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Green Chemistry

COMMUNICATION

Zemplén Transesterification: A Name Reaction Having Been Misleading Us for 90 Years

Bo Ren,[a] Meiyan Wang,[b] Jingyao Liu,[b] Jiantao Ge,[a] Xiaoling Zhang[a] and Hai Dong[a],*

We demonstrated that using NaOH and NaOMe in methanol for deacylation are identical, indicating that Zemplén condition has been misleading us for almost 90 years. The traditional base-catalyzed mechanism cannot be used to explain our results. We proposed that H-bond complexes play key roles in the base-catalyzed process, explaining why deacylation in methanol can be catalyzed by hydroxide.

Acyl groups are widely used as protecting groups in organic synthesis strategies, especially in carbohydrate chemistry.[1] With the addition of acylation reagents under mild conditions, the hydroxyl groups of substrates readily form esters as intermediate products, and the esters are easily removed under Zemplén conditions when required.[1-2] For almost 90 years, it has been believed that the regular hydrolysis of an ester using a base such as potassium hydroxide (KOH) or sodium hydroxide (NaOH) requires a stoichiometric amount of base for each ester functional group, and generates a large amount of potassium or sodium acetate, whereas Zemplén deacylation uses only a catalytic amount of sodium methoxide (NaOMe).[2] Today, Zemplén deacylation, performed with a catalytic amount of sodium methoxide in methanol, is a standard tool in laboratories and industry settings.[1] Its inherent disadvantage is the retention in solution of sodium ions. As the sodium ions can be removed using H^{+}-exchanged resin, industrial deacylation techniques normally involve ion-exchanged columns. The H^{+}-exchanged resin can be regenerated with acid after ion exchange. The ion exchange procedure would be omitted from deacylation in laboratories, and especially in industry settings, supposed that the reaction were catalyzed by methoxyl anion resin. At first appearance, it seems impossible due to the difficulty of acquiring methoxyl anion resin. In 1981, Goodman's group found that hydroxyl anion exchanged resin could be used for the catalytic deacylation of sugars in methanol.[3] They believed that the deacylation be catalyzed by methoxyl anion and the methoxyl anion be generated by a series of ion exchanges with the hydroxyl anion at the resin surface. Despite its reported efficiency,[4] this method has unfortunately not been extensively adopted, likely because of the unconvincing explanation.

In this study, we proved that Zemplén condition had been misleading us for almost 90 years. We found that deacylation using a hydroxyl anion base in methanol does not in fact require a stoichiometric amount of base for each ester functional group. The results of our experiments indicate that the use of NaOH in methanol is identical to that of NaOMe in methanol for deacylation. The development of Zemplén condition was based on the tranditional base-catalyzed mechanim which cannot be used to explain our results (Figure **1a**). Therefore, deacylation can be performed with a catalytic amount of hydroxyl anion resin and the resin can be repeatedly reused in the same process after simply filtered. These results cannot be explained by traditional base-catalyzed mechanism. We proposed that H-bond complex play key roles in this base-catalyzed process (Figure **1b**), supported by theoretical studies. An inverse kinetic isotope effect (KIE) may give direct evidences to support the H-bond involved principle. Therefore, the tranditional base-catalyzed principle in textbook might be discarded.
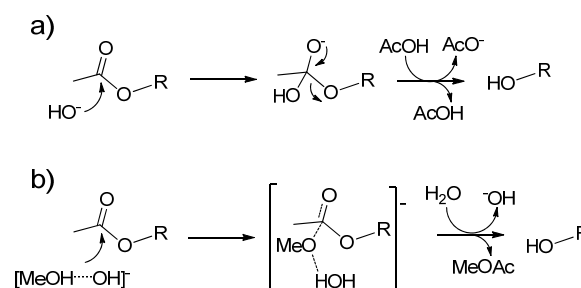

Figure 1. a) Traditional mechanism of deacylation catalyzed by hydroxyl anion. b) Our proposed mechanism of deacylation catalyzed by H-bond complex.

We were surprised to find that the penta-acetyl glucosides were completely deacetylated by 0.1 equiv. of NaOH in methanol. Indeed, only 0.02 equiv. of NaOH was used for each ester functional group of the glucoside. At first, this result seemed impossible due to the preconception that deacylation with NaOH in methanol requires a

stoichiometric amount of base for each ester functional group, and generates a large amount of sodium acetate. To clarify the result, additional experiments were conducted to compare the use of NaOH with that of NaOMe: 0.1, 0.02 and 0.01 equiv. of each of the two bases was used to deacetylate glucoside **1** (entries **1** and **2** in Table **1**). The free glucoses **2** were obtained in quantitative yields in 0.5 h. and 4 h. with the use of 0.1 and 0.02 equiv., respectively, of either NaOH or NaOMe. When the amount of either base was decreased by 0.01 equiv., the deacetylation of glycoside **1** remained incomplete until 24 hours. These results indicate that the use of NaOH in methanol is identical to the use of NaOMe in methanol for the deacylation of glucoside **1**. In the following experiments, various bases including KOH, sodium sulfide (Na$_2$S), potassium sulfide (K$_2$S), sodium carbonate (Na$_2$CO$_3$), potassium carbonate (K$_2$CO$_3$), calcium oxide (CaO) and magnesium oxide (MgO), were used as catalysts (entries **3-9** in Table **1**). The deacetylation of **1** was completed in 0.5 h. with 0.1 equiv. of KOH; in 1 h. with 0.1 equiv. of Na$_2$S and K$_2$S; in 4 h. with 0.1 equiv. of Na$_2$CO$_3$ and K$_2$CO$_3$; and in 8 h. with 0.2 equiv. of CaO. With 0.2 equiv. of MgO, the deacetylation remained incomplete until 24 hours. These results indicate that it is incorrect to assume that deacetylation can only be catalyzed by the methoxyl anion in methanol. Dry methanol has traditionally been used as the solvent on the grounds that any water in the methanol will consume the NaOMe, thereby preventing deacetylation. However, our experiments showed that water has little effect on the deacetylation (entries **10** and **11** in Table **1**). With 0.1 equiv. of NaOH or NaOMe, the deacetylation of **1** was completed in 0.5 h. and 1 h. when the methanol contained 1% and 10% of water, respectively. The deacetylation achieved around 60% completion (observed from TLC plate) even when the methanol contained 50% of water.

Table 1. Deacylation of penta-acetyl glucoside **1** catalyzed by various bases.[a]

Entry	Base	Amount (eq.)	Time/h	Yield[b]
1	NaOMe	0.1	0.5	Quant.
		0.02	4	Quant.
		0.01	24	-[c]
2	NaOH	0.1	0.5	Quant.
		0.02	4	Quant.
		0.01	24	-[c]
3	KOH	0.1	0.5	Quant.
4	Na$_2$S	0.1	1	Quant.
5	K$_2$S	0.1	1	Quant.
6	Na$_2$CO$_3$	0.1	4	Quant.
7	K$_2$CO$_3$	0.1	4	Quant.
8	CaO	0.2	8	Quant.
9	MgO	0.2	24	-[c]
10[d]	NaOMe	1/100	0.5	Quant.
		10/90	1	Quant.
		50/50	24	-[c]
11[d]	NaOH	1/100	0.5	Quant.
		10/90	1	Quant.
		50/50	24	-[c]

[a] Reagents and conditions: substrates (100 mg), MeOH (1 mL), rt.; [b] NMR yield; [c] uncompleted deacylation; [d] bases (0.1 eq.), addition of water (1 - 50%).

Table 2. Deacylation catalyzed by NaOMe, NaOH or ⁻OH-resin.

Entry	Substrate	Product	Yield[e]
1[a,b]	**3a: R = Ac; 3b: R = Bz**	**4**	Quant
2[a,b]	**5**	**2**	Quant
3[a,b]	**6a: R = Ac; 6b: R = Bz**	**7**	Quant
4[a,b]	**8: R$_1$ = OAc, R$_2$ = H** / **9: R$_2$ = OAc, R$_1$ = H**	**10: R$_1$ = OH, R$_2$ = H** / **11: R$_2$ = OH, R$_1$ = H**	Quant
5[a,b]	**12: R$_1$ = OAc, R$_2$ = H** / **13: R$_2$ = OAc, R$_1$ = H**	**14: R$_1$ = OH, R$_2$ = H** / **15: R$_2$ = OH, R$_1$ = H**	Quant
6[a,b]	**16**	**17**	Quant
7[a]	**18**	**11**	Quant
8[a]	**19**	**11**	Quant
9[c]	**20**	**21**	Quant
10[d]	**22**	**23**	Quant

Reagents and conditions: [a] substrates (100 mg), NaOMe or NaOH (0.1 eq.), MeOH (1 mL), rt.; [b] substrates (100 mg), hydroxyl anion resin (85 mg/ 0.1 eq.), MeOH (1 mL), rt.; [c] substrates (100 mg), NaOMe or NaOH (1.1 eq.), MeOH (1 mL), rt.; [d] substrates (100 mg), NaOMe or NaOH (2.1 eq.), MeOH (1 mL), rt.; [e] NMR yield. Isolation yield > 90%.

In the further experiments, various substrates including the penta-acetyl/benzoyl-galactosides **3**, glucosides **5** and mannosides **6**, and the methyl tetra-acetyl α-galactosides **8**, α-glucosides **9**, β-galactosides **12**, β-glucosides **13** and α-mannosides **16**, were deacylated in methanol using 0.1 equiv. of NaOH and NaOMe separately. It showed that (Table **2**), irrespective of whether NaOH or NaOMe was used, the deacetylated free glycosides were obtained from the acetylated substrates in quantitative yields in 2 - 12 h. Additional experiments were conducted to compare the use of NaOH and NaOMe in the deprotection of benzyloxycarbonyl and pivaloyl groups. All of the deprotections were completed in 2 h. In the case of the deacylation of acetylated thio-containing glycosides, a little more than a stoichiometric amount of the base is necessary for each thioacetate group because the sulfhydryl group formed will

neutralize the base. Therefore, 1.1 equiv. and 2.1 equiv. of NaOMe were used in the deacetylation of penta-acetyl 1-thio-glucoside **20** and methyl tetra-acetyl 2,4-dithio-glucoside **22**, producing free thioglucosides in quantitative yields in 2 h, respectively. Testing NaOH with these substrates gave the same results. The results of all of these experiments indicate that the use of NaOH is identical to the use of NaOMe. As the effects on deacylation of using NaOH in methanol and NaOMe in methanol are identical, it is reasonable that hydroxyl anion resin is used in deacylation instead of NaOH. When hydroxyl anion resin was used in the deacylation of each of compounds **3**, **5**, **6**, **8**, **9**, **12**, **13**, **16**, **18** and **19**, all of the deacylations were completed in 2-12 h. As hydroxyl anion resin is a catalyst, we hypothesized that it should be reused repeatedly in this process without time restrictions. To test this assumption, we used hydroxyl anion resin (425 mg, 1 equiv. for the substrate but 0.2 eq. for each of the acetyl groups) to deacetylate penta-acetyl glucoside **1** (100 mg) in 1 mL of methanol with stirring. The first deacetylation was completed in 0.5 h. After filtration, the resin was reused. The second deacetylation was completed in 1 h. With repetition, the deacetylation extended the reaction time to 2, 2.5, 3, 4 and 5 h, until the seventh deacetylation (**a** in Figure **2**). We suspected that tiny chips of hydroxyl anion chipped from the resin surface by stirring had reduced the catalytic activity of the resin. Therefore, no stirring took place in the subsequent experiments, during which deacetylation extended the reaction time from 0.5 to 2 h, with repetition until the 10th deacetylation (**b** in Figure **2**), confirming our conjecture.
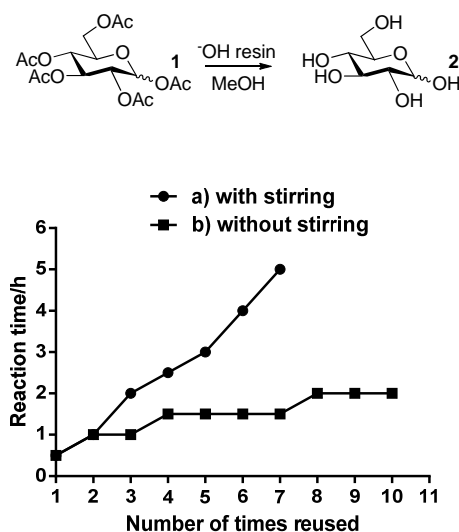

Figure 2. Deacetylation with the repeated reuse of a catalytic amount of $^-$OH-exchange resin.

The process by which hydroxyl anion catalyzes deacylation is of interest. According to the traditional base-catalysis principle (Figure **1a**),[2] there are only two possible reaction paths (Figure **3**). One possibility is the reaction path proposed by Goodman[3] and shown in Figure **3a**: the hydroxyl anion first deprotonates methanol to form the methoxyl anion, followed by deacylation catalyzed by the methoxide formed. If this were the case, the addition of water should restrain the formation of methoxyl anion so as to stop the reaction. Thus, the experimental results of adding water (entries **10** and **11** in Table **1**) proved this path inefficient. The other possibility is shown

in Figure **3b**: deacylation is catalyzed by the hydroxyl anion to form an acetate anion, followed by esterification of methanol with the acetate anion. However, as the esterification of methanol does not occur when sodium acetate is dissolved in methanol, path **b** is also excluded. The above analyses indicate that transesterification catalyzed by hydroxyl cannot be explained by traditional base-catalysis principle.
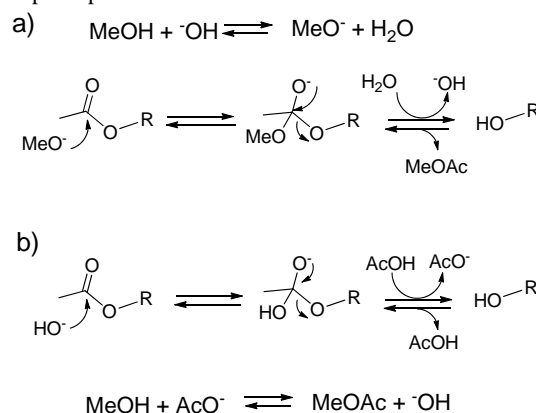

Figure 3. Proposed two possible transesterification paths catalyzed by hydroxide in light of traditional base-catalysis principle.

Recently, a principle that hydrogen bonds between hydroxyl groups and acetate anions involve the constitution of the rate-determining transition state structure in pyridine catalyzed acetylation of hydroxyl groups has been widely accepted with the theoretical chemistry studies on the mechanism.[5] In our previous studies, we have developed new and improved reaction routes where intermolecular non-covalent forces play key roles.[6-8] The mechanism studies also showed that the hydrogen bonds between hydroxyl group and anions play key roles in the intramolecular acetyl group migration[6] and the regioselective acetylation catalyzed by acetate anions[8]. These results inspired us to propound that the H-bonds between hydroxyl groups and anions must also play key roles in deacylation. Only the principle involving H-bond could perfectly explain all our experimental results obtained in this study. Thus, during deacylation catalyzed by NaOMe, an H-bond complex [MeOH······OMe]$^-$ may instantly form when a catalytic amount of NaOMe is dissolved in methanol without considering about solvation (**a** in Figure **4**). Then the acetyl group is transformed into methoxide through transition state **a**. During deacylation catalyzed by NaOH, an H-bond complex [MeOH······OH]$^-$ may instantly form (**b** in Figure **4**). Then it has to be hypothesized that the energy barrier of transition state **b** lower than that of transition state **c** so that the acetyl group can be transformed into methoxide through transition state **b**; otherwise the acetyl group would be transformed into hydroxide through transition state **c** so as to restrain the catalytic process. In order to support this, the theoretical calculations were performed (Figure **S7**). In order to simplify the calculation, the deacetylations of ethyl acetate catalyzed by methoxide and hydroxide in methanol were as models for DFT calculations without considering about solvation. The energy barrier of ethyl acetate with [MeO······H······OMe]$^-$ for transesterification is 19.9 kcal/mol (Figure **4a**). The process with [MeO······H······OH]$^-$ involves two pathways with energy barriers of 18.4 and 21.1 kcal/mol, respectively, giving the former process be preferred (Figure **4b**).
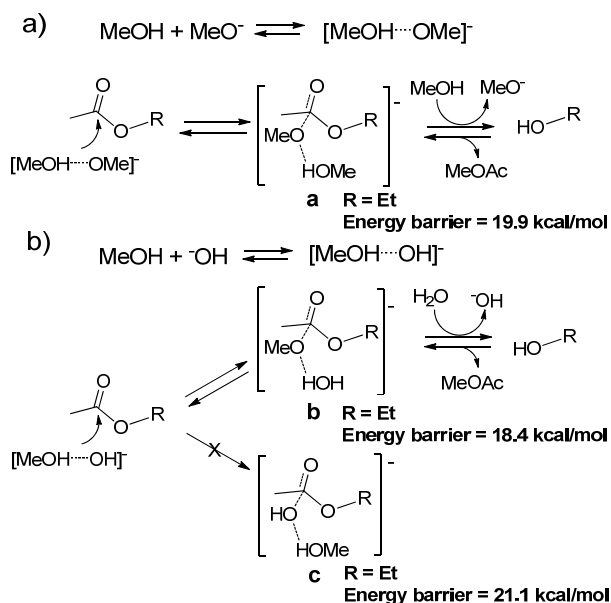
a)

b)

Figure 4. Proposed transesterification paths catalyzed by ⁻OH and MeO⁻ via the H-bond complex.

It is known that an inverse secondary isotope effect would be led when the bending vibration of OH bonds in transition state become more restricted.[9] Clearly, the bending vibration of OH bonds in transition states **a** and **b**, which are the rate-determining transition state structures (Figure **4**), become more restricted due to involving H-bond, thus leading to inverse secondary isotope effects. Thus, an inverse kinetic isotope effect (KIE) may give direct evidences to support the H-bond involved principle. We chose two simple molecules, ethyl benzoate and phenylmethyl acetate, as models, and measured their KIE values through the measurement of their rate constants for deacylation catalyzed separately by NaOH and NaOMe in normal methanol and *d*-methanol (Figure **S1-S4**). For both of the model molecules, the measured KIE values (k_H/k_D) were less than 0.5 (Figure **S3** and **S4**), irrespective of whether NaOH or NaOMe was used, showing inverse secondary isotope effects. The ^{1}H NMR spectrum of deacylation catalyzed by NaOH showed only the esters that functioned as starting materials (ethyl benzoate and phenylmethyl acetate), the esters formed by transesterification (methyl benzoate and methyl acetate) and the alcohols produced (enthanol and phenylmethanol) (Figure **S5** and **S6**). No acids formed by hydrolysis could be seen, indicating that the outcomes of the transesterifications were identical to those of NaOMe-catalyzed deacylation.

In this study, all the yields reported were based on NMR analysis. In order to demonstrate the potential for industry, penta-acetyl-glucoside **1** (10g) were deacylated in methanol (100 mL) using 0.1 equiv. of NaOH (105 mg), KOH (144 mg) and hydroxyl anion resin (8.5 g) separately. After stirring at room temperature for 2 hours (experiments in detail in SI), the free glucoses **2** were obtained in 92% (4.24 g), 97% (4.48 g) and 89% (4.1 g) isolation yields respectively.

Conclusions

We have shown that using NaOH in methanol and using NaOMe in methanol for deacylation are identical. It indicates that the Zemplén condition has been misleading us for almost 90 years and methoxide can be completely replaced by hydroxide in the deacylation. The traditional base-catalyzed mechanism can not be used to explain our results. We proposed that H-bond play key roles in this base-catalyzed process. Both kinetic isotope effect (KIE) studies and theoretical calculations may support this principle. Therefore, hydroxyl anion exchanged resin as a catalyst is used in deacylation instead of NaOMe or NaOH which is fully supported by theory. The resin can be repeatedly reused in the same process without additional treatment. We believe that application of hydroxyl anion in deacylation has great theoretical and practical significance in both laboratory and industry settings. With the use of hydroxyl anion resin in industry, the H⁺-exchange columns in deacylation may be reduced, and substantial savings may be made in terms of equipment, materials and operations.

Notes and references

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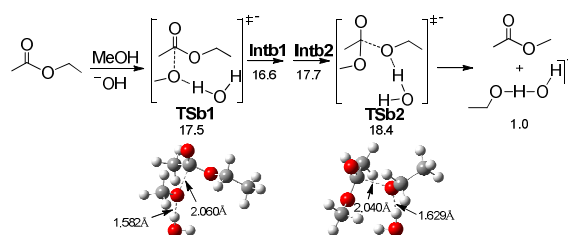
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† Supplementary Information (ESI) available: [General methods, general method for measuring KIE values, Figure S1-S6, computational methods, and Cartesian coordinates, energies and results of frequency calculations]. See DOI: 10.1039/c000000x/

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Table of content:

We demonstrated ⁻OH as deacylation catalyst in methanol, indicating that Zemplén condition had been misleading us for almost 90 years.

Supporting Information

Zemplén Transesterification: A Name Reaction Having Been Misleading Us for 90 Years

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Contents

General methods: All commercially available starting materials and solvents were of reagent grade and used without further purification. Chemical reactions were monitored with thin-layer chromatography using precoated silica gel 60 (0.25 mm thickness) plates (Macherey-Nagel). Flash column chromatography was performed on silica gel 60 (SDS 0.040-0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded at 298K in CDCl$_3$, D$_2$O, CD$_3$OD and d_6-DMSO using the residual signals from CHCl$_3$ (^{1}H: δ = 7.25 ppm; ^{13}C: δ = 77.2 ppm), D$_2$O (^{1}H: δ = 4.80 ppm), CD$_3$OD (^{1}H: δ = 3.31 ppm; ^{13}C: δ = 49.1 ppm) and d_6-DMSO (^{1}H: δ = 2.50 ppm; ^{13}C: δ = 39.5 ppm) as internal standard. ^{1}H peak assignments were made by first order analysis of the spectra, supported by standard ^{1}H-^{1}H correlation spectroscopy (COSY).
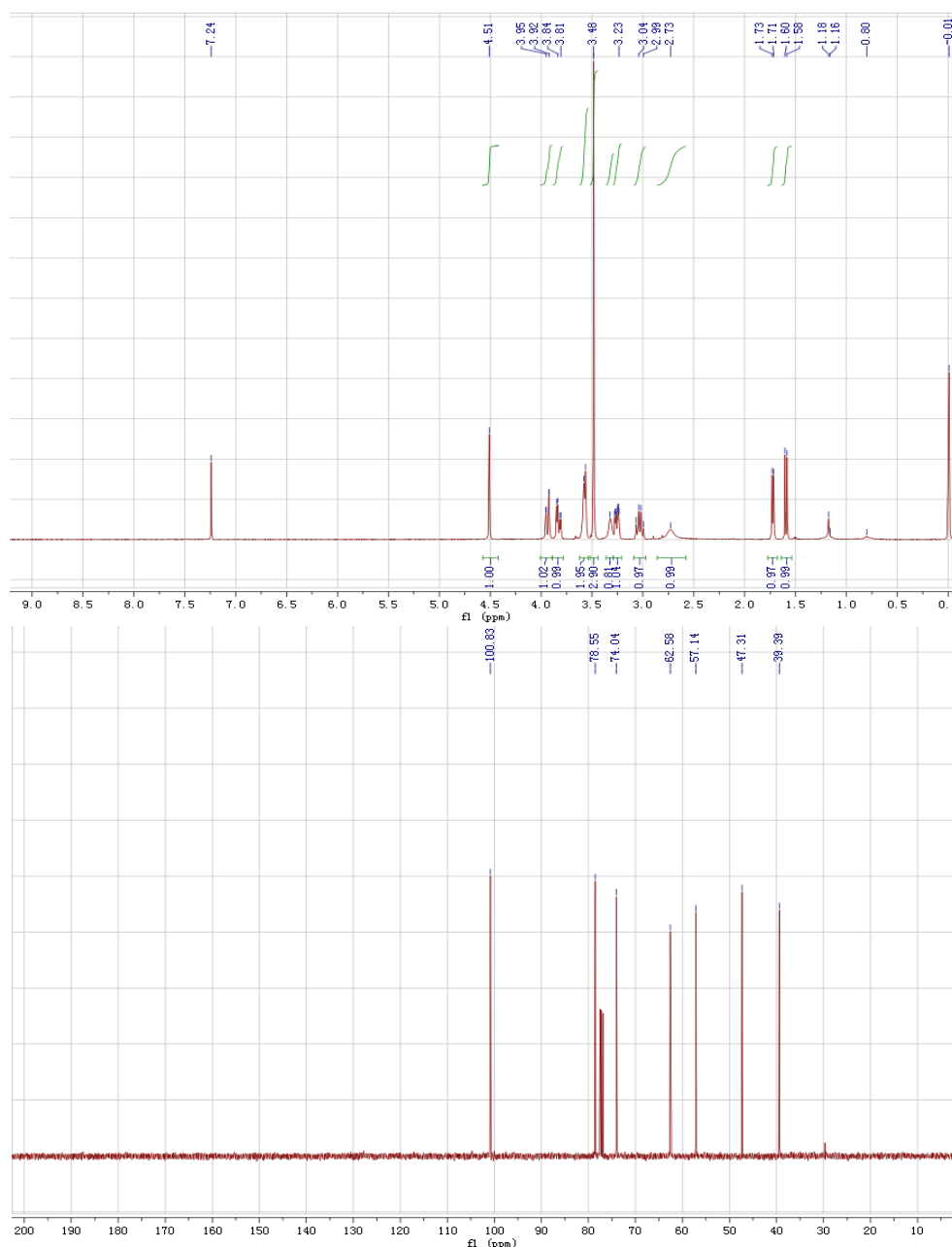
General Deacylation Catalyzed by NaOH or NaOMe: carbohydrate substrates (100 mg) in dry methanol (1 mL) were added NaOH or NaOMe (0.1 eq.). The mixtures were stirred at room temperature for 2 - 12 h, followed by ion exchange with H$^+$ exchanged resin. After being filtered, the filtrate was concentrated to afford the products. All the products **2**, **4**, **7**, **10**, **11**, **14**, **15**, **17** and **21** are known compounds.

General Deacylation Catalyzed by $^-$OH exchanged resin: carbohydrate substrates (100 mg) in dry methanol (1 mL) were added $^-$OH exchanged resin (85 mg). The mixtures were stirred at room temperature for 2 - 12 h. After being filtered, the filtrate was concentrated to afford the products.

Large Scale: penta-acetyl-glucoside **1** (10g) were deacylated in methanol (100 mL) using 0.1 equiv. of NaOH (105 mg), KOH (144 mg) and hydroxyl anion resin (8.5 g) separately. After stirring at room temperature for 2 hours, the reaction mixtures were treated with H$^+$ exchanged resin until neutrality (it is not necessary for reaction mixture with hydroxyl anion resin as a catalyst). After being filtered, the filtrate was concentrated and crystallized. The free glucoses **2** were obtained in 92% (4.24 g), 97% (4.48 g) and 89% (4.1 g) yields respectively.

1-Thio-β-D-mannopyranose 21[1]: Compound **20** (101 mg, 0.25 mmol) was dissolved in 3 mL dry MeOH, and sodium hydroxide (11 mg, 0.27 mmol) in methanol (1 mL) was added dropwise. After 40 minutes, the reaction mixture was neutralized with Amberlite IR-120 H$^+$ ion exchange resin, filtered, concentrated in vacuum, and lyophilized to afford compound **2** (48.5 mg, 99%). ^{1}H NMR (400 MHz, D$_2$O) δ = 5.05 (d, J = 1.0, 1H, H-1), 4.26 (dd, J=1.0 Hz and 3.1 Hz, 1H, H-2), 4.00 (dd, J=2.2 Hz, 12.4 Hz, 1H, H-3), 3.82 (dd, J = 5.9 Hz, 12.4 Hz, 1H, H-6), 3.74 (dd, J = 3.2 Hz, 9.6 Hz 1H, H-6'), 3.69 (t, J = 9.4 Hz, 1H, H-4), 3.57–3.48 (m, 1H, H-5).

Methyl 2,4-thio-β-D-mannopyranoside 23: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 4.51 (s, 1H, H-1), 3.94 (dd, J = 12.2, 2.1, 1H, H-6), 3.83 (dd, J = 4.6 Hz and 12.2 Hz, 1H, H-6'), 3.57 (m, 2H, H-2, H-3), 3.48 (s, 3H, OMe), 3.35 (s, 1H, OH), 3.29–3.21 (m, 1H, H-5), 3.12 – 2.97 (m, 1H, H-4), 2.77 (s, 1H, OH), 1.72 (d, J = 6.3 Hz, 1H, SH), 1.59 (d, J = 8.2 Hz, 1H, SH). ^{13}C NMR (100 MHz, CDCl$_3$) δ = 100.8, 78.6, 74.0, 62.6, 57.1, 47.3, 39.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_7$H$_{14}$O$_4$S$_2$Na 249.0231; found 249.0226.

Comparison of ^{1}H NMR spectrum (H₁ peak) of crude product from deacylation with that of reagent grade sample indicating a quantitative NMR yield: carbohydrate substrates (100 mg) in dry methanol (1 mL) were added NaOH (0.1 eq.). The mixtures were stirred at room temperature for 2, followed by ion exchange with H^+ exchanged resin. After being filtered, the filtrate was concentrated and directly tested by NMR instrument.

Deacylation of compound 3 (tested in D_2O): a) reagent grade sample; b) crude product.
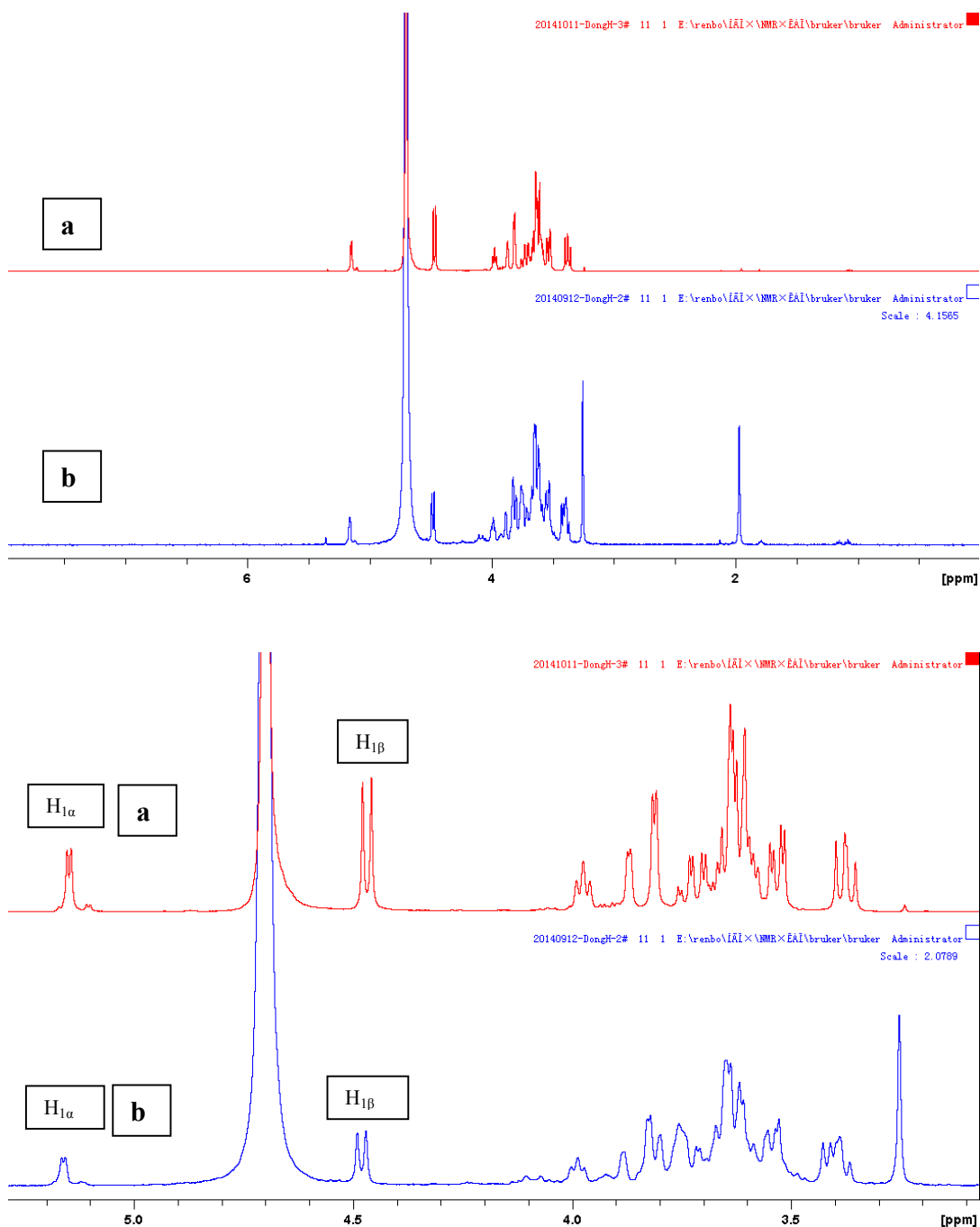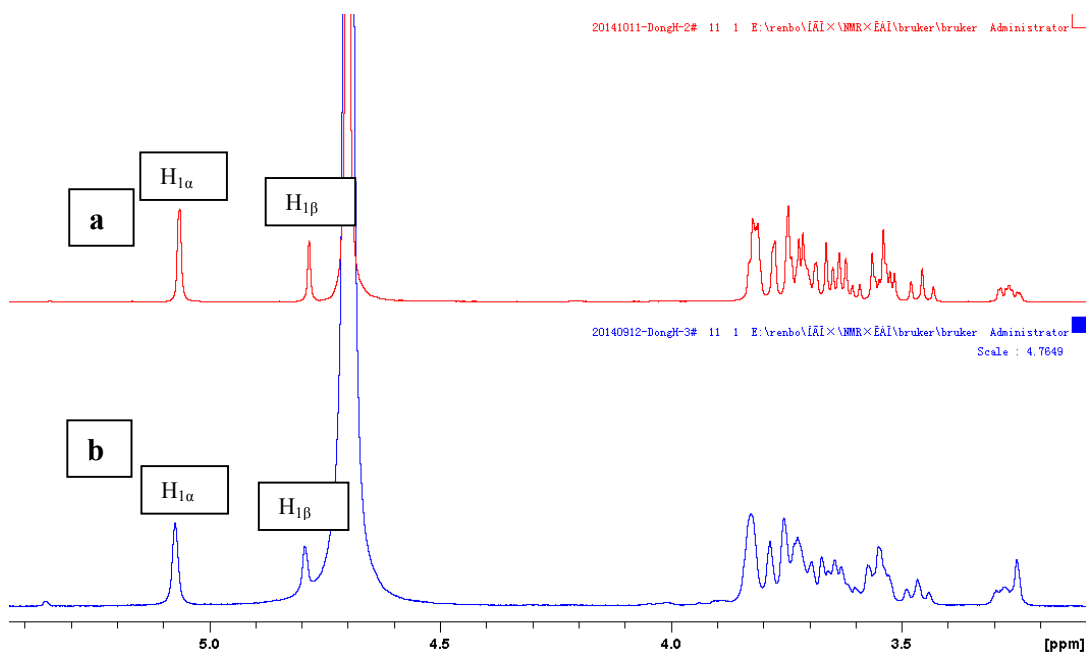
Deacylation of compound 5 (tested in D₂O): a) reagent grade sample; b) crude product.
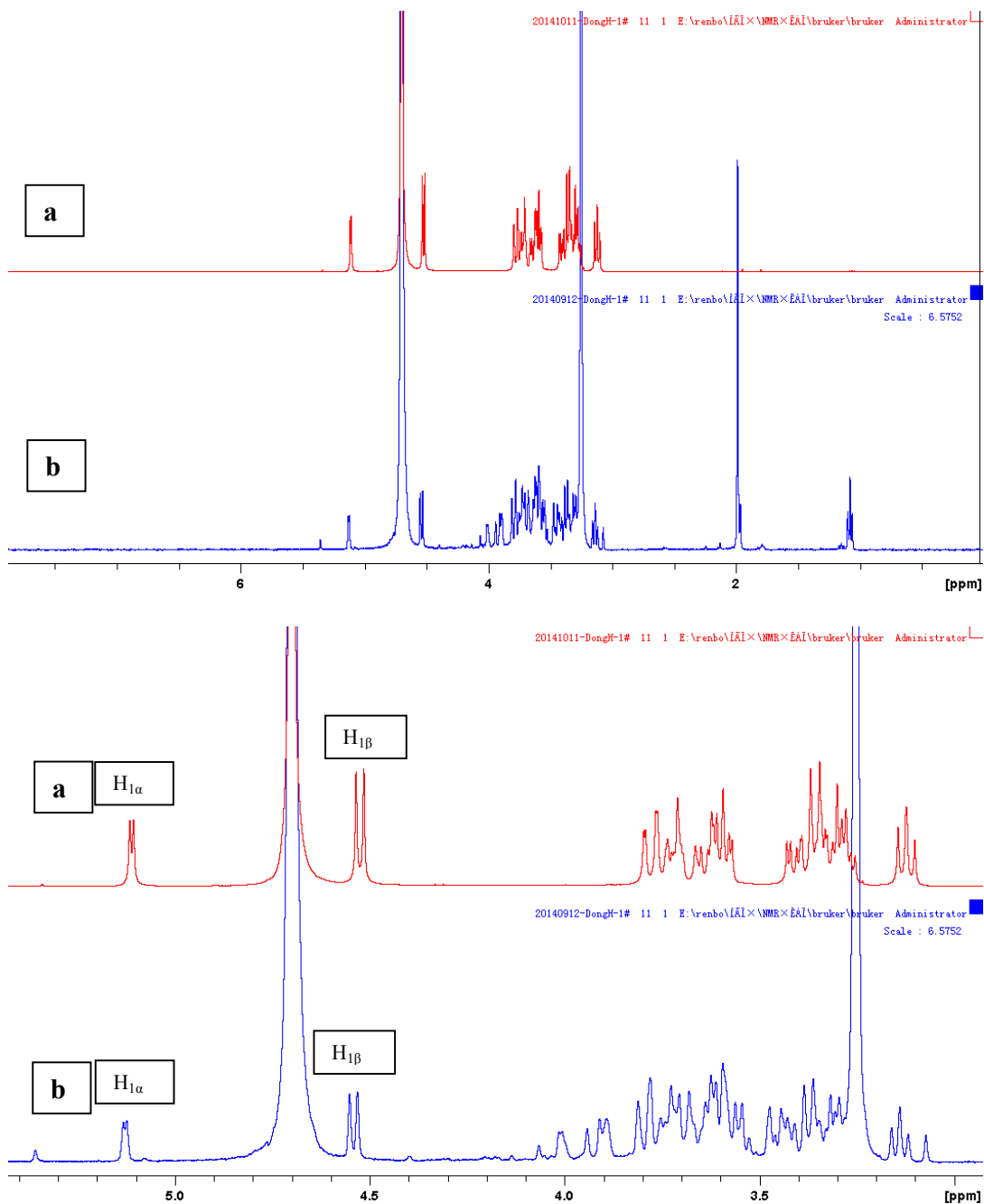
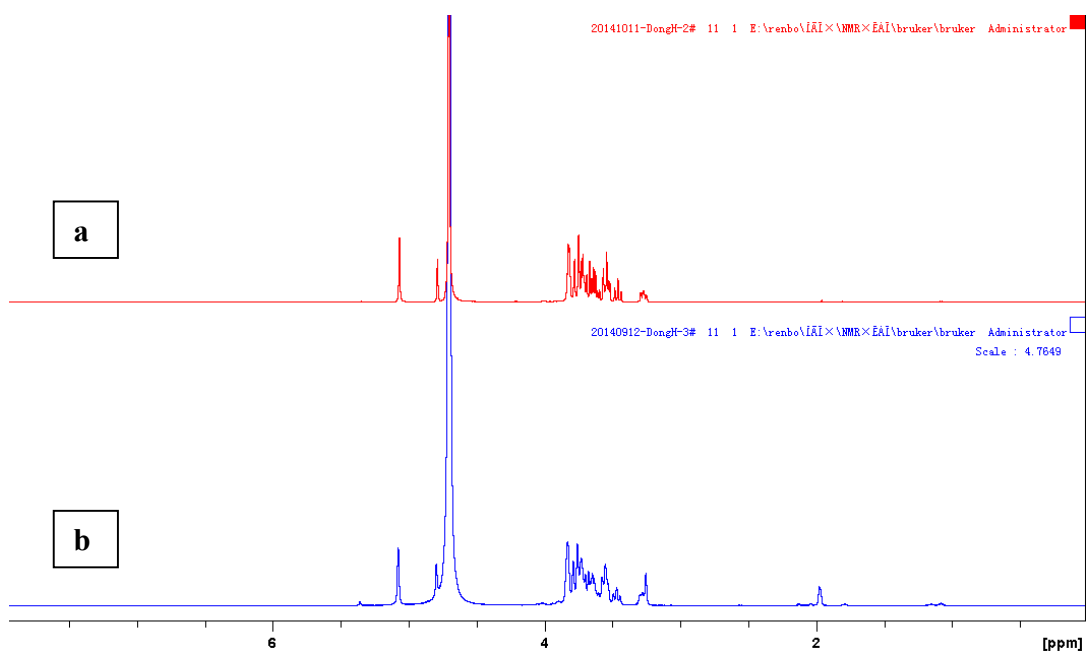**Deacylation of compound 6 (tested in D₂O)**: a) reagent grade sample; b) crude product.

Deacylation of compound 8 (tested in *d₆*-DMSO): a) reagent grade sample with addition of a drop of D_2O; b) reagent grade sample; c) crude product.
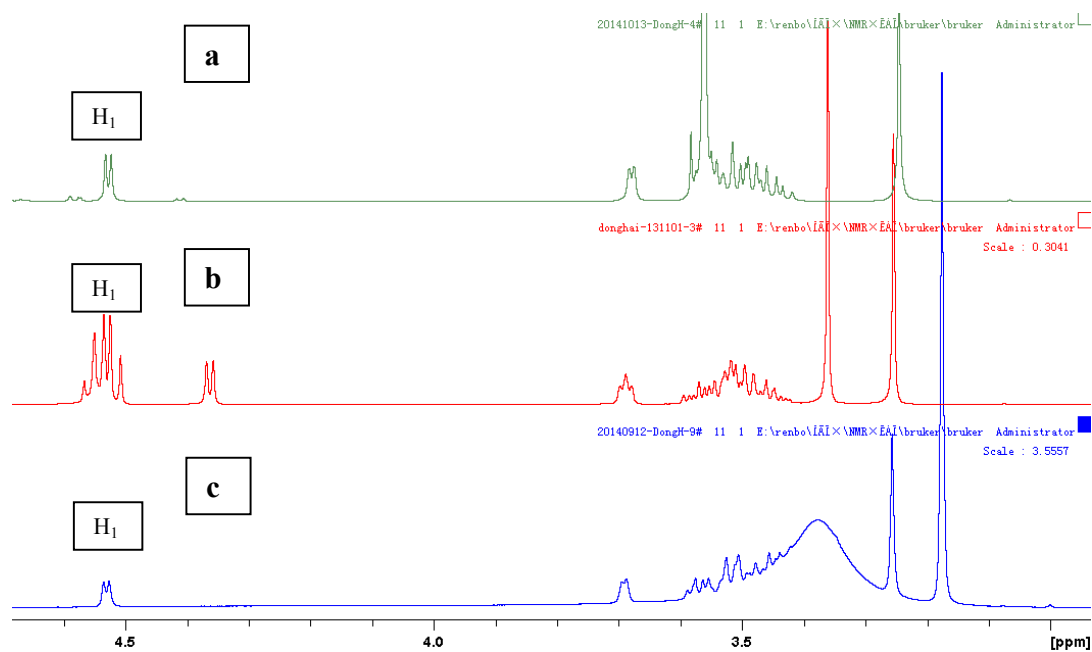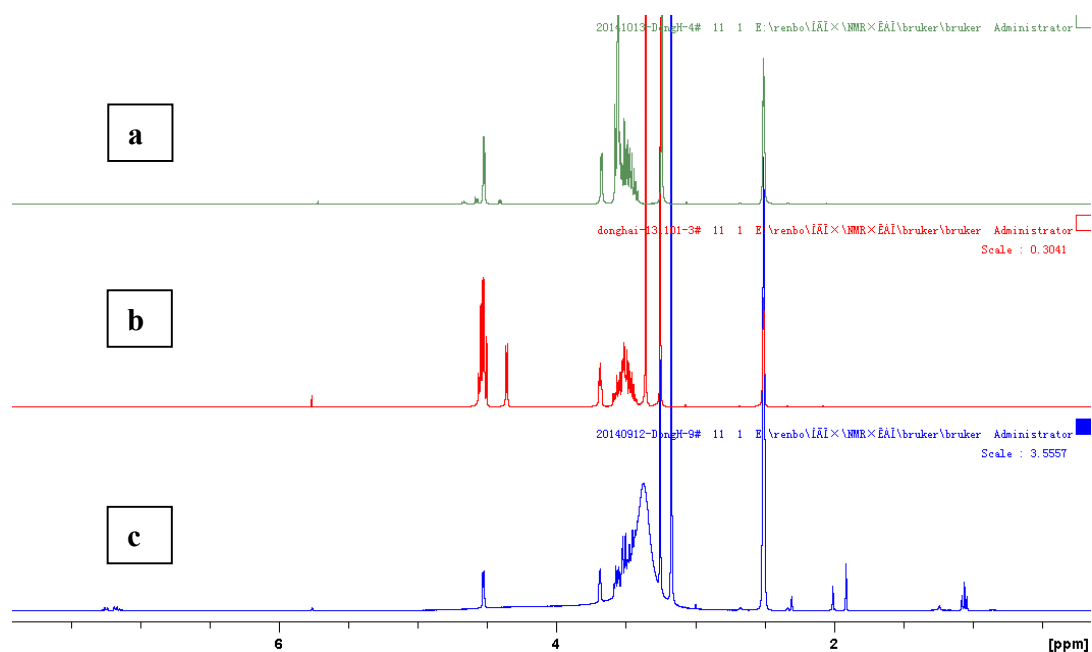
Deacylation of compound 12 (tested in *d₆*-DMSO): a) reagent grade sample with addition of a drop of D_2O; b) reagent grade sample; c) crude product.
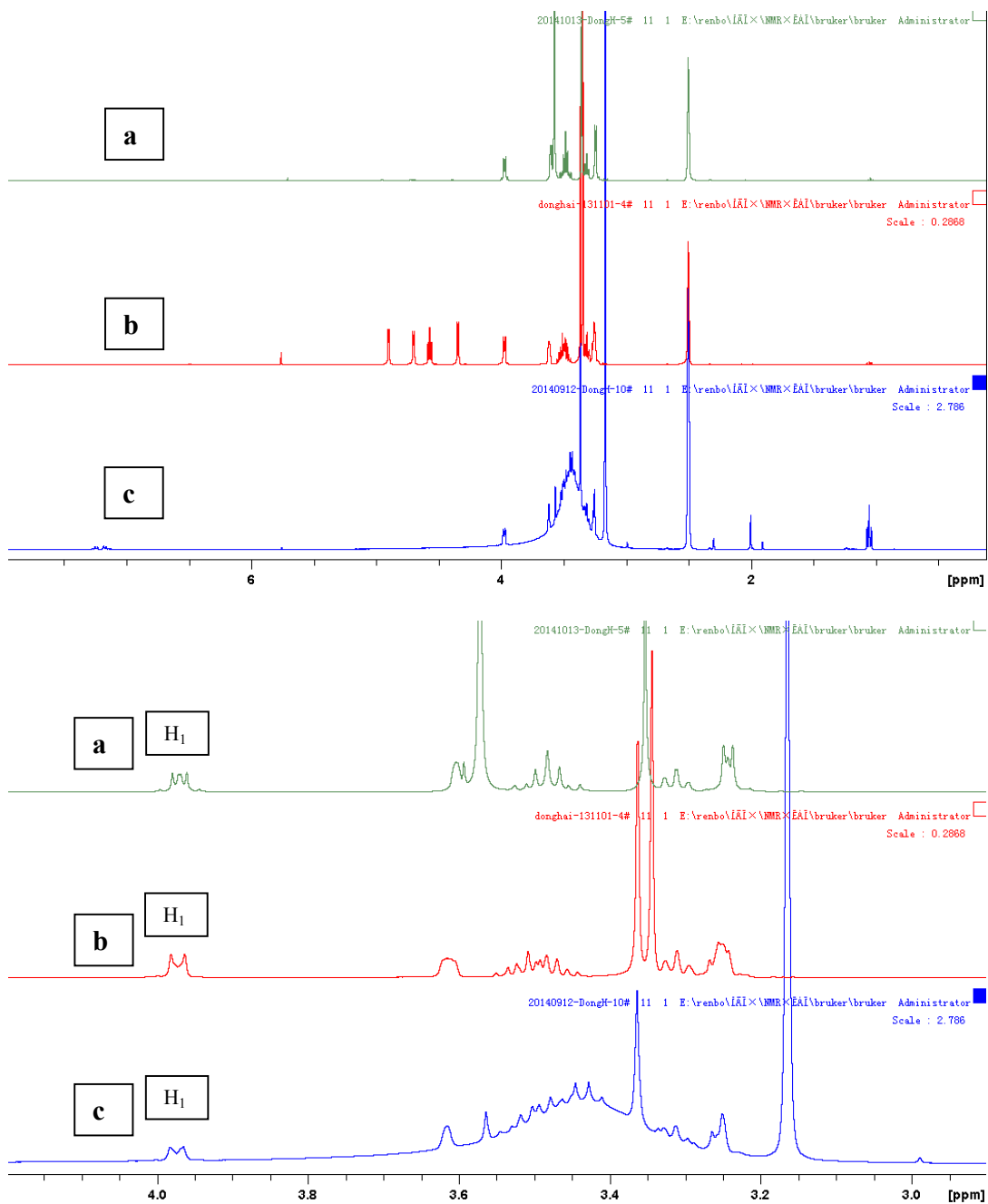
Deacylation of compound 13 (tested in *d₆*-DMSO): a) reagent grade sample with addition of a drop of D_2O; b) reagent grade sample; c) crude product.

S9

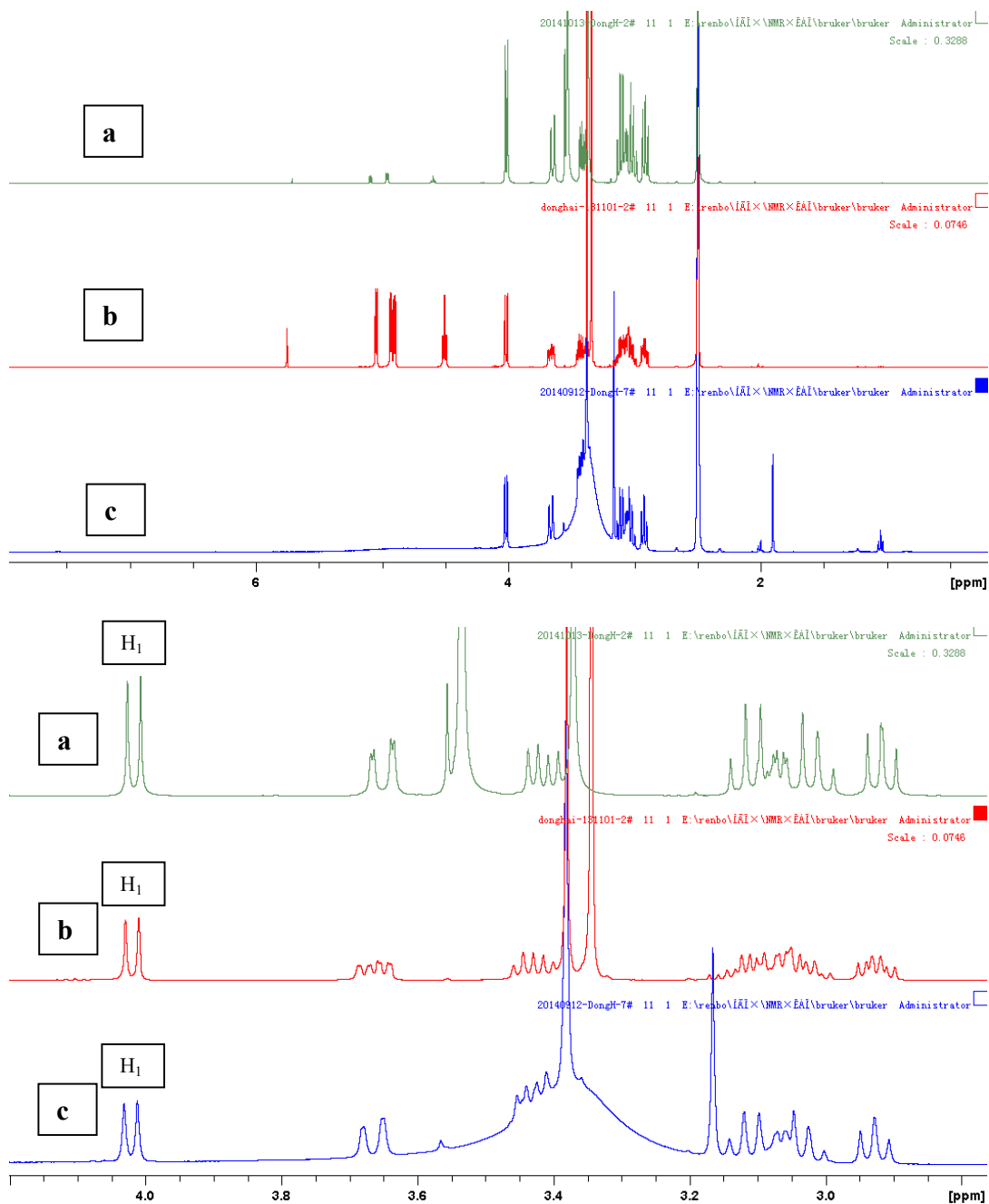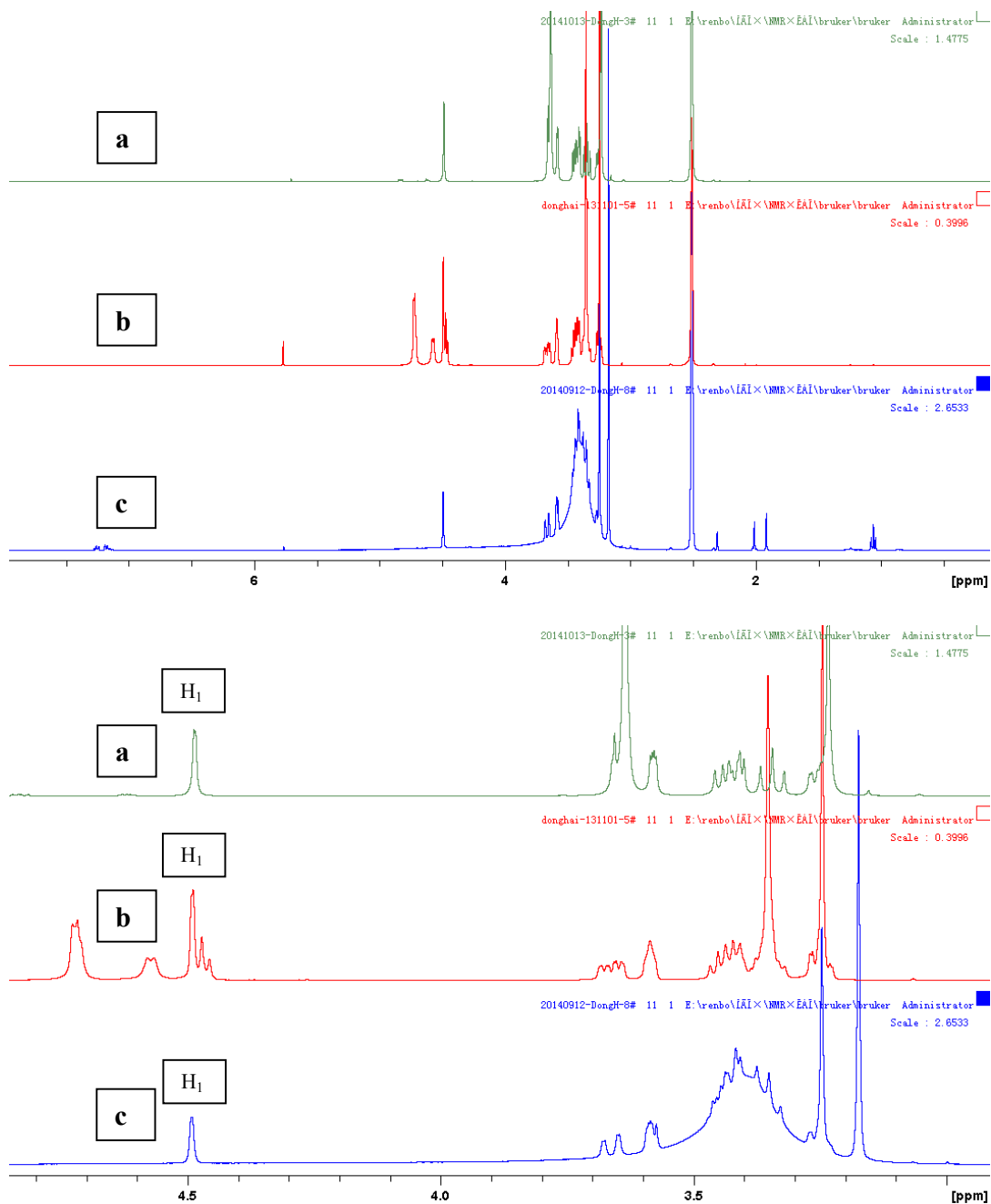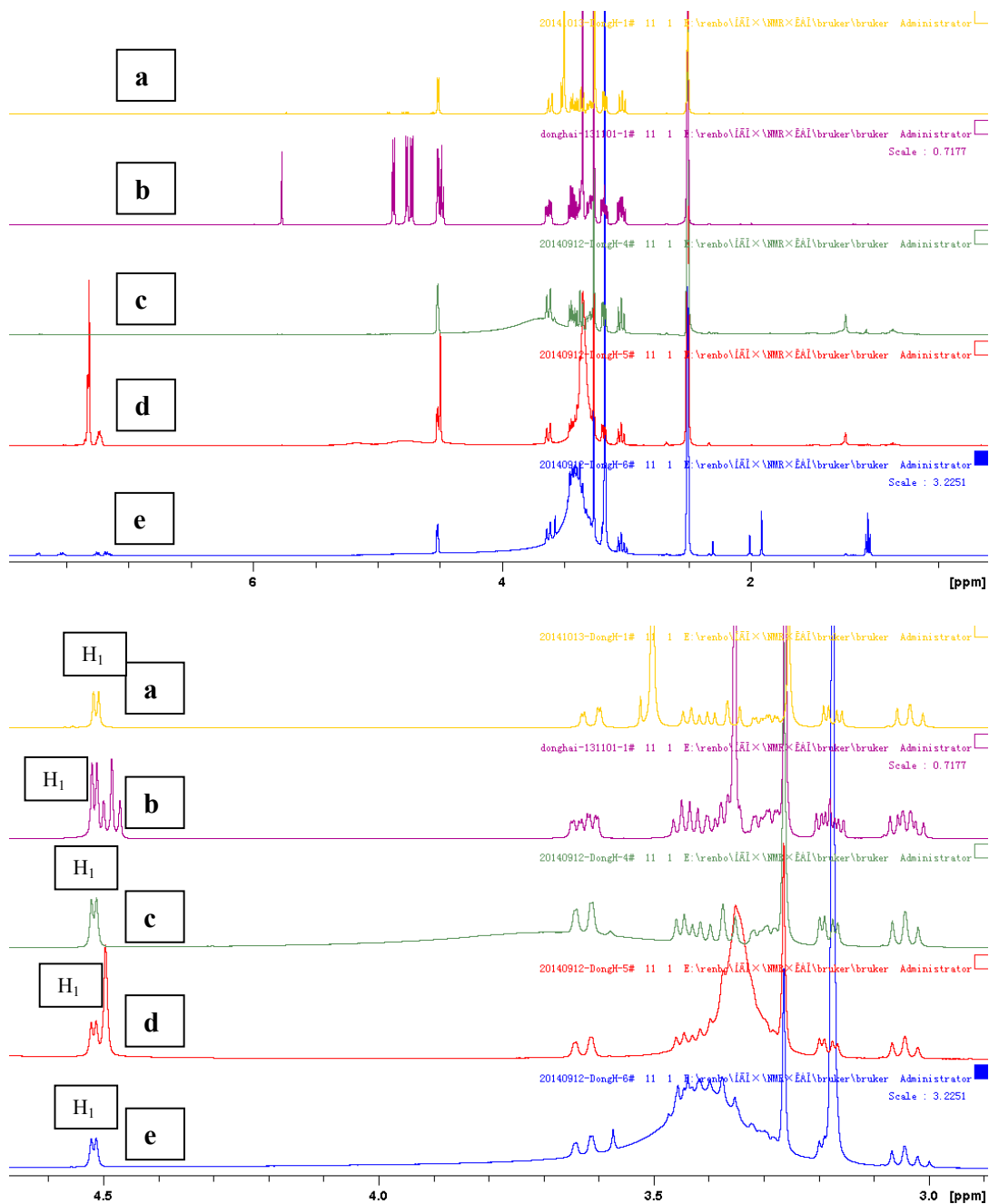**Deacylation of compound 16 (tested in *d₆*-DMSO)**: a) reagent grade sample with addition of a drop of D_2O; b) reagent grade sample; c) crude product.

Deacylation of compound 9, 18 and 19 (tested in d_6-DMSO): a) reagent grade sample with addition of a drop of D_2O; b) reagent grade sample; c) crude product for compound **18**; d) crude product for compound **19**; e) crude product for compound **9**.

General Method for Measuring KIE Value: As step b) is the rate-determining step, the rate constants can be measured using the following equation: $\ln (B_0/B) = k*A*t$, where A stands for the concentration of base catalysts, B stands for the concentration of esters, k stands for the rate constant, and t is the reaction time. The values of B_0/B can be measured over time using 1H NMR tests. In Figure **S1**, A stands for the concentration of the H-bonding complex and X stands for MeO or OH group. As methanol acts as solvent in the reaction, A equals to the concentration of hydroxyl anion or methoxyl anion and is a constant. Therefore, we can get the differential equation (1) which is related to the rate constant k and the concentration of the esters (B). To solve the differential equation (1) gets equation (2). B_0 stands for the initial concentration of the esters in equation (2). Therefore, the value of k can be measured through recording the concentration of the esters (B) with time (t).

$$dB/dt = k*A*B \qquad (1)$$

$$\ln(B/B_0) = k*A*t \qquad (2)$$
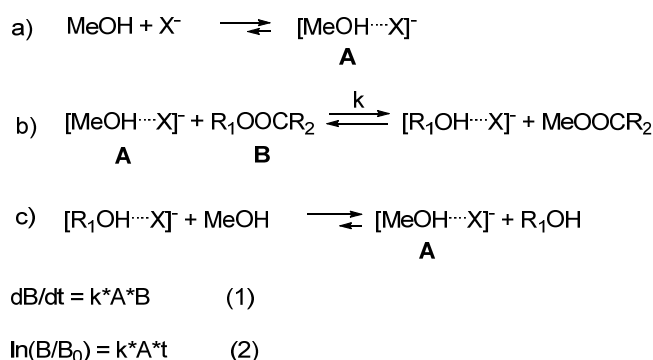
Figure **S1**. The value of k can be measured via recording the concentration of the esters (B) with time (t).
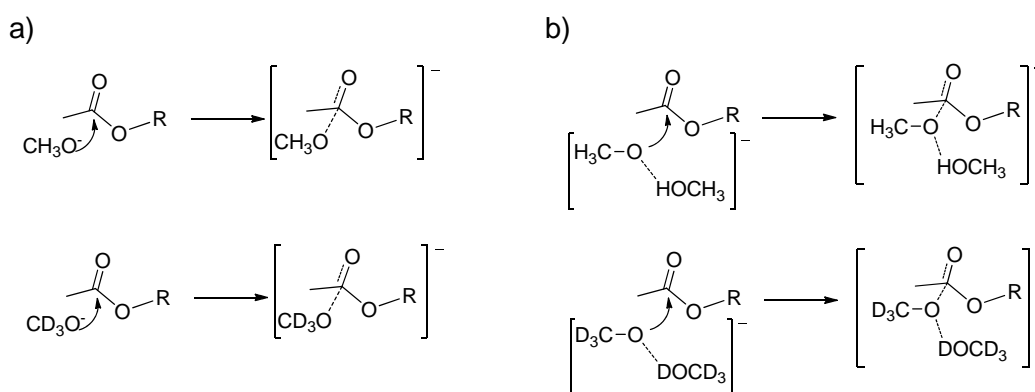
Figure **S2**. Inverse isotope effect supporting H-bond involved transesterification mechanism. a) The traditional base-catalyzed transesterification mechanism should not lead to isotope effect since no hydrogen atom is involved in the reaction. b) The proposed H-bond involved transesterification mechanism should lead to an inverse isotope effect as the case involving conversion of a dicoordinate COH bond to a tricoordinate transition state.

S12
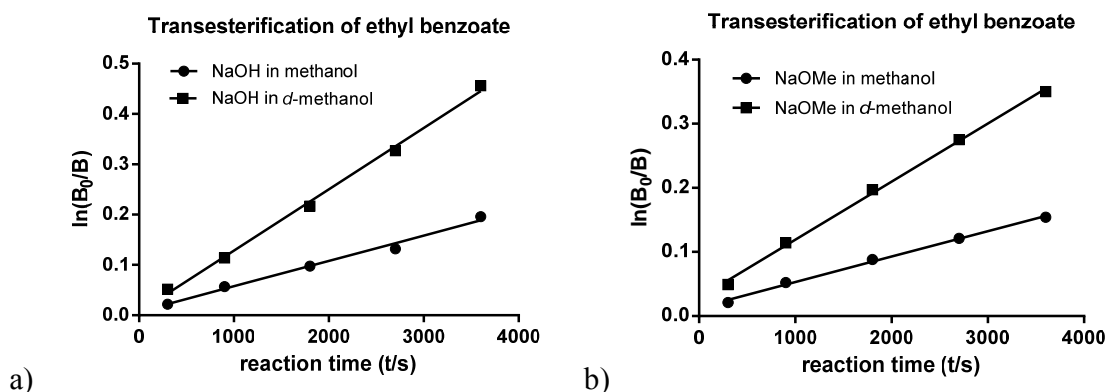
Figure **S3**. The values of k were measured for transesterification of ethyl benzoate in methanol. a) NaOH (0.1 eq.) as catalyst, $k_H*A = 5.035 \times 10^{-5}$/s, $R^2 = 0.9953$, $k_D*A = 1.189 \times 10^{-4}$/s, $R^2 = 0.9963$, therefore, $k_H/k_D = 0.42$; b) NaOMe (0.1 eq.) as catalyst, $k_H*A = 3.971 \times 10^{-5}$/s, $R^2 = 0.9962$, $k_D*A = 9.057 \times 10^{-5}$/s, $R^2 = 0.9980$, therefore, $k_H/k_D = 0.44$.
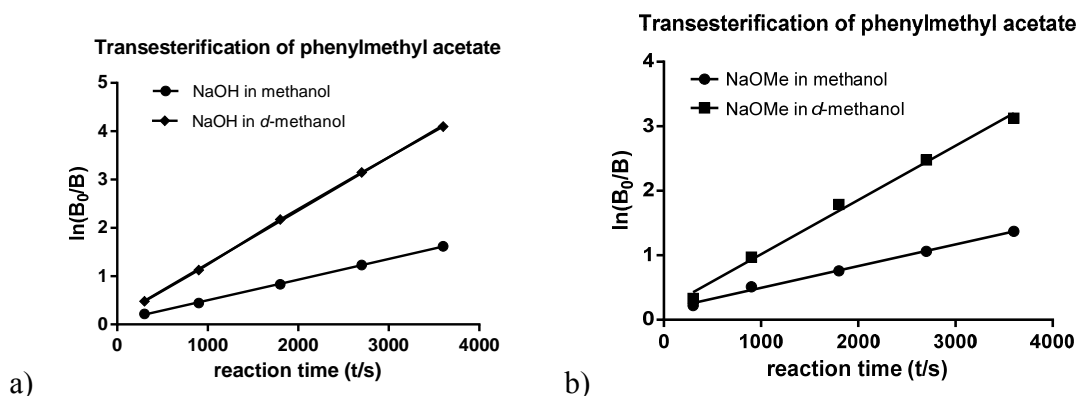
Figure **S4**. The values of k were measured for transesterification of phenylmethyl acetate in methanol. a) NaOH (0.02 eq.) as catalyst, $k_H*A = 4.277 \times 10^{-4}$/s, $R^2 = 0.9995$, $k_D*A = 1.102 \times 10^{-3}$/s, $R^2 = 0.9997$, therefore, $k_H/k_D = 0.39$; b) NaOMe (0.02 eq.) as catalyst, $k_H*A = 3.371 \times 10^{-4}$/s, $R^2 = 0.9952$, $k_D*A = 8.406 \times 10^{-4}$/s, $R^2 = 0.9944$, therefore, $k_H/k_D = 0.40$.
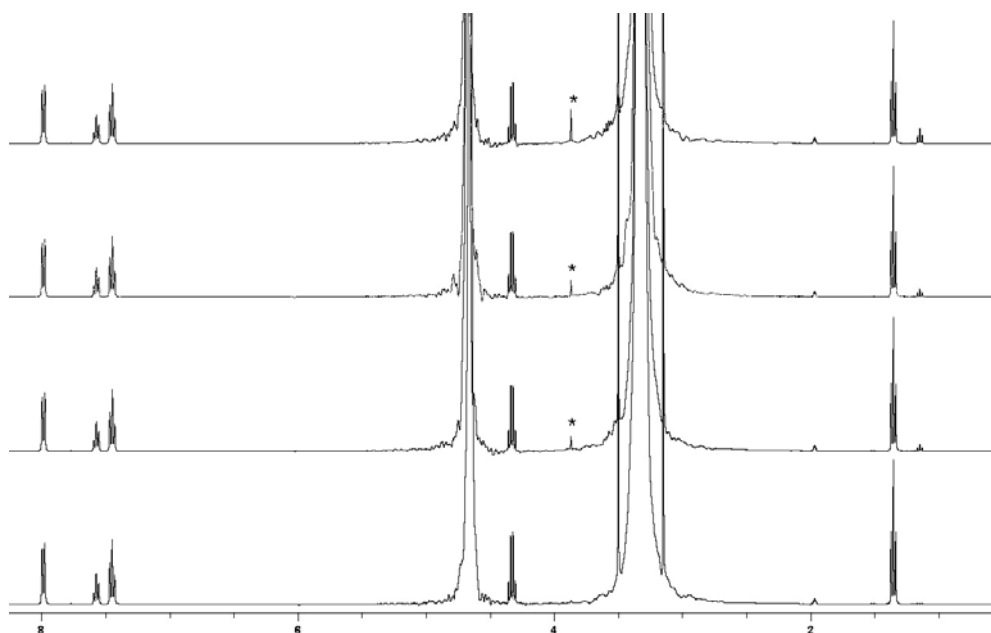
Figures **S5**. Recorded transesterification of ethyl benzoate in methanol catalyzed by NaOH with time. * stands for the methyl peak of the formed methyl benzoate.
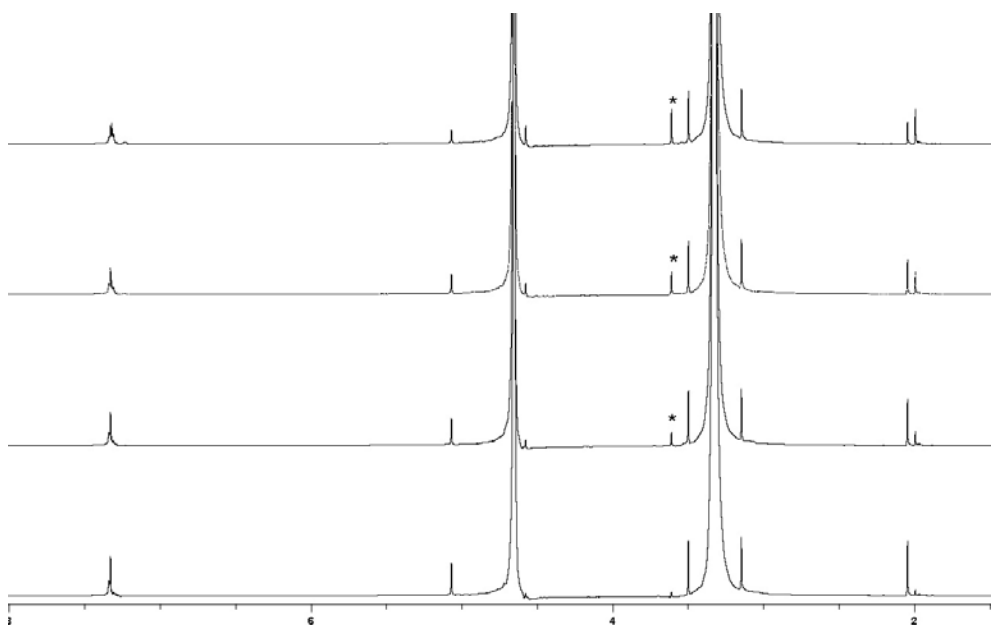
Figures **S6**. Recorded transesterification of phenylmethyl acetate in methanol catalyzed by NaOH with time. * stands for the methyl peak of the formed methyl acetate.

Computational methods

Molecular geometries of all species were optimized without constraints via DFT calculations using the B3LYP functional.[2] The 6-31+G(d,p) basis set was used for C, H and O atoms. Frequency calculations were carried out at the same level of theory to identify the stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency), and to provide the thermal correction to free energies at 298.15 K. Intrinsic reaction coordinates (IRC)[3] were calculated for all transition states to confirm that the structures indeed connect two relevant minima. To take the solvent effect into account, single-point energy calculations were performed at the M06 level[4] using 6-311++G(d,p) basis set for all the atoms with continuum solvent model SMD[5] in methanol. The solvation- and entropy-corrected relative free energies are used to analyze the reaction mechanism. All calculations were performed with the Gaussian 09 software package.[6]
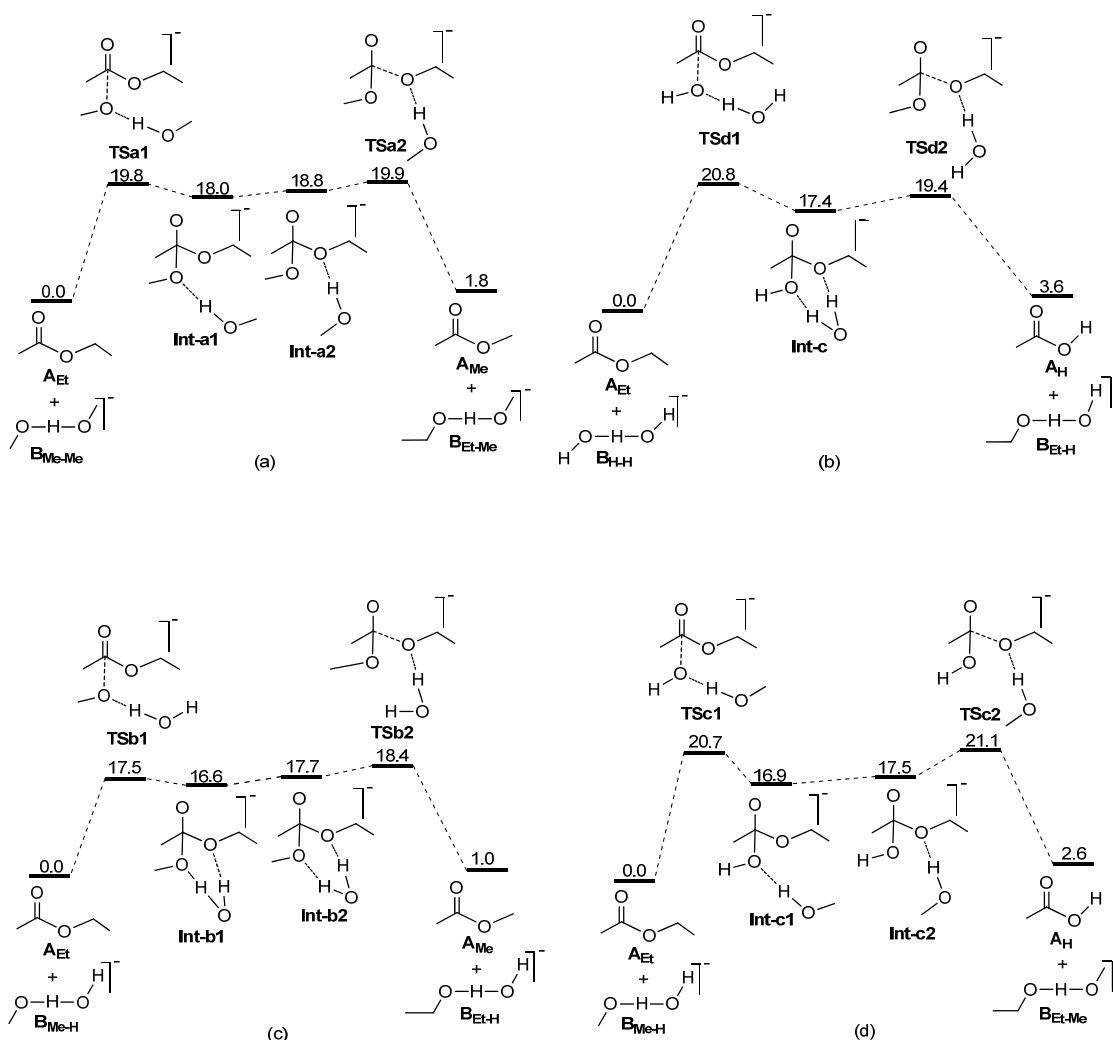
Figure S7. The possible four approaches for transesterification of ethyl acetate in methanol with hydroxide as a catalyst. a) Process through [MeO····H····OMe]⁻, b) Process through [HO····H····OH]⁻), and (c) and (d) Process through [MeO····H····OH]⁻. The energy values are all in kcal/mol.

References

1. Floyd, N.; Vijayakrishnan, B.; Koeppe, J. R.; Davis, B. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 7798-7802.
2. (a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. (b) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, 157, 200. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785.
3. (a) Fukui, K. *J. Phys. Chem.* **1970**, 74, 4161. (b) Fukui, K. *Acc. Chem. Res.* **1981**, 14, 363.
4. Zhao, Y.; Truhlar, D. G.; *Theor. Chem. Acc.* **2008**,120,215.
5. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, 113, 6378.
6. Frisch, M. J. In Gaussian 09, revision A.02; Gaussian, Inc., Wallingford, CT, 2009.

Cartesian coordinates and free energies for all calculated species

[MeO····H····OMe]⁻
G = –230.8599036 a.u.

O	–1.89974	2.09015	1.43042
H	–2.46805	3.10467	1.53166
O	–3.08995	4.19558	1.59961
C	–4.44179	4.01880	1.40981
H	–4.73002	2.95125	1.27105
H	–4.83839	4.55716	0.51294
H	–5.05843	4.38645	2.26668
C	–1.45089	1.92551	0.13224
H	–1.66698	2.80574	–0.50815
H	–1.91035	1.04713	–0.37893
H	–0.35002	1.76271	0.07653

[MeO····H····OH]⁻
G = –191.6143201 a.u.

O	–2.01494	1.86227	1.46947
H	–1.49473	2.03812	2.26187
H	–2.48158	2.81623	1.26110
O	–3.04463	4.10075	1.07202
C	–4.38326	4.17241	1.33977
H	–5.04614	3.94761	0.45975
H	–4.71164	5.18669	1.68777
H	–4.73121	3.46758	2.14102

[EtO····H····OMe]⁻
G = –270.1265687 a.u.

O	–1.70435	2.57110	–2.51352
H	–2.49373	3.61302	–2.04734
O	–3.13405	4.40369	–1.66560
C	–4.28341	3.83298	–1.12849
H	–4.07208	3.08767	–0.33425
H	–4.91612	4.61683	–0.67326
H	–4.90950	3.31317	–1.88369
C	–0.59608	2.31896	–1.75442
H	–0.49593	3.01715	–0.88489
H	0.36012	2.44364	–2.32954
C	–0.56592	0.88184	–1.17568
H	0.34694	0.69362	–0.58400
H	–1.44144	0.71665	–0.53379
H	–0.61101	0.15013	–1.99339
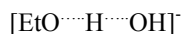
[EtO·····H·····OH]⁻
G = −230.8823468 a.u.
O   −1.84705   2.52771   −2.25556
H   −2.61782   3.43202   −1.42103
O   −3.17004   4.15222   −0.86377
C   −0.58155   2.27044   −1.81889
H   −0.23345   2.98624   −1.02745
H   0.18604   2.35759   −2.63569
C   −0.41076   0.84850   −1.22141
H   0.62615   0.65997   −0.89047
H   −1.08321   0.72107   −0.36302
H   −0.68315   0.09446   −1.97224
H   −3.14304   4.93466   −1.42602
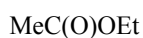
MeC(O)OEt
G = −307.5288120 a.u.
C   −1.85776   0.37122   0.16603
O   −1.28541   0.15062   1.21493
C   −3.34453   0.24169   −0.06285
H   −3.53994   −0.47796   −0.86388
H   −3.82588   −0.08679   0.85818
H   −3.76050   1.20350   −0.37868
O   −1.22222   0.77144   −0.95897
C   0.21584   0.93366   −0.86721
H   0.65588   −0.02278   −0.56821
H   0.43499   1.66276   −0.08100
C   0.71294   1.39149   −2.22580
H   1.79944   1.52562   −2.19389
H   0.48046   0.65296   −2.99922
H   0.25723   2.34492   −2.51023
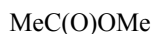
MeC(O)OMe
G = −268.2592136 a.u.
C   −1.88836   0.35269   0.16382
O   −1.25549   0.05545   1.15685
C   −3.38277   0.21972   0.00163
H   −3.61039   −0.45107   −0.83267
H   −3.81374   −0.17322   0.92228
H   −3.82351   1.19369   −0.23214
O   −1.31698   0.85447   −0.95639
C   0.11319   1.02218   −0.91380
H   0.60505   0.06060   −0.74710
H   0.38608   1.43110   −1.88644
H   0.39267   1.71095   −0.11269
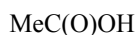
MeC(O)OH
G = −229.0124747 a.u.
C   −1.88827   0.38991   0.07352
O   −1.15669   0.04693   0.97827
C   −3.38191   0.20345   0.02129
H   −3.65229   −0.39147   −0.85659
H   −3.71871   −0.29542   0.92942
H   −3.87488   1.17549   −0.07808
O   −1.41856   1.00802   −1.04227
H   −0.45580   1.09300   −0.93669

TSa1
```
G = -538.3571985 a.u.
C   -1.61986   0.13532   0.05921
O   -1.65068   1.06329   0.89016
C   -2.88511  -0.62032  -0.33192
H   -2.65520  -1.50060  -0.93660
H   -3.40462  -0.92943   0.57789
H   -3.53846   0.05363  -0.90334
O   -0.82287   0.26222  -1.10798
C    0.37868   0.99805  -0.92200
H    0.97802   0.51343  -0.14038
H    0.14563   2.01724  -0.58520
C    1.13199   1.01185  -2.24588
H    2.06293   1.58591  -2.14850
H    1.38692  -0.00776  -2.55272
H    0.52500   1.47074  -3.03605
O   -0.70471  -1.31215   0.80714
O    1.14075  -2.64210  -0.48839
H    0.45121  -2.10641   0.02329
C   -0.52937  -1.19633   2.18216
H   -1.16486  -1.90722   2.75334
H    0.51984  -1.39507   2.47809
H   -0.78415  -0.17555   2.51846
C    0.49297  -3.22378  -1.59133
H    1.24784  -3.71756  -2.22045
H   -0.24605  -3.99072  -1.29428
H   -0.03303  -2.47746  -2.20860
```

Inta1
```
G = -538.3600854 a.u.
C   -1.5149    0.03605   0.10718
O   -1.59274   1.05244   0.85051
C   -2.80721  -0.67200  -0.32443
H   -2.60233  -1.56317  -0.92560
H   -3.36530  -0.95987   0.57159
H   -3.41603   0.02831  -0.90940
O   -0.71939   0.14368  -1.10885
C    0.45147   0.92708  -0.96567
H    1.16786   0.41170  -0.30747
H    0.19919   1.88666  -0.49526
C    1.05946   1.13656  -2.34859
H    1.97311   1.74242  -2.27953
H    1.31879   0.17749  -2.81159
H    0.35124   1.65222  -3.00850
O   -0.68217  -1.20876   0.84771
O    1.05075  -2.88115  -0.34324
H    0.42689  -2.24633   0.10590
C   -0.63951  -1.12016   2.24544
H   -1.41417  -1.74948   2.72795
H    0.34251  -1.46221   2.61190
H   -0.79524  -0.07802   2.56063
C    0.49191  -3.21284  -1.59478
H    1.26745  -3.70244  -2.20007
H   -0.35506  -3.91701  -1.50390
H    0.13428  -2.32337  -2.13285
```

S18

Inta2
```
G = -538.3588040 a.u.
C   -1.75817   0.16648  -0.13951
O   -1.94113   1.08622  -0.97414
C   -2.88218  -0.81975   0.18377
H   -2.52963  -1.63947   0.81549
H   -3.27296  -1.22605  -0.75236
H   -3.68589  -0.28059   0.70137
O   -1.16680   0.51175   1.13452
C   -0.17382   1.51225   1.04749
H    0.71096   1.14467   0.50608
H   -0.55060   2.40605   0.53388
O   -0.54337  -0.94156  -0.70658
O    0.64255  -2.82746   0.76690
H    0.18554  -2.14345   0.19857
C   -0.10440  -0.71542  -2.01356
H    1.00295  -0.68673  -2.03483
H   -0.46863   0.27073  -2.34416
C    1.14461  -2.17480   1.91115
H    2.06987  -1.60753   1.70108
H    1.38727  -2.93600   2.66611
H    0.41409  -1.47442   2.34065
H    0.11253   1.76494   2.07535
C   -0.59008  -1.79501  -2.99489
H   -1.68560  -1.80116  -3.03817
H   -0.20563  -1.60852  -4.00955
H   -0.25643  -2.79009  -2.67564
```

TSa2
```
G = -538.3569332 a.u.
C   -1.91700   0.30623  -0.06522
O   -2.07880   1.20631  -0.91661
C   -3.01838  -0.70656   0.23453
H   -2.65185  -1.52276   0.86165
H   -3.38907  -1.11243  -0.70924
H   -3.84061  -0.19167   0.74931
O   -1.32284   0.64494   1.19316
C   -0.32219   1.63999   1.10477
H    0.54574   1.26966   0.54081
H   -0.69979   2.54558   0.61351
O   -0.64515  -0.84985  -0.64370
O    0.52025  -2.72830   0.81639
H    0.06807  -2.03959   0.24202
C   -0.20644  -0.61916  -1.94483
H    0.90180  -0.56501  -1.97101
H   -0.58786   0.35926  -2.28473
C    1.03881  -2.07408   1.95044
H    1.95992  -1.50464   1.72660
H    1.29477  -2.83280   2.70395
H    0.31457  -1.37403   2.39255
H   -0.01706   1.87096   2.13182
C   -0.66484  -1.70882  -2.93059
H   -1.76008  -1.74078  -2.97602
H   -0.28263  -1.51323  -3.94468
H   -0.30941  -2.69610  -2.61043
```

TSb1
```
G = -499.1153172 a.u.
C    -1.73665   0.35501   0.05244
O    -1.74818   0.97348   1.12107
C    -2.96020  -0.33543  -0.51779
H    -2.68841  -1.05023  -1.29558
H    -3.47462  -0.85744   0.29108
H    -3.63604   0.42636  -0.93457
O    -0.89426   0.74063  -0.99346
O    -0.70999  -1.39111   0.42507
H    -0.17492  -2.60107  -2.16566
O    -0.50325  -3.17012  -1.46001
H    -0.60041  -2.52440  -0.67404
C    -0.70029  -1.72629   1.76460
H    -1.39980  -2.55679   2.01962
H    -0.98876  -0.85952   2.39295
C     0.33292   1.33053  -0.57556
H     0.13455   2.25135  -0.01114
H     0.84095   0.62244   0.09004
H     0.30481  -2.05347   2.11386
C     1.16207   1.61711  -1.82025
H     2.11849   2.07889  -1.54264
H     1.37215   0.69134  -2.36697
H     0.63340   2.29999  -2.49624
```

Intb1
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G = -499.1166832 a.u.
C    -1.59163   0.00843   0.16107
O    -1.62289   0.88280   1.07634
C    -2.92307  -0.44987  -0.45939
H    -2.77603  -1.20230  -1.24064
H    -3.55064  -0.87104   0.33321
H    -3.43348   0.42249  -0.88333
O    -0.73672   0.31841  -1.02420
O    -0.89605  -1.35276   0.62263
H    -0.16609  -1.51231  -2.03807
O     0.01031  -2.43279  -1.78145
H    -0.24250  -2.36146  -0.83636
C    -1.01549  -1.61825   1.99490
H    -1.95991  -2.14285   2.24301
H    -0.98170  -0.68374   2.57144
C     0.45997   1.00013  -0.69755
H     0.23719   1.79996   0.02032
H     1.17051   0.30908  -0.21479
H    -0.18110  -2.26750   2.30144
C     1.06441   1.56693  -1.97895
H     1.99447   2.10886  -1.75876
H     1.29806   0.76960  -2.69500
H     0.36473   2.26063  -2.46024
```

Intb2
```
G = -499.1148689 a.u.
C    -1.79481   0.01979  -0.10638
O    -1.86051   0.79678  -1.09982
C    -3.06978  -0.30128   0.68408
```

```
H    -2.88798   -1.03894    1.47179
H    -3.81843   -0.69257   -0.01037
H    -3.44615    0.62467    1.13355
O    -0.80648    0.39173    0.94917
O    -1.28186   -1.47358   -0.50477
H    -0.13990   -1.39668    2.08062
O    -0.05892   -2.33062    1.83023
H    -0.46138   -2.27103    0.93321
C    -0.83471   -1.62788   -1.82650
H    -0.92538   -0.66168   -2.34390
H     0.23363   -1.91792   -1.82898
C    -1.64757   -2.69618   -2.56896
H    -1.26531   -2.84273   -3.59045
H    -1.60292   -3.65830   -2.04329
H    -2.69917   -2.39319   -2.63256
C     0.37818    0.95866    0.43075
H     0.14983    1.75084   -0.29333
H     0.93576    1.37622    1.27862
H     1.00776    0.20153   -0.06475
```

TSb2
```
G = -499.1138356 a.u.
C    -1.85664    0.29893   -0.02215
O    -1.82927    0.94210   -1.07603
C    -3.13726   -0.17821    0.63339
H    -2.93705   -0.96683    1.36047
H    -3.80468   -0.55976   -0.14022
H    -3.61668    0.67356    1.13759
O    -0.89719    0.53355    0.97868
O    -1.24703   -1.59292   -0.48317
H     0.01659   -1.62043    2.09846
O     0.11454   -2.44220    1.60142
H    -0.38192   -2.21220    0.75044
C    -0.84439   -1.72688   -1.79562
H    -0.98156   -0.76843   -2.33777
H     0.24152   -1.97243   -1.87281
C    -1.62641   -2.82337   -2.54818
H    -1.28554   -2.91907   -3.59184
H    -1.50107   -3.79358   -2.05061
H    -2.69735   -2.58413   -2.55261
C     0.35687    0.98858    0.48900
H     0.24183    1.89215   -0.12050
H     0.97197    1.20186    1.36898
H     0.83323    0.20555   -0.11275
```

TSc1
```
G = -499.1102010 a.u.
C    -1.89175    0.38964    0.26604
O    -1.76246    0.88275    1.39546
C    -3.11967   -0.40172   -0.14948
H    -2.93872   -0.95168   -1.07426
H    -3.37155   -1.10256    0.64744
H    -3.95678    0.29710   -0.29444
O    -1.36384    1.02528   -0.85666
C    -0.18041    1.78379   -0.61668
H     0.49004    1.19590    0.01874
```

```
H    -0.43343    2.71090   -0.08226
C     0.46962    2.07310   -1.96241
H     1.36351    2.69583   -1.82463
H     0.77071    1.13421   -2.43705
H    -0.22174    2.60548   -2.62759
O    -0.65597   -1.21607    0.23544
O     1.31376   -1.55128   -1.36225
H     0.54083   -1.38789   -0.69280
H    -0.40409   -1.21101    1.16795
C     0.90518   -2.53909   -2.26542
H     0.00742   -2.24746   -2.84162
H     1.71600   -2.72430   -2.98744
H     0.67321   -3.50193   -1.77223
```

Intc1
```
G = -499.1161756 a.u.
C    -1.56645    0.01738    0.14841
O    -1.63397    1.08916    0.84483
C    -2.88283   -0.62263   -0.32908
H    -2.70946   -1.55185   -0.88351
H    -3.50304   -0.83462    0.54689
H    -3.40535    0.08967   -0.97620
O    -0.75806    0.09854   -1.10514
C     0.40904    0.88454   -0.99090
H     1.20324    0.32315   -0.46803
H     0.18760    1.78084   -0.39594
C     0.88226    1.26376   -2.39210
H     1.80301    1.86167   -2.34255
H     1.08713    0.36964   -2.99343
H     0.11418    1.85022   -2.91029
O    -0.85932   -1.09845    0.95088
O     0.97251   -2.89382    0.00238
H     0.32940   -2.23347    0.36626
H    -0.62426   -0.60439    1.74906
C     0.57458   -3.19169   -1.32038
H     0.25697   -2.29064   -1.86221
H     1.42976   -3.63992   -1.84447
H    -0.25627   -3.91927   -1.35154
```

Intc2
```
G = -499.1153200 a.u.
C    -1.36314   -0.08706   -0.12478
O    -1.28135    0.93092   -0.89120
C    -2.75192   -0.54234    0.35027
H    -2.69847   -1.44153    0.97318
H    -3.37617   -0.74594   -0.52466
H    -3.19902    0.27184    0.93028
O    -0.51802    0.03883    1.08341
O    -0.82880   -1.42146   -0.78869
O    -0.43625   -3.58375    0.83685
H    -0.61022   -2.80510    0.24740
H    -0.04613    0.86038    0.88565
C     0.28264   -1.23156   -1.63544
H     0.23560   -0.21373   -2.04617
H     1.22750   -1.32457   -1.06678
C     0.25896   -2.26840   -2.75885
```

S22

```
H      1.13242   -2.14916   -3.41632
H      0.26995   -3.28732   -2.35392
H     -0.64910   -2.15191   -3.36179
C      0.40026   -3.15439    1.89488
H      0.19179   -3.77323    2.77953
H      1.47061   -3.27754    1.64807
H      0.22686   -2.10036    2.14414
```

TSc2
```
G = -499.1094938 a.u.
C     -1.42885    0.06785    0.10022
O     -0.97817    1.03466   -0.53983
C     -2.82662   -0.48380   -0.13769
H     -2.95224   -1.46071    0.33328
H     -2.99585   -0.57316   -1.21209
H     -3.55865    0.22119    0.28138
O     -1.12533   -0.04281    1.46971
O     -0.47428   -1.51223   -0.47066
O      0.94315   -2.69056    1.39113
H      0.40306   -2.21530    0.67686
H     -0.25011    0.36309    1.55505
C      0.26047   -1.31017   -1.63225
H      0.31599   -0.22751   -1.85548
H      1.30510   -1.66108   -1.50048
C     -0.33766   -2.03947   -2.85107
H      0.27092   -1.87629   -3.75464
H     -0.39647   -3.11908   -2.66216
H     -1.35344   -1.67683   -3.05156
C      0.03828   -3.22911    2.32223
H     -0.55291   -4.06554    1.90435
H      0.60762   -3.62297    3.17719
H     -0.67029   -2.47355    2.69642
```

S23