178 × 10 ⁻³ h ⁻¹	239 × 10 ⁻³ h ⁻¹
	τ'	42 h	11 h	-	-
NO-3	τ _{1/2} a	506 h	437 h	249 h	135 h
	kª	1.4 × 10 ⁻³ h ⁻¹	1.6 × 10 ⁻³ h ⁻¹	2.8 × 10 ⁻³ h ⁻¹	5.1 × 10 ⁻³ h ⁻¹
	τ'	-	-	-	
NO-4	τ _{1/2} a	23 h	17 h	5.8 h	5.8 h
	kª	30 × 10 ⁻³ h ⁻¹	41 × 10 ⁻³ h ⁻¹	120 × 10 ⁻³ h ⁻¹	120 × 10 ⁻³ h ⁻¹

^aCalculated by the initial reaction rate.

Having four types of NOs in hand, we performed the thermal isomerization of NOs at 60 °C in CDCl3 and detected the reaction by ¹H NMR spectroscopy (Scheme 3).^[12] Because the thermal isomerization of NO-4 hardly occurred at 60 °C in CDCl₃, the reaction of NO-4 was performed at 140 °C in 1,2-dichlorobenzene-d4 (o-C₆D₄Cl₂). The thermal treatments of NOs were found to afford the corresponding Isocs with a small amount of 1,3-dialkyl urea caused by the partial hydrolysis of Isoc, while the time scales of four isomerization reactions were very different. We estimated the conversions of NOs to Isocs by the integral ratio in the ¹H NMR spectra. In the time-course plots for the isomerization reactions (Figure 2), we found that the higher concentration remarkably accelerates the thermal isomerization of NOs. This is the first time to reveal the dependence of concentration on the isomerization rate of NO. The results clearly provide the experimental evidence for the existence of intermediate generated by plural NOs on the isomerization of NO to Isoc. Therefore, we ruled out the possibility of Scheme 1A as the unimolecular pathway at this moment.

In addition, it is indicated that the isomerization reactions of **NO-1** and **NO-3** under diluted conditions hardly proceeded at the initial reaction stages, suggesting that the isomerization reactions include induction periods (τ ') for the initiation. On the other hand, we didn't observe any signals attributed to the intermediate in the ¹H NMR spectra, suggesting that the isomerization would be driven by a very small amount of intermediate generated *in situ*.

From the slopes of plots on the initial reaction stages after τ ', we created approximate lines to estimate each kinetic constant (*k*) for the initial reaction rate and the half-lives ($\tau_{1/2}$) of **NOs** based on the *k* values. The kinetic parameters are summarized in Table 1. Through the comparison of *k* and $\tau_{1/2}$ values for aromatic **NOs**, we found that the electron-donating group at the *para*-position facilitates the thermal isomerization. It is well known that the electron-rich aromatics tend to easily migrate on the skeletal rearrangements.^[13,14] Our observations are in a good agreement with the tendency of typical rearrangement reactions. The higher activation energy for the isomerization of aliphatic **NO-4** could be dependent on the lower migration capacity of the aliphatic framework than those of aromatics.



Figure 3. Logarithm of reaction velocity (Inv) as a function of the logarithm of concentration (In[NO]).

Then, we compared the τ ' values of aromatic **NO**s. The time scale of τ ' could be regarded as the period to form the intermediate. Since the order of τ ' values is **NO-2** < **NO-1** < **NO-3**, we concluded that the electron-donation of substituent would facilitate not only the skeletal rearrangement but also the self-association to form the intermediate.

To know the reaction orders of each isomerization reaction, we plotted the logarithm of reaction velocity $(\ln v)$ as a function of the logarithm of **NO** concentration $(\ln[NO])$ (Figure 3). From the slopes of the approximate lines in the plots, we found that the reaction orders are in a range from one to two (1.2-1.7), implying that the association reactions of **NO**s would be a reversible reaction step, which could be biased by the electronic character of substituent. The trend of reaction orders indicates that the equilibrium between **NO-3** and the intermediate would be biased to the side of **NO-3** compared with the equilibrium of **NO-2**, because the higher reaction order should indicate the large contribution of intermediate-forming rate on the total reaction rate of isomerization.^[14]

The reaction order itself has hardly suggested the association number of **NO** in the intermediate structure. However, it has been reported that several **NO**s easily form cyclic polymers with molecular weight distributions.^[15] 1,4,2,5-Dioxadiazine skeleton as the central structure of dimeric intermediate can be regarded as a thermally stable hetero-aromatics. The thermal degradation of 3,6-diphenyl-1,4,2,5dioxadiazine affords benzonitrile and nitrosocarbonylbenzene, which never produces phenyl isocyanate nor benzonitrile *N*-oxide.^[16] Therefore, the polymeric structure described in Scheme 4 might be the most plausible intermediate for the isomerization of **NO**.



Scheme 4. Plausible mechanism for the isomerization of NO to Isoc via cyclic polymer formation.

Finally, we considered the correlations of kinetic parameters to Hammett parameters. Hammett parameters are regarded as one of the most widely used means for the study of organic reaction mechanisms. According to the parameter list in the literature,^[17] the Hammett substituent constants for the *para* substituent (σ_p) are 0 for H in NO-3 and +0.26 for NMe(COMe) in NO-1. Although the σ_p value of NMeEt for NO-2 is not included in the list, the numerical value for NMe2 (-0.83) should be almost similar to that of NMeEt in NO-2. Based on the typical interpretation of Hammett parameters, the positive value for NMe(COMe) in NO-1 suggests the electron-withdrawing capacity, while the negative value for NMeEt in NO-2 indicates the electrondonating capacity. We found that the σ_p value for NMe(COMe) in NO-1 is discrepant to our observed phenomena such as the upfield-shift of aromatic proton signal in ¹H NMR spectrum of NO-1 compared with that of NO-3 (Figure 1) and the higher isomerization rate of NO-1 than NO-3. The results indicate that Hammett parameters are not appropriate to generalize the substituent effects of **NO**-isomerization on the kinetic parameters in our system. Since we didn't directly catch the signals attributed to the intermediate in the ¹H NMR spectra, the theoretical study may unveil the intermediate structure. In our near future, we will synthesize the isolable cyclic polymers according to the literature^[15] and investigate the thermal reaction of the cyclic polymers. Such experiments can eventually evaluate the isomerization mechanism and the possibility of thermal depolymerisation.

Conclusion

In conclusion, we found that the thermal isomerization of **NO** to **Isoc** is strongly dependent on the concentration for the first time, which suggests the existence of intermediate from plural **NOs**. The substituent effects of **NO** on the isomerization have been clarified with the kinetic parameters and the reaction order, in which it turned out that an electron-donating substituent facilitates both the intermediate-forming reaction and the rearrangement reaction. The trend of reaction order indicates that the electron demand of *para*-substituent would strongly relate to the dynamic formation of polymeric intermediate. On the basis of the substituent effects on the isomerization of **NO**, the creation of new ligation tool comprising **NO** with improved thermal stability is currently underway.

Experimental Section

Materials: Acetic anhydride (Kanto Chemical Co., Inc., Tokyo, Japan), 3,5-dimethoxyaniline (Tokyo Chemical Industry Co., Inc., Tokyo, Japan), iodomethane (Fujifilm Wako Pure Chemicals Corp., Osaka, Japan), sodium hydride (Fujifilm Wako Pure Chemicals Corp., Osaka, Japan), anhydrous DMF (Fujifilm Wako Pure Chemicals Corp., Osaka, Japan), anhydrous CH2Cl2 (Kanto Chemical Co. Inc., Tokyo, Japan), dichloromethyl methyl ether (Tokyo Chemical Industry Co., Inc., Tokyo, Japan), titanium chloride (Fujifilm Wako Pure Chemicals Corp., Osaka, Japan), hydroxylamine hydrochloride (Kanto Chemical Co., Inc., Tokyo, Japan), sodium acetate (Tokyo Chemical Industry Co., Inc., Tokyo, Japan), N-chlorosuccinimide (NCS, sigma-aldrich Co. LLC., St. Louis, USA), triethylamine (Nacalai tesque Inc., Kyoto, Japan), chloroform (Kanto Chemical Co., Inc., Tokyo, Japan), triethylsilane (Tokyo Chemical Industry Co., Inc., Tokyo, Japan). tris(pentafluorophenyl)borane (Fujifilm Wako Pure Chemicals Corp., Osaka, Japan), and anhydrous dichloromethane (CH₂Cl₂, Kanto Chemical Co., Inc., Tokyo, Japan) were used without further purification. The other chemicals were used without purification. Nitrile N-oxides (NO-3 and NO-4) were prepared according to the literature.[6a,11]

Measurements: ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on Bruker AVANCE II 400 spectrometers (Brucker, Fällanden, Switzerland) using CDCl₃, DMSO-*d*₆, and 1,2dichlorobenzene-*d*₄ (*o*-C₆D₄Cl₂) as the solvent, calibrated using an internal standard and residual undeuterated solvent signals. FT-IR spectra via an attenuated total reflection (ATR) method were measured using an IRSpirit spectrometer (Shimadzu Co. Ltd., Kyoto, Japan). MALDI-TOF MS spectra were recorded on a Shimadzu AXIMA-CFR plus mass spectrometer (matrix: CHC α).

Synthesis of 2.^[18]

3,5-Dimethoxyaniline (10.0 g, 65.3 mmol) was dissolved in Ac₂O (7.40 mL, 78.3 mmol) and stirred for 1 h at room temperature. The mixture was neutralized with sat. aq. NaHCO₃. The products were extracted with CHCl₃. The combined organic layer was washed with water, dried over MgSO₄, filtered, and concentrated in vacuo to give the corresponding acetylamide as white solids (11.8 g) in 93% yield; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 6.74 (d, *J* = 1.8 Hz, 2H), 6.23 (t, *J* = 1.8 Hz, 1H), 2.16 (s, 6H), 1.56 (s, 3H) ppm.

The obtained amide (10.0 g, 51.2 mmol) was added to the suspension of NaH (60%, 4.10 g, 102 mmol) in a mixed solvent of THF (76.5 mL) and DMF (25.5 mL) at 0 °C. Iodomethane (4.40 mL, 70.7 mmol) was then added to the mixture. The mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was cooled to 0 °C and quenched by the addition of water. The products were extracted with EtOAc. The combined organic layer was washed with sat. aq. NaHCO₃, dried over MgSO₄, filtered, and concentrated in vacuo to give a crude material. The crude was purified by a silica gel column chromatography (eluent: hexane : EtOAc = 1:2) to give **2** as yellow solids (9.68 g, 46.3 mmol) in 90% yield; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 6.43 (t, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.2 Hz, 2H), 3.80 (s, 6H), 3.24 (s, 3H), 1.92 (s, 3H) ppm.

Synthesis of 3.^[18]

To the mixture of **2** (2.00 g, 9.56 mmol) and MeOCHCl₂ (5.12 mL, 57.4 mmol) in CH₂Cl₂ (95.6 mL) was slowly added TiCl₄ (6.25 mL, 57.4 mmol) at 0 °C. The mixture was warmed to room temperature, stirred for 5 h, and quenched by the addition of water. The layers were separated and the products were extracted with CHCl₃. The combined organic layer was washed with sat. aq. NaHCO₃, dried over MgSO₄, filtered, and concentrated in vacuo to give a crude material. The crude was purified by a silica gel column chromatography (eluent: EtOAc) to give **3** as white solids (640 mg, 2.70 mmol) in 28% yield; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 10.4 (s, 1H), 6.33 (s, 3H), 3.82 (s, 6H), 3.21 (s, 3H), 1.93 (s, 3H) ppm.

Synthesis of 4.

A mixture of hydroxylamine hydrochloride (164 mg, 2.50 mmol) and sodium acetate (205 mg, 2.50 mmol) in water (2.6 mL) was added to the mixture of **3** (500 mg, 2.11 mmol) in *i*-PrOH (8.4 mL) at room temperature. The mixture was stirred for 2 h at the same temperature and concentrated in vacuo. The mixture was repeatedly washed with water and the residue was dried in vacuo to give **4** (429 mg) as white solids in 80% yield. The obtained compound was used for next reaction without further purification; mp 242.4-248 °C (decomp.); ¹H NMR (400 MHz, CDCl₃, 298 K) δ 8.52 (s, 1H), 6.42 (s, 2H), 3.88 (s, 6H), 3.28 (s, 3H), 2.00 (s, 3H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆, 298 K) δ 169.2, 158.7, 146.3, 142.1, 103.6, 56.2, 36.5, 22.4 ppm; IR (ATR) υ 3245 (N-OH) cm⁻¹; MALDI-TOF MS (matrix: CHC α) calc'd for C₁₂H₁₇N₂O₄⁺ [M+H⁺] 253.12, found 252.91.

Synthesis of NO-1.

To a mixture of 4 (200 mg, 0.792 mmol) and Et₃N (165 μ L, 1.19 mmol) in CHCl₃ (7.9 mL) was added NCS (158 mg, 1.19 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of water. The layers were separated and the products were extracted with CHCl₃. The combined organic layer was washed with sat. aq. NaHCO₃, dried over MgSO₄, filtered, and concentrated in vacuo to give a crude material. The crude was purified by a silica gel column chromatography (eluent: hexane : EtOAc = 1:3 \rightarrow EtOAc) to give **NO-1** as yellow solids (179 mg, 0.715

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mmol) in 91% yield; mp 168.9-172.2 °C; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 6.37 (s, 2H), 3.88 (s, 6H), 3.27 (s, 3H), 1.98 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃, 298 K) d 169.9, 167.7, 148.2, 130.8, 128.7, 102.8, 56.3, 37.1 (CNO), 30.3, 28.8, 23.6, 22.3 ppm (Several signals appear to be split due to the presence of amide rotamers.); IR (ATR) υ 2303 (CNO) cm⁻¹; MALDI-TOF MS (matrix: CHCα) calc'd for C₁₂H₁₅N₂O₄⁺ [M+H⁺] 251.10, found 250.92.

Synthesis of 5.

To a solution of **2** (800 mg, 3.82 mmol) in CH₂Cl₂ (38.2 mL) was slowly added (C₆F₅)₃B (196 mg, 0.382 mmol) and triethylsilane (3.03 mL, 19.1 mmol) at room temperature. The mixture was refluxed for 19 h, cooled to room temperature, and concentrated in vacuo. The crude was purified by a silica gel column chromatography (eluent: hexane : EtOAc = 3:1) to give **5** as colorless solids (530 mg, 2.71 mmol) in 71% yield; ¹H NMR (400 MHz, CDCl₃, 298 K) d 5.89 (m, 3H), 3.78 (s, 6H), 3.36 (q, J = 7.1 Hz, 2H), 2.89 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 161.6, 150.9, 91.6, 88.1, 55.1, 46.9, 37.6, 11.3 ppm; IR (ATR) υ 2964 cm⁻¹; MALDI-TOF MS (matrix: CHC α) cale'd for C₁₁H₁₈NO₂⁺ [M+H⁺] 196.13, found 196.13.

Synthesis of 6.

To the mixture of 5 (440 mg, 2.25 mmol) and MeOCHCl₂ (2.40 mL, 27.0 mmol) in CH₂Cl₂ (22.5 mL) was slowly added TiCl₄ (980 µL, 9.00 mmol) at 0 °C. The mixture was warmed to room temperature, stirred for 20 h, and quenched by the addition of water. The aqueous layer was neutralized by the addition of NaOH. The layers were separated and the products were extracted with CHCl₃. The combined organic layer was washed with sat. aq. NaHCO3, dried over MgSO4, filtered, and concentrated in vacuo to give a crude material. The crude was purified by a florisil column chromatography (eluent: hexane-EtOAc = 1:3) to give 6 as gray solids (240 mg, 1.08 mmol) in 48% yield; mp 82.7-87.9 °C; ¹H NMR (400 MHz, CDCl₃, 298 K) & 10.2 (s, 1H), 5.73 (s, 2H), 3.87 (s, &H), 3.47 (q, J = 7.1 Hz, 2H), 23.03 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 186.3, 164.2, 154.7, 104.9, 86.8, 55.5, 46.7, 37.6, 11.7 ppm; IR (ATR) v 1647 (C=O) cm⁻¹; MALDI-TOF MS (matrix: CHCa) calc'd for C12H18NO3⁺ [M+H⁺] 224.13, found 224.10.

Synthesis of 7.

A mixture of hydroxylamine hydrochloride (832 mg, 1.29 mmol) and sodium acetate (910 mg, 1.29 mmol) in water (1.1 mL) was added to the mixture of **6** (240 mg, 1.08 mmol) in *i*-PrOH (4.3 mL) at room temperature. The mixture was stirred for 1.5 h at the same temperature and concentrated in vacuo. The mixture was repeatedly washed with water and the residue was dried in vacuo to give **7**. The obtained compound was used for next reaction without further purification; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 8.51 (s, 1H), 5.85 (s, 2H), 3.86 (s, 6H), 3.43 (q, *J* = 7.1 Hz, 2H), 2.98 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 160.2, 151.1, 143.8, 98.4, 88.2, 55.5, 46.7, 37.5, 11.6 ppm; IR (ATR) υ 3193 (N-OH) cm⁻¹; MALDI-TOF MS (matrix: CHC α) calc'd for C₁₂H₁₉N₂O₃⁺ [M+H⁺] 239.14, found 239.09.

Synthesis of NO-2.

To a mixture of 7 (254 mg, 1.07 mmol) and Et₃N (163 μ L, 1.17 mmol) in CHCl₃ (10.7 mL) was added NCS (157 mg, 1.17 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched by the addition of water. The layers were separated and the products were extracted with CHCl₃. The combined organic layer was washed with water, dried over MgSO₄, filtered, and

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concentrated in vacuo to give **NO-2** (242 mg) as yellow solid in 96% yield; ¹H NMR (400 MHz, CDCl₃, 298 K) δ 5.75 (s, 2H), 3.83 (s, 6H), 3.42 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 163.4, 152.3, 98.6, 87.5, 55.6, 46.9, 37.7, 11.6 ppm (The ¹³C signal of nitrile *N*-oxide functionality is silent because of the quadrupolar relaxation of the adjacent ¹⁴N nucleus.^[19]); IR (ATR) υ 2245 cm⁻¹; MALDI-TOF MS (matrix: CHC α) cale'd for C₁₂H₁₇N₂O₃⁺ [M+H⁺] 237.12, found 237.13.

Typical procedure for the thermal isomerization reaction of NO.

A solution of an arbitrary amount **NO** in CDCl₃ (0.60 mL) was added to an NMR tube, which was firmly sealed. The NMR spectrum was measured to give the NMR proton signals for 0 h. The tube was directly heated in an oil bath at 60 °C. The signal change was detected by ¹H NMR spectroscopy after the defined time. Upon heating, the proton signals of **NO** progressively decreased, while the signals of Isoc increased. The system was kept heated for one week. The phenomena clearly suggest the thermal isomerization of **NO** to **Isoc**. The conversion of **NO** was determined by the integral ratio of proton signals of methoxy groups.

Determination of kinetic parameters for the isomerization of NO to Isoc.

The conversion of **NO** was plotted as a function of heating time (Figure 2). Since the conversion at the initial stage linearly correlates to the time, we drew an approximate straight line and calculated the apparent half-life ($\tau_{1/2}$) of **NO** based on the initial reaction rate as a reference value. From the intersection of the plots to x-axis, we estimated the induction period (τ ') of isomerization reaction. On the assumption that the reaction obeys the first-order kinetics, we also estimated the apparent kinetic constant (*k*) based on the $\tau_{1/2}$ value according to the following equation: $k = \ln([\mathbf{NO}])/(\mathbf{INO}])/\tau_{1/2} = \ln 2/\tau_{1/2}$. To know the initial reaction velocity (ν), we also plotted the concentration of **NO** as a function of reaction time and drew the approximate straight line. The slope of the approximate line indicates the ν value. The logarithm of ν (ln ν) was plotted as a function of logarithm of concentration (ln[**NO**]) (Figure 3).

Supporting Information

Time-course plots of conversion at initial reaction stage, plots of **NO** concentration as a function of reaction time, and ¹H NMR ¹³C NMR, IR, and MALDI-TOF MS spectra are provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: nitrile *N*-oxide • postpolymerization functionalization • thermal isomerization • isocyanate

- a) L. I. Belen'kii, In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, 2nd ed., (Eds.: H. Feuer), Wiley-VCH, New York, **2008**, pp. 1-128.
 b) C. Grundmann, P. Grünanger, *The Nitrile Oxides*, Springer-Verlag, Berlin, **1971**.
- a) Functional Polymers by Post-Polymerization Modification: Concepts, Guidelines and Applications (Eds.: P. Theato, H.-A. Klok), Wiley-VCH, New York, 2012. b) E. Blasco, M. B. Sims, A. S. Goldmann, B. S. Sumerlin, C. Barner-Kowollik, Macromolecules, 2017, 50, 5215-5252. c) M. A. Gauthier, M. I. Gibson, H.-A. Klok, Angew. Chem. 2008, 121, 50-60; Angew. Chem. Int. Ed. 2009, 48, 48-58. d) D. P. Nair, M. Podgórski, S. Chatani, T. Gong, W. Xi, C. R. Fenoli, C. N. Bowman, Chem. Mater. 2014, 26, 724-744. e) A. Das, P. Theato, Chem. Rev. 2016, 116, 1434-1495. f) P. R. Sruthi, S. Anas, J. Polym. Sci. 2020, 58, 1039-1061.g) K. Sada, M. Takeuchi, N. Fujita, M. Numata, S. Shinkai, Chem. Soc. Rev. 2007, 36, 415-435.
- [3] a) Z.-X. Yu, P. Caramella, K. N. Houk, J. Am. Chem. Soc. 2003, 125, 15420-15425. b) T. Takata, Y. Koyama, H. Sogawa, In Click polymerization (Eds.: B. Z. Tang, A. Qin), Royal Society of Chemistry, Cambridge, 2018, pp. 122-166.
- [4] a) Y.-G. Lee, M. Yonekawa, Y. Koyama, T. Takata, *Macromolecules*. 2010, 43, 4070-4080. b) T. Matsumura, Y. Koyama, S. Uchida, M. Yonekawa, T. Yui, O. Ishitani, T. Takata, *Polym. J.*, 2014, 46, 609-616. c) T. Tsutsuba, H. Sogawa, S. Kuwata, T. Takata, *Chem. Lett.* 2017, 46, 315-318.
- a) Y. Koyama, K. Miura, S. Cheawchan, A. Seo, T. Takata, *Chem. Commun.* **2012**, *48*, 10304-10306. b) S. Cheawchan, Y. Koyama, S. Uchida, T. Takata, *Polymer.* **2013**, *54*, 4501-4510.
- [6] a) C.-G. Wang, Y. Koyama, M. Yonekawa, S. Uchida, T. Takata, *Chem. Commun.* 2013, 49, 7723-7725. b) C.-G. Wang, Y. Koyama, S. Uchida, T. Takata, *ACS Macro Lett.* 2014, *3*, 286-290. c) T. Tsutsuba, H. Sogawa, T. Takata, *Polym. Chem.* 2017, 8, 1445-1448.
- [7] C. Grundmann, P. Kochs, Angew. Chem. 1970, 82, 637-638; Angew. Chem. Int. Ed. 1970, 9, 635-635.
- [8] C. Grundmann, P. Koch, J. R. Boal, Justus Liebigs Ann. Chem. 1972, 761, 162-181.
- [9] G. A. Taylor, J. Chem. Soc. Perkin Trans. I. 1985, 1181-1184.
- [10] a) O. García, E. Nicolás, F. Albericio, *Tetrahedron Lett.* 2003, 44, 4961-4963.
 b) A. Rieche, H. Gross, E. Hoft, *Chem. Ber.* 1960, 93, 88-94.
- [11] J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Tetrahedron Lett.* 2003, 44, 3555-3558.
- [12] See, supporting information.
- [13] Molecular Rearrangements in Organic Synthesis (English Edition), (Ed.: C. M. Rojas), Wiley, New York, 2015.
- [14] The reaction rate for the formation of furazan *N*-oxides exhibits the opposite trend as substituent effects, see: G. Barbaro, A. Battaglia, A. Dondoni, *J. Chem. Soc.* (b). **1970**, 588-592.
- [15] F. de Sarlo, A. Guarna, A. Brandi, P. Mascagni, *Gazz. Chim. Ital.* 1980, 110, 341-344.
- [16] W. R. Mitchell, R. M. Pato, J. Chem. Res. 1984, 58-59.
- [17] C. Hansch, A. Leo, W. Taft, Chem. Rev. 1991, 91, 165-195.
- [18] C. Costentin, M. Robert, S. Drouet, G. Passard, J.-M. Saveant, A. Tatin, *PCT Int. Appl.* 2015, WO 2015169763 A1.
- [19] Y. Koyama, Y.-G. Lee, S. Kuroki, T. Takata, *Tetrahedron Lett.* 2015, 56, 7038-7042.

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Entry for the Table of Contents

Nitrile N-Oxides



Thermal isomerization of nitrile *N*-oxide (**NO**) gives isocyanate. However, the reaction mechanism for the isomerization has not been systematically evaluated. Herein, we report the concentration-dependent isomerization of **NO**s for the first time. The time-course plots indicate that the isomerization of **NO** would be driven by a very small amount of polymeric intermediate generated *in situ* in a substituent-dependent equilibrium.