

Kinetics and Mechanism of the Anilinolysis of Bis(2,6-dimethylphenyl) Chlorophosphate in Dimethyl Sulfoxide

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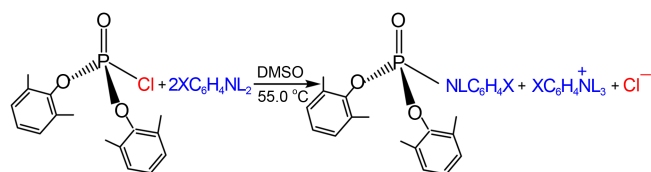
Continuing the kinetic studies of the anilinolyses of diphenyl chlorophosphate derivatives, Y-aryl phenyl [**1**: (C₆H₅O)(YC₆H₄O)P(=O)Cl],¹ Y-aryl 4-chlorophenyl [**2**: (4-ClC₆H₄O)(YC₆H₄O)P(=O)Cl],² and bis(aryl) chlorophosphates [**3**: (YC₆H₄O)₂P(=O)Cl],³ the nucleophilic substitution reactions of bis(2,6-dimethylphenyl) chlorophosphate [**4**: [2,6-(CH₃)₂-C₆H₃O]₂P(=O)Cl] with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in dimethyl sulfoxide (DMSO) at 55.0 ± 0.1 °C (Scheme 1) to gain further information into the substituent effects, steric effects, and deuterium kinetic isotope effects (DKIEs) on the reactivity and anilinolysis mechanism. The numbering of the substrates of **1-4** follows the sequence of the size of the two ligands, R₁O and R₂O.

Results and Discussion

The observed pseudo-first-order rate constants (k_{obsd}) were found to follow eq. (1) for all of the reactions under pseudo-first-order conditions with a large excess of aniline nucleophile. The k_0 values were negligible ($k_0 \approx 0$) in DMSO. The second-order rate constants ($k_{\text{H(D)}}$) were determined for at least five concentrations of anilines. The linear plots of eq. (1) suggest that there is no base-catalysis or noticeable side reaction and that the overall reaction is described by Scheme 1.

$$k_{\text{obsd}} = k_0 + k_{\text{H(D)}} [\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)] \quad (1)$$

The k_{H} and k_{D} values are summarized in Table 1, together with the DKIEs ($k_{\text{H}}/k_{\text{D}}$) and the Hammett ρ_{X} and Brønsted β_{X} selectivity parameters. The β_{X} values listed in Table 1 seem to be less reliable since the $\text{p}K_{\text{a}}$ values used are not those determined in DMSO, but rather in water. Using the



L=H or D
X=4-MeO, 4-Me, 3-Me, H, 4-F, 3-MeO, 4-Cl, 3-Cl

Scheme 1. The studied reaction system.

$\text{p}K_{\text{a}}$ values for the anilinium ions determined in DMSO, an approximate straight line is obtained when they are plotted against those determined in water.⁴ Spillane and coworkers reported that the β_{X} value for the reactions of *N*-phenyl sulfamoyl chloride (PhNHSO₂Cl) with X-anilines in DMSO is similar when determined using the $\text{p}K_{\text{a}}$ values of anilines measured in water ($\beta_{\text{X}} = 0.69$) and DMSO ($\beta_{\text{X}} = 0.62$).⁵ Accordingly, it may be inferred that the β_{X} values in Table 1 are reasonably positive. The $\text{p}K_{\text{a}}$ and σ values of deuterated anilines are assumed to be the same as those of anilines. The $\text{p}K_{\text{a}}(\text{X})$ values of deuterated X-anilines may be slightly greater than those of X-anilines, however, the difference is too small to be taken into account.⁶ Figures 1 and 2 show the Hammett ($\log k_{\text{H(D)}} \text{ vs } \sigma_{\text{X}}$) and Brønsted ($\log k_{\text{H(D)}} \text{ vs } \text{p}K_{\text{a}}(\text{X})$) plots, respectively, for substituent X variations in the nucleophiles. The rate consistently increases with a more electron-donating substituent X in the nucleophile, which is consistent with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom in the transition state (TS). The magnitudes of the ρ_{X} and β_{X} values with the deuterated anilines are slightly greater than those with the anilines, suggesting more sensitive to substituent effects of the deuterated anilines compared to the

Table 1. The Second-Order Rate Constants ($k_{\text{H(D)}} \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$), Selectivity Parameters (ρ_{X} and β_{X}),^a and DKIEs ($k_{\text{H}}/k_{\text{D}}$) of the Reactions of Bis(2,6-dimethylphenyl) Chlorophosphate (**4**) with XC₆H₄NH₂(D₂) in DMSO at 55.0 °C

X	$k_{\text{H}} \times 10^3$	$k_{\text{D}} \times 10^3$	$k_{\text{H}}/k_{\text{D}}$
4-MeO	10.1 ± 0.1 ^b	11.6 ± 0.1	0.871 ± 0.011 ^g
4-Me	8.32 ± 0.01	9.47 ± 0.04	0.879 ± 0.004
3-Me	7.15 ± 0.04	8.05 ± 0.03	0.888 ± 0.006
H	5.98 ± 0.03	6.68 ± 0.01	0.895 ± 0.005
4-F	5.30 ± 0.02	5.89 ± 0.01	0.900 ± 0.004
3-MeO	4.79 ± 0.03	5.32 ± 0.01	0.900 ± 0.006
4-Cl	3.86 ± 0.01	4.25 ± 0.02	0.908 ± 0.005
3-Cl	3.00 ± 0.01	3.28 ± 0.01	0.915 ± 0.004
$-\rho_{\text{X(H,D)}}$	0.83 ± 0.01 ^c	0.87 ± 0.01 ^c	
$\beta_{\text{X(H,D)}}$	0.29 ± 0.02 ^d	0.31 ± 0.02 ^f	

^aThe σ values were taken from ref. 7. The $\text{p}K_{\text{a}}$ values of X-anilines in water were taken from ref. 8. ^bStandard deviation. ^cCorrelation coefficient, $r = 0.999$. ^d $r = 0.993$. ^e $r = 0.999$. ^f $r = 0.993$. ^gStandard error $\{= 1/k_{\text{D}}[(\Delta k_{\text{H}})^2 + (k_{\text{H}}/k_{\text{D}})^2 \times (\Delta k_{\text{D}})^2]^{1/2}\}$ from ref. 9.

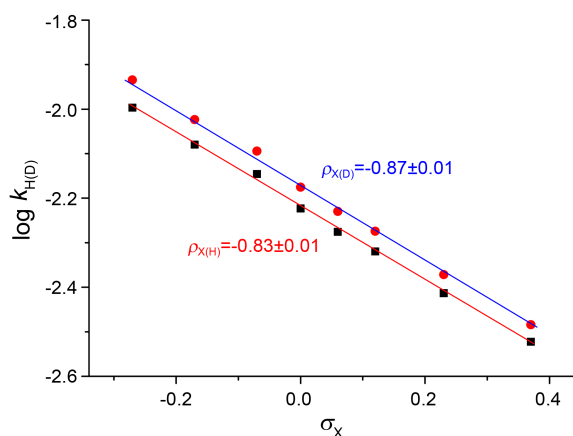


Figure 1. The Hammett plots ($\log k_{\text{H(D)}} \text{ vs } \sigma_{\text{X}}$) of the reactions of bis(2,6-dimethylphenyl) chlorophosphate (**4**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in DMSO at 55.0 °C.

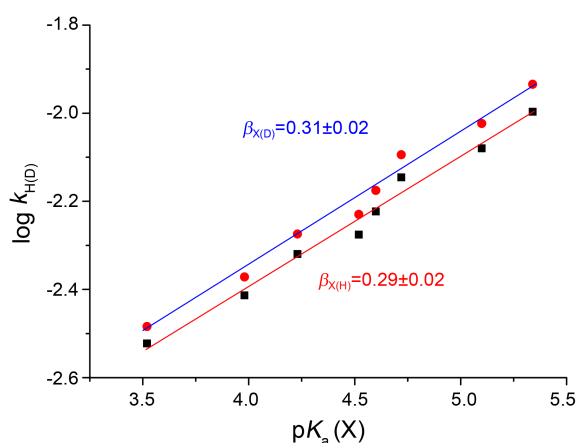


Figure 2. The Brønsted plots [$\log k_{\text{H(D)}} \text{ vs } \text{p}K_{\text{a}}(\text{X})$] of the reactions of bis(2,6-dimethylphenyl) chlorophosphate (**4**) with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in DMSO at 55.0 °C.

anilines. The obtained DKIEs ($k_{\text{H}}/k_{\text{D}}$) are secondary inverse ($k_{\text{H}}/k_{\text{D}} < 1$) and the magnitude of $k_{\text{H}}/k_{\text{D}}$ value increases as the X-aniline becomes weaker.

The employed solvents, second-order rate constants (k_{H}) with unsubstituted aniline at 55.0 °C, Brønsted coefficients ($\beta_{\text{X(H)}}$), $k_{\text{H}}/k_{\text{D}}$ values, variation trends of DKIEs with substituent X, and cross-interaction constants (CICs; ρ_{XY})¹⁰ of the reactions of **1**, **2**, **3**, and **4** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ are summarized in Table 2. The vertical arrows (\uparrow or \downarrow) indicate the direction of the consistent increase of the $k_{\text{H}}/k_{\text{D}}$ values with substituent X in the nucleophiles. The arrow of \uparrow

(substrates **1** and **2**) indicates that the magnitude of the DKIE increases with a stronger nucleophile, while the arrow of \downarrow (substrates **3** and **4**) indicates that the magnitude of the DKIE increases with a weaker nucleophile.

It needs to be stressed that the anilinolysis of **4** has been carried out not in MeCN but in DMSO, since the rate is too slow to obtain the rate constant in MeCN.¹¹ The anilinolysis rate of **2** is slightly faster than that of **1**, $k_{\text{H}}(\mathbf{2})/k_{\text{H}}(\mathbf{1}) = 1.35$ when $\text{Y} = \text{H}$, due to an additional electron-withdrawing substituent, $\text{Y} = 4\text{-Cl}$, in the substrate **2**. Taking into account $k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = 4\text{-Me})/k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = \text{H}) = 0.82$ when $\text{X} = \text{H}$,¹ the inductive effects of the two 2,6-dimethyl substituents on the rate of **4** in MeCN at 55.0 °C can be calculated roughly as follows:¹² (i) assuming that the inductive effects of 4-Me and 2-(and 6)-Me are the same; (ii) assuming that the inductive effects of substituents Y are additive, i.e., no cross-interaction between 2- and 6-Me; (iii) according to the Hammett eq. $\log [k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = 4\text{-Me})/k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = \text{H})] = \rho_{\text{Y}}\sigma_{\text{Y}}$, $\rho_{\text{Y}} = 0.51$ is obtained from $k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = 4\text{-Me}) = 0.730 \times 10^{-3}$, $k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = \text{H}) = 0.891 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, and $\sigma(4\text{-Me}) = -0.17$; (iv) $k_{\text{H}}(\mathbf{4}) = 0.401 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ is obtained from $\log [k_{\text{H}}(\mathbf{4})/k_{\text{H}}(\mathbf{1} \text{ with } \text{Y} = \text{H})] = 0.51(4 \times -0.17)$. As mentioned earlier, however, the anilinolysis rate of **4** cannot be observed due to much slower rate than expected one from the inductive effects of the two 2,6-dimethyl substituents in MeCN.¹¹ This strongly suggests that another factor plays an important role to determine the anilinolysis rate of **4**.

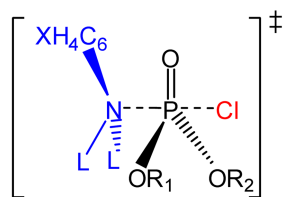
It is known that solvolysis rates of phosphinates [$\text{R}_1\text{R}_2\text{P}(=\text{O})\text{OC}_6\text{H}_4\text{Z}$ -type; R_1 and R_2 are alkyl and/or aryl] are mainly influenced by the steric effects of the substrates over the inductive effects of the ligands, R_1 and R_2 .¹³ The authors also reported that the steric effects of the substrates play an important role to determine the anilinolysis rates of phosphinic chlorides [$\text{R}_1\text{R}_2\text{P}(=\text{O})\text{Cl}$ -type; R_1 and R_2 are alkyl and/or aryl],¹⁴ phosphinates [$\text{R}_1\text{R}_2\text{P}(=\text{O})\text{OC}_6\text{H}_4\text{Z}$ -type; R_1 and R_2 are alkyl and/or aryl],¹⁵ and chlorophosphates [$(\text{R}_1\text{O})(\text{R}_2\text{O})\text{P}(=\text{O})\text{Cl}$ -type; R_1 and R_2 are alkyl and/or aryl].¹⁶ The substrate of **4** has four *ortho*-methyl substituents in the two benzene rings, and the steric hindrance should be much greater than **1** when the aniline attacks the reaction center P atom, resulting in much slower rate than **1**. The anilinolysis rate ($\text{C}_6\text{H}_5\text{NH}_2$) of **4** in DMSO is 6.7 times faster than that of **1** in MeCN at the same temperature of 55.0 °C, indicating that the TS of **4** is considerably polar in DMSO.¹⁷

In the anilinolysis of **1**, a concerted mechanism with a product-like TS was proposed on the basis of a large negative CIC ($\rho_{\text{XY}} = -1.31$) and large secondary inverse DKIEs.¹

Table 2. Summary of Employed Solvents, Second-Order Rate Constants ($k_{\text{H}} \times 10^3/\text{M}^{-1} \text{ s}^{-1}$) with $\text{C}_6\text{H}_5\text{NH}_2$ at 55.0 °C, Brønsted Coefficients ($\beta_{\text{X(H)}}$), DKIEs ($k_{\text{H}}/k_{\text{D}}$), Variation Trends of DKIEs with Substituent X, and CICs of the Reactions of **1**, **2**, **3**, and **4** with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$

Substrate	Solvent	$k_{\text{H}} \times 10^{3a}$	$\beta_{\text{X(H)}}$	$k_{\text{H}}/k_{\text{D}}$	trend	ρ_{XY}	ref
1: $(\text{C}_6\text{H}_5\text{O})(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{O})\text{Cl}$	MeCN	0.891	1.24-1.68	0.61-0.87	\uparrow	-1.31	1
2: $(4\text{-ClC}_6\text{H}_4\text{O})(\text{YC}_6\text{H}_4\text{O})\text{P}(=\text{O})\text{Cl}$	MeCN	1.20	1.43-1.49	0.64-0.87	\uparrow	-0.31	2
3: $(\text{YC}_6\text{H}_4\text{O})_2\text{P}(=\text{O})\text{Cl}$	MeCN	0.891	1.29-1.56	0.55-0.98	\downarrow	+1.91	3
4: $[2,6\text{-}(\text{CH}_3)_2\text{C}_6\text{H}_3\text{O}]_2\text{P}(=\text{O})\text{Cl}$	DMSO	5.98	0.29	0.87-0.92	\downarrow	-	this work

^aThe values with unsubstituted aniline ($\text{X} = \text{H}$) and $\text{Y} = \text{H}$ at 55.0 °C. ^bThe values with $\text{Y} = \text{H}$.



Scheme 2. Backside nucleophilic attack TS where L = H or D.

In the anilinolysis of **2**, the proposed mechanism was the same as in **1**, and smaller magnitude of CIC ($\rho_{XY} = -0.31$) compared to **1** was rationalized by partial electron loss towards the electron-acceptor equatorial ligand (4-ClC₆H₄O) in the bipyramidal pentacoordinated TS.² In the anilinolysis of **3**, on the contrary, a stepwise mechanism with a rate-limiting leaving group departure from the intermediate was proposed on the basis of a large positive CIC ($\rho_{XY} = +1.91$).³ Considering the difference between **1** and **3** (**3** has one more identical substituent Y compared to **1**), the change of the reaction mechanism from a concerted (**1**) to a stepwise with rate-limiting bond breaking (**3**) is remarkable, implying the surprising substituent effects on the reaction mechanism. The values of $\beta_{X(H)}$ of **1**, **2**, and **3** are comparable, suggesting that the clarification of the reaction mechanism with the values of β_X is sometimes dangerous. The secondary inverse DKIEs of **1**, **2**, and **3** were substantiated by a backside nucleophilic attack towards the leaving group Cl (Scheme 2), since the N–H(D) vibrations on the aniline are severely hindered so that the frequencies increase substantially in the TS.^{1-3,16,18}

The variation trends of the k_H/k_D values with substituent X of **1** and **2** are the same; the k_H/k_D value becomes smaller as the aniline becomes weaker.^{1,2} This indicates that the degree of bond formation is greater as the aniline becomes weaker: the greater the bond formation, the steric congestion becomes greater, and the k_H/k_D value becomes smaller.¹⁸ Taking into account the variations of ρ_X and ρ_Y values with substituent Y and X, respectively, a greater degree of bond formation accompanies the greater degree of bond breaking and the results are in line with $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X = (-)/(+) < 0$.^{1,2} In the anilinolysis of **3**, on the contrary, the k_H/k_D value becomes smaller as the aniline becomes stronger, which means that the degree of bond formation is greater as the aniline becomes stronger. The variation trends of ρ_X and ρ_Y values with substituent Y and X, respectively, are opposite to **1** and **2**, thus, in line with $\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X = (+)/(+) > 0$.^{3,19}

In the present work (**4**), the authors propose a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate involving a backside nucleophilic attack towards the leaving group Cl (Scheme 2) based on the following reasons: (i) the variation trends of the k_H/k_D values with substituent X are the same as in **3** although the ρ_{XY} value is not available; (ii) the k_H/k_D values are less than unity or secondary inverse DKIEs; (iii) great solvent effect on the rate due to large charge separation in the TS. The severe steric hindrance of the two 2,6-dimethyl substituents pre-

vents close proximity of aniline to the reaction center P atom. As a result, the considerably small value of $\beta_{X(H)} = 0.29$ (and $\beta_{X(D)} = 0.31$)²⁰ and greater magnitudes of $k_H/k_D = 0.87-0.92$ (i.e., smaller secondary inverse DKIEs) of **4** compared to **1** ($k_H/k_D = 0.61-0.87$), **2** ($k_H/k_D = 0.64-0.87$), and **3** ($k_H/k_D = 0.55-0.98$) are obtained.²¹

In summary, the nucleophilic substitution reactions of bis(2,6-dimethylphenyl) chlorophosphate (**4**) with substituted anilines (XC₆H₄NH₂) and deuterated anilines (XC₆H₄ND₂) are investigated kinetically in dimethyl sulfoxide at 55.0 °C. The anilinolysis rate of **4** is much slower than bisphenyl chlorophosphate (**1**) due to the steric hindrance of four *ortho*-methyl substituents in **4**. The magnitudes of secondary inverse deuterium kinetic isotope effects ($k_H/k_D < 1$) invariably increase as the nucleophiles change from the strongly basic to weakly basic anilines contrary to **1**. A stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate involving a backside nucleophilic attack towards the leaving group Cl is proposed on the basis of the variation trends of the k_H/k_D values with substituent X in the nucleophiles.

Experimental Section

Materials. Bis(2,6-dimethylphenyl)chlorophosphate (97%) was used for kinetic studies without further purification. The GR grade dimethyl sulfoxide was dried over molecular sieves and used after three distillations under reduced pressure prior to use. Anilines were redistilled or recrystallized before use as previously described.¹⁻³ Deuterated anilines were prepared by heating anilines and deuterium oxide (99.9 atom % D) and one drop of HCl as catalyst at 90.0 °C for 72 hr, and after numerous attempts, anilines were deuterated more than 98%, as confirmed by ¹H-NMR.

Kinetic Measurement. Rates were measured conductometrically as previously described.¹⁻³ The concentrations of [substrate] = 3.0×10^{-4} M and [nucleophile] = 0.10-0.30 M were used. Each pseudo-first-order rate constant values were averaged from three separate runs (at least), which were reproducible within $\pm 3\%$.

Product Analysis. Bis(2,6-dimethylphenyl)chlorophosphate was reacted with excess 4-methoxyaniline, for more than 15 half-lives at 55.0 °C in DMSO. The 4-methoxyaniline hydrochloride salt was separated by filtration. The product was separated by solvent extraction process using ethylacetate and water mixture with several attempts. Solvent was removed under reduced pressure. Finally, the product was isolated through column chromatography (30% ethyl acetate/*n*-hexane) after treatment with ether, then dried under reduced pressure using oil diffusion pump. The analytical and spectroscopic data of the product are summarized as follows:

[(C₁₆H₁₈O₂)P(=O)NHC₆H₄(4-OCH₃)]. Fawn crystal solid, mp (157-158) °C; ¹H-NMR (400 MHz, CDCl₃ & TMS) δ 2.18-2.25 (aliphatic, 12H, m), 3.77 (aliphatic, 3H, s), 5.56-5.74 (aliphatic, 1H, m), 6.76-7.07 (aromatic, 10H, m); ¹³C-NMR (100 MHz, CDCl₃ & TMS) δ 17.39 (aliphatic, 4C, s),

55.50 (aliphatic, 1C, s), 114.42-148.46 (aromatic, 18C, m); ^{31}P -NMR (162 MHz, CDCl_3 & TMS) δ -1.61 (1P, s, P=O); m/z , 411 (M⁺); Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_4\text{P}$: C 67.1, H 6.4, N 3.4; Found: C 67.0, H 6.7, N 3.4.

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- The authors tried to obtain the anilinolysis rate of **4** in MeCN even at 75.0 °C (note that the boiling point of MeCN is 81.6 °C), however, the rate is too slow to obtain the second-order rate constant. The polarity of DMSO is greater than that of MeCN; $\Delta\epsilon_r$ (dielectric constant) = 46.45 (DMSO) - 35.94 (MeCN) = 10.51.
- The two assumptions to calculate the rate constant of the anilinolysis of **4** in MeCN at 55.0 °C are not correct. The inductive effect of *para*-position is absolutely different from *ortho*-position and the substituent effects are not additive. However, the rate constant of **4** in MeCN can be approximately obtained from the two assumptions.
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- Taking into account the slow anilinolysis rate of **4** in MeCN, the rate ratio of $k_{\text{H}}(\mathbf{4} \text{ in DMSO})/k_{\text{H}}(\mathbf{1} \text{ in MeCN}) = 6.7$ at the same temperature (55.0 °C) is a great value. This indicates the strong solvent effects on the anilinolysis rate of **4** due to the large charge separation in the TS, since the rate-determining step is bond breaking.
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- See ref. 3 for more detailed discussion.
- In general, it is well known that the β_{X} value for a stepwise mechanism with a rate-limiting bond breaking is greater than that for a concerted mechanism. The anilinolysis rate, DKIEs, and mechanism of **4** are strongly affected by the two 2,6-dimethyl substituents in the substrate.
- The values of $k_{\text{H}}/k_{\text{D}} = 0.87\text{-}0.92$ of **4** is still small (i.e., relatively large secondary inverse DKIEs) with exceptionally small value of $\beta_{\text{X(H)}} = 0.29$.