

Nucleophilic Substitution Reactions of Phenyl Y-Substituted-Phenyl Carbonates with Butane-2,3-dione Monoximate and 4-Chlorophenoxide: Origin of the α -Effect

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Second-order rate constants have been measured spectrophotometrically for the reactions of phenyl Y-substituted-phenyl carbonates **7a-g** with butane-2,3-dione monoximate (Ox^-) in 80 mol % H_2O /20 mol % DMSO at 25.0 ± 0.1 °C. The α -nucleophile Ox^- is 53-95 times more reactive than the corresponding normal-nucleophile 4-ClPhO $^-$ toward **7a-g**, indicating that the α -effect is operative. The magnitude of the α -effect (e.g., the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio) is independent of the electronic nature of the substituent Y. The cause of the α -effect for the reactions of **7a-g** has been suggested to be ground-state (GS) effect rather than transition-state (TS) stabilization through a six-membered cyclic TS, in which Ox^- behaves a general acid/base catalyst. This idea is further supported by the result that OH^- exhibits negative deviation from the linear Brønsted-type plot composed of a series of aryloxides, while Ox^- deviates positively from the linearity. Differential solvation of the GS of Ox^- and 4-ClPhO $^-$ has been suggested to be responsible for the α -effect exerted by Ox^- .

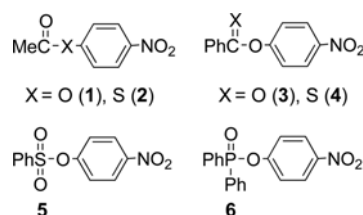
Key Words : The α -Effect, Transition-state stabilization, Solvent effect, Concerted mechanism, Rate-determining step

Introduction

A certain group of nucleophiles has been reported to exhibit abnormally enhanced reactivity than would be expected from their basicity.¹ A common feature of these nucleophiles is possession of one or more nonbonding electron pairs at the atom α to the nucleophilic center. Thus, the term α -effect was given to the enhanced reactivity shown by α -nucleophiles.¹ Numerous studies have been performed to investigate the origin of the α -effect since this phenomenon was brought to light by Edwards and Pearson in 1962.²⁻¹⁴ The most popular theories suggested as the origin of the α -effect include destabilization of the ground state (GS), stabilization of the transition state (TS), thermodynamic stabilization of products, and solvent effects.²⁻¹⁴

However, none of these theories can fully account for the α -effect phenomenon. Particularly, solvent effects on the α -effect are controversial. DePuy *et al.* found that HOO^- does not exhibit any enhanced reactivity in gas-phase reactions of methyl formate with HOO^- and HO^- .^{11b} Accordingly, the α -effect observed for the reactions with HOO^- in H_2O was attributed to a solvent effect. This was further supported by the report that HOO^- is 12 kcal/mol less strongly solvated than HO^- in H_2O .¹⁵ On the contrary, solvent effect has been suggested to be unimportant on the basis of the observation that the magnitude of the α -effect is similar for reactions performed in H_2O and in neat organic solvents such as MeCN and toluene.⁷ Besides, α -nucleophiles have been reported to be intrinsically more reactive than normal nucleophiles of similar basicity (e.g., HOO^- vs MeO^-) in gas-phase reactions with methyl formate.¹² Recent theoretical calculations have also shown that α -nucleophiles exhibit lower activation energies than normal nucleophiles of similar basicity in gas-

phase $\text{S}_{\text{N}}2$ reactions, implying that solvent effect on the α -effect is unimportant.^{13,14}



We have shown that solvent effect on the α -effect is significant for nucleophilic substitution reactions of various substrates (e.g., **1-6**) with butane-2,3-dione monoximate (Ox^- , α -nucleophile) and 4-chlorophenoxide (4-ClPhO $^-$, normal nucleophile) in DMSO- H_2O or MeCN- H_2O mixtures of varying compositions.³⁻⁵ Our first study on the reactions of 4-nitrophenyl acetate (**1**) with Ox^- and 4-ClPhO $^-$ has demonstrated that the α -effect ($k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$) increases with increasing DMSO content in the reaction medium up to ca. 50 mol % DMSO and then decreases thereafter, i.e., a bell-shaped profile (Figure 1, ○),^{3c} while the α -effect for the corresponding reactions of 4-nitrophenyl thioacetate (**2**) increases up to 30-40 mol % DMSO and then remains constant beyond that point (Figure not shown).^{4c} In contrast, the α -effect for the reactions of **1** with Ox^- and 4-ClPhO $^-$ performed in MeCN- H_2O mixtures increases continuously as the MeCN content in the medium increases (Figure 1, ●).^{5c}

Bell-shaped α -effect profiles have also been reported for the reactions of 4-nitrophenyl benzoate (**3**), *O*-4-nitrophenyl thionobenzoates (**4**), 4-nitrophenyl benzenesulfonate (**5**), and 4-nitrophenyl diphenylphosphinate (**6**), although the magnitude of the α -effect was found to be strongly depen-

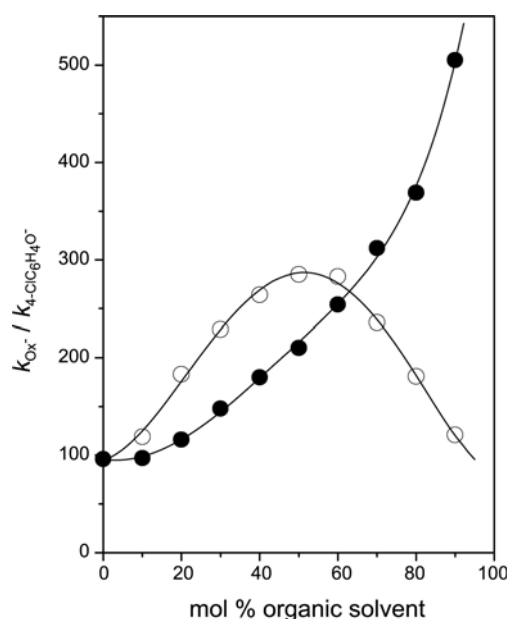
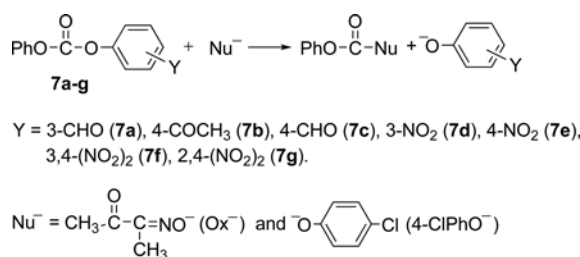


Figure 1. Plots showing medium effects on the α -effect for the reactions of 4-nitrophenyl acetate **1** with Ox^- and 4-ClPhO $^-$ in DMSO-H $_2$ O (○) and in MeCN-H $_2$ O (●) mixtures of varying compositions at 25.0 ± 0.1 °C. Kinetic data were taken from refs 3(e) and 5(c).



Scheme 1

dent on the nature of the electrophilic centers (C=O, C=S, SO $_2$ and P=O).³⁻⁵ Such solvent dependent α -effects clearly suggest that solvent effect on the α -effect is indeed an important factor for the α -effect.

We have now carried out nucleophilic substitution reactions of phenyl Y-substituted-phenyl carbonates **7a-g** with Ox^- in 80 mol % H $_2$ O/20 mol % DMSO (Scheme 1). The kinetic data have been compared with those reported previously for the reactions of **7a-g** with a series of Z-substituted-phenoxide to investigate the origin of the α -effect.

Results and Discussion

All reactions in this study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{\text{obsd}}t + C$. The plots of k_{obsd} vs $[\text{Ox}^-]$ were linear and passed through the origin, indicating that the contribution of H $_2$ O and/or OH $^-$ from hydrolysis of Ox^- to k_{obsd} is negligible. Thus, the rate law can be expressed as Eq. (1) and the second-order rate constants (k_{Ox^-}) were calculated from the slope of the linear plots of k_{obsd} vs $[\text{Ox}^-]$. The correlation coefficient for the linear

Table 1. Summary of Second-Order Rate Constants for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates (**7a-g**) with Butane-2,3-dione Monoximate (Ox^-) and 4-Chlorophenoxide (4-ClPhO $^-$) in 80 mol % H $_2$ O/20 mol % DMSO at 25.0 ± 0.1 °C^a

Entry	Y	$k_{\text{Ox}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{4\text{-ClPhO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$
7a	3-CHO	155	2.00	77.5
7b	4-COCH $_3$	372	5.43	68.5
7c	4-CHO	609	9.35	65.1
7d	3-NO $_2$	897	9.47	94.7
7e	4-NO $_2$	1390	25.9	53.7
7f	3,4-(NO $_2$) $_2$	14700	276	53.3
7g	2,4-(NO $_2$) $_2$	8060	131	61.5

^aThe kinetic data for the reactions with 4-ClPhO $^-$ were taken from ref 16.

regression was usually higher than 0.9995. The uncertainty in the k_{Ox^-} values is estimated to be less than $\pm 3\%$ from replicate runs. The k_{Ox^-} values calculated in this study are summarized in Table 1 together with the $k_{4\text{-ClPhO}^-}$ values reported previously for the corresponding reactions with 4-ClPhO $^-$ to calculate the magnitude of the α -effect.

$$\text{Rate} = k_{\text{obsd}}[\mathbf{7a-g}], \text{ where } k_{\text{obsd}} = k_{\text{Ox}^-}[\text{Ox}^-] \quad (1)$$

Effect of Substituent Y on Reactivity and Reaction Mechanism. As shown in Table 1, the second-order rate constant for the reactions of **7a-g** with Ox^- increases as the substituent Y in the leaving aryloxy becomes a stronger electron-withdrawing group (EWG) except **7g**, e.g., the k_{Ox^-} for the reactions with Ox^- increases from $155 \text{ M}^{-1}\text{s}^{-1}$ to 897 and $14700 \text{ M}^{-1}\text{s}^{-1}$ as the substituent Y changes from 3-CHO to 3-NO $_2$ and 3,4-(NO $_2$) $_2$, in turn. A similar result is shown for the reactions with 4-ClPhO $^-$, although $k_{4\text{-ClPhO}^-}$ is 53-95 times smaller than k_{Ox^-} . It is also noted that substrate **7g** is less reactive than **7f** although the former possesses a less basic leaving group than the latter. Similar results were reported for reactions of 2,4-dinitrophenyl and 3,4-dinitrophenyl benzoates with piperidine¹⁷ and for those of diaryl carbonates with quinuclidine.¹⁸ In all cases the substrates possessing 2,4-dinitro group were reported to be less reactive than those bearing 3,4-dinitro group. Gresser and Jencks have suggested that the steric hindrance exerted by 2-NO $_2$ is responsible for the fact that the substrate possessing 2,4-dinitro group is less reactive than that bearing 3,4-dinitro group.¹⁸

Hammett plots correlated with σ^0 and σ^- constants have often been used to deduce reaction mechanisms, especially to investigate whether the leaving-group departure occurs in the rate-determining step (RDS) or after the RDS. However, we have recently shown that the Yukawa-Tsuno plot is much better than the Hammett plots correlated with σ^0 and σ^- constants in studying the reaction mechanism for various acyl-group transfer reactions.¹⁹ In fact, the Hammett plots correlated with σ^0 or σ^- constants for the reactions of **7a-f** with Ox^- and 4-ClPhO $^-$ resulted in highly scattered points (e.g., $R^2 = 0.963$, Figure not shown). Accordingly, Yukawa-Tsuno plots have been constructed. As shown in Figure 2, the Yukawa-Tsuno plots for the reactions of **7a-f** exhibit

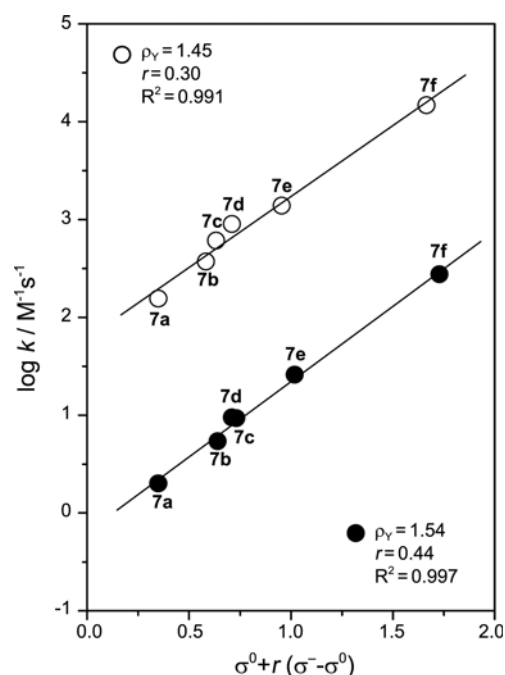


Figure 2. Yukawa-Tsuno plots for the reactions of phenyl Y-substituted-phenyl carbonates (**7a-f**) with Ox^- (○) and 4-ClPhO^- (●) in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

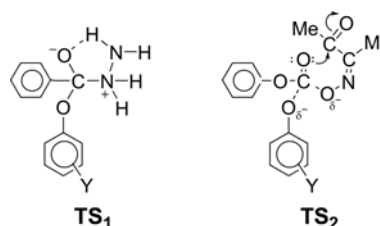
good linear correlations ($R^2 = 0.991$ or 0.997) with $\rho_Y = 1.45$ and $r = 0.30$ for the reactions with Ox^- while $\rho_Y = 1.54$ and $r = 0.44$ for the reactions with 4-ClPhO^- .

The r value in the Yukawa-Tsuno equation (Eq. 2) represents the resonance demand of the reaction center or the extent of resonance contribution between the reaction site and the substituent.^{20,21} The r value of 0.30 or 0.44 shown in Figure 2 clearly indicates that a partial negative charge develops on the O atom of the leaving aryloxy in the TS, which can be delocalized on the substituent Y through resonance interactions. Thus, one can suggest that breakdown of the C–OAr bond occurs in the RDS and that the degree of bond rupture is more advanced for the reactions with 4-ClPhO^- than for those with Ox^- on the basis of the magnitude of the r values.

$$\log k_Y/k_H = \rho_Y (\sigma^0 + r (\sigma^- - \sigma^0)) \quad (2)$$

It is apparent that breakdown of the C–OAr bond should occur after the RDS if the reactions of **7a-f** proceed through a stepwise mechanism. This is because the incoming Ox^- and 4-ClPhO^- are more basic and poorer nucleofuges than the leaving Y-substituted-phenoxide. Thus, no negative charge would develop on the O atom of the leaving group in the rate-determining TS, if the reaction proceeds through a stepwise mechanism. The fact that $r = 0.30$ or 0.44 implies that a partial negative charge develops on the O atom of the leaving aryloxy in the TS. This is only possible for reactions in which breakdown of the C–OAr bond is involved in the RDS. Accordingly, one can conclude that the reactions of **7a-f** with Ox^- and 4-ClPhO^- proceed through a concerted mechanism.

Origin of the α -Effect: TS Stabilization vs GS Destabilization. TS stabilization through TS_1 , in which hydrazine stabilizes the TS (or the intermediate) through intramolecular H-bonding interactions in the 5-membered cyclic TS, has been suggested to be a cause of the α -effect found for the reactions of aryl benzoates with hydrazine.²² Such an intramolecular H-bonding interaction in TS_1 would be influenced by the electronic nature of the substituent Y in the leaving aryloxy. This idea can be supported by the report that the magnitude of the α -effect for the reactions of Y-substituted-phenyl benzoates with hydrazine increases linearly as the substituent Y becomes a weaker EWG.²²



A similar TS structure is possible for the reactions of **7a-g** with Ox^- (*i.e.*, TS_2 , in which Ox^- behaves as a general acid/base catalyst through a six-membered cyclic TS). It is evident that the electronic nature of the substituent Y could affect the charge polarization of the C=O bond of **7a-g**. Thus, if the reactions with Ox^- proceed through TS_2 , the electronic nature of the substituent Y should influence the stability of TS_2 and the magnitude of the α -effect (*i.e.*, the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio). As shown in Table 1, Ox^- is 53–95 times more reactive than 4-ClPhO^- . However, the magnitude of the α -effect exhibits no correlation with the electronic nature of the substituent Y. Thus, one can suggest that the α -effect exerted by Ox^- in the current reactions is not due to TS stabilization through TS_2 .

It has often been reported that HOO^- is significantly more reactive than OH^- (*i.e.*, the α -effect), although the former is *ca.* 4 pK_a units less basic than the latter. Destabilization of the ground state (GS) of HOO^- was suggested as an origin of the α -effect, since HOO^- was reported to be 12 kcal/mol less strongly solvated than OH^- in H_2O .¹⁵ Similarly, our calorimetric study has previously shown that Ox^- is 5.7 kcal/mol less strongly solvated than 4-ClPhO^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO, the reaction medium employed in this study.^{3f} Since Ox^- and 4-ClPhO^- are used as an α -nucleophile and the corresponding normal-nucleophile, the difference in solvation energy between the two nucleophiles is kept constant at 5.7 kcal/mol in the reaction medium throughout the reactions of **7a-g**. Thus, if the origin of the α -effect for the reactions with Ox^- is solvent effect rather than TS stabilization through TS_2 , the magnitude of the α -effect is expected to be nearly constant regardless of the electronic nature of the substituent Y. On the contrary, if stabilization of TS_2 is responsible for the α -effect in the current system, the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio should be dependent on the electronic nature of the substituent Y. In fact, as mentioned above, the magnitude of the α -effect (*i.e.*, $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$) is independent of the substituent Y. Thus, one can propose that the α -effect found

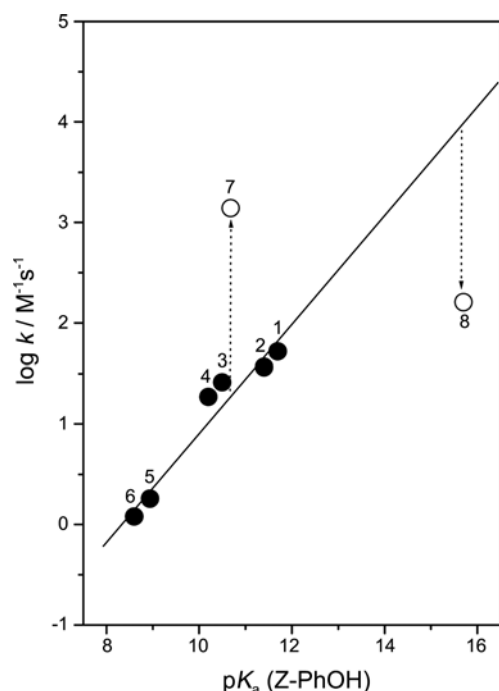
Table 2. Summary of Second-Order Rate Constants for the Reactions of 4-Nitrophenyl Phenyl Carbonate **7e** with Z-Substituted-Phenoxides, Ox^- , and OH^- in 80 mol % H_2O /20 mol % DMSO at $25.0 \pm 0.1^\circ\text{C}$

Entry	Z	pK_a (Z-PhOH)	$k_{\text{Z-PhO}^-}/\text{M}^{-1}\text{s}^{-1}$
1	4-Me	11.7 ^a	52.0 ^b
2	H	11.3 ^a	36.5 ^b
3	4-Cl	10.5 ^a	25.9 ^b
4	3-Cl	10.2 ^a	18.6 ^b
5	4-COMe	8.94 ^a	1.80 ^b
6	4-CN	8.60 ^a	1.20 ^b
7	Ox^-	10.68 ^a	1390
8	OH^-	15.7	160 ^c

^aThe pK_a data were taken from ref 23. ^{b,c}The kinetic data were taken from refs 16 and 24, respectively.

in this study is mainly due to solvent effect.

To examine the above argument that the solvent effect is the main factor to determine the α -effect in this study, a Brønsted-type plot has been constructed using the kinetic data in Table 2 for the reactions of **7e** with a series of aryloxides, Ox^- , and OH^- . As shown in Figure 3, OH^- exhibits negative deviation from the linear Brønsted-type plot composed of the aryloxides, while Ox^- deviates positively from the linearity. One can suggest that the positive and negative deviation shown by Ox^- and OH^- is not due to any difference in the reaction mechanism. This is because the reactions of **7a-f** with Ox^- and 4-ClPhO⁻ have been concluded to proceed through a concerted mechanism on the basis of the linear

**Figure 3.** Brønsted-type plot for the reactions of 4-nitrophenyl phenyl carbonate **7e** with Z-substituted phenoxides, Ox^- , and OH^- in 80 mol % H_2O /20 mol % DMSO at $25.0 \pm 0.1^\circ\text{C}$. The identity of points is given in Table 2.

Yukawa-Tsuno plots (Figure 2). Besides, the corresponding reactions with OH^- were also reported to proceed through a concerted pathway.^{24b} Thus, it is proposed that the positive deviation shown by Ox^- is due to solvent effect as discussed above (e.g., Ox^- is 5.7 kcal/mol less strongly solvated than 4-ClPhO⁻ in 80 mol % H_2O /20 mol % DMSO), while the negative deviation shown by OH^- is due to the strong solvation of the highly basic OH^- in H_2O . Thus, one can conclude that solvent effect is more important than TS stabilization through TS_2 for the α -effect shown by Ox^- in this study.

Conclusions

The current study has allowed us to conclude the following: (1) 2,4-Dinitrophenyl phenyl carbonate (**7g**) is less reactive than 3,4-dinitrophenyl phenyl carbonate (**7f**), although the former possesses a less basic leaving group than the latter. (2) The fact that the Yukawa-Tsuno plots exhibit excellent linear correlations with $r = 0.30$ – 0.44 suggests that the reactions of **7a-f** with Ox^- and 4-ClPhO⁻ proceed through a concerted mechanism. (3) Ox^- is 53–95 times more reactive than 4-ClPhO⁻ toward substrates **7a-g**. However, the magnitude of the α -effect is independent of the electronic nature of the substituent Y. (4) Ox^- deviates positively from the linear Brønsted-type plot composed of aryloxides, while OH^- exhibits negative deviation from the linearity. (5) The kinetic results support that the origin of the α -effect in the current study is solvent effect rather than TS stabilization through TS_2 .

Experimental Section

Materials. Phenyl Y-substituted-phenyl carbonates **7a-g** were readily prepared from the reaction of phenyl chloroformate with Y-substituted phenol in anhydrous ether under presence of triethylamine as reported previously.²⁵ DMSO and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. Due to low solubility of **7a-g** in pure water, aqueous DMSO (80 mol % H_2O /20 mol % DMSO) was used as the reaction medium.

Kinetics. The kinetic study was performed using a stopped-flow spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at $25.0 \pm 0.1^\circ\text{C}$. The reactions were followed by monitoring the appearance of Y-substituted phenoxide ion. All the reactions were carried out under pseudo-first-order conditions. All solutions were transferred by gas-tight syringes. Generally, the Ox^- concentration was varied over the range $(5\text{--}100) \times 10^{-3}\text{ M}$, while the substrate concentration was *ca.* $4 \times 10^{-5}\text{ M}$. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{\text{obsd}}t + C$. The plots of $\ln(A_\infty - A_t)$ vs. time were linear over 90% of the total reaction. Usually, five different Ox^- concentrations were employed and replicate values of k_{obsd} were determined to obtain the second-order rate constants (k_{Ox^-}) from the slope of linear plots of k_{obsd} vs. Ox^- concentrations.

Products Analysis. Y-Substituted phenoxide was liberated quantitatively and identified as one of the products in the reaction of **7a-g** by comparison of the UV-vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

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