Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Comment on "Zemplén transesterification: a name reaction that has misled us for 90 years" Green Chem. 2015, 17, 1390-1394

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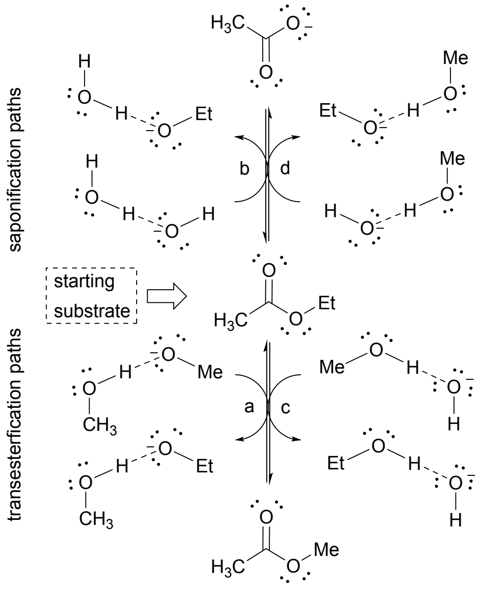
Content

1. Estimation of the relative rates of mechanisms a-d in Figure S7 of the original paper



Scheme 1. The four mechanisms, a-d, computed in the title manuscript. a) Transesterification via methanol-assisted methoxy anion [Me–O–H···O–Me]⁻ addition. b) Saponification via water-assisted hydroxyl anion addition [H–O–H···OH]⁻ c) Transesterification via hydroxyl-anion-assisted methanol addition [Me–O–H···OH]⁻. d) Saponification via methanol-assisted hydroxyl anion addition [HO···H–O–Me]⁻.

The ratio between the Arrhenius equations relative to the two competing global activation energies (E_a), as from the DFT computational study by H. Dong *et al*,[1] (see **Figure S7** of their article), gives the ratio between the rate constants concerned in the competing mechanisms. Accordingly, the ratio between rate constants between the transesterification mechanisms a) and c) can be obtained as follows[2]:

$$k = Ae^{\frac{-E_a}{RT}}$$

$$\frac{k_a}{k_c} = \frac{A_a}{A_c}e^{\frac{-(E_a^a - E_a^c)}{RT}} \cong e^{\frac{(-19.9 + 18.4)\,kcal/mol}{0.593\,kcal/mol}} = e^{-2.53} = 0.08$$

Thus, the rate constant of the hydroxyl-anion-assisted transesterification path c) is 12.5 times as fast as that of the methanol-assisted path a).

Let us now take, for example, the reaction conditions for the large scale transesterification experiment: penta-acetyl-glucose (10 g), NaOH (105 mg), methanol (100 mL). Converting the amounts of the reagents in moles:

$$MeOH{:}100\,mL \Rightarrow 79.2\,g \Rightarrow 2.472\,mol$$

$$NaOH{:}105\,mg \Rightarrow 2.625 \cdot 10^{-3}\,mol$$

$$\frac{n_{MeOH}}{n_{NaOH}} = 941.609$$

The first row of table 1 shows the initial amounts of the components, while the second one discloses the new amounts of the components as a function of the equilibrium constant K_{eq}, x representing the equal amounts of MeONa and H_2O present at equilibrium.

Table 1. Amounts of the components of the transesterification reaction.

$$\text{MeOH} + \text{NaOH} \xrightleftharpoons{K_{eq}} \text{MeONa} + \text{H}_2\text{O}$$

	MeOH	HONa	MeONa	H_2O
t_0	941.609	1.000	0	0
t_{equil}	941.609 - x	1.000 - x	x	x

The equilibrium constant pK_{eq} can be found by subtracting the dissociation constant of methanol (18.2 ± 0.5) from the dissociation constant of water in methanol as a solvent. The latter was estimated by extrapolation as 18.7 ± 1.2 (see the Excel spreadsheet for the details of calculation).

Considering a $pK_{eq} \cong -0.5$ for such equilibrium, the value for x is found:

$$K_{eq} = \frac{[MeONa]\cdot[H_2O]}{[MeOH]\cdot[NaOH]} \quad \Rightarrow \quad 10^{0.5} = \frac{x^2}{(941.609 - x)(1.000 - x)} \quad \Rightarrow \quad x = 0.9997$$

This allows us to update our values as described in Table 2.

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[1] B. Ren, M. Wang, J. Liu, J. Ge, X. Zhang, H. Dong, *Green Chem.*, **2015**, *17*, 1390.

[2] The values of the pre-exponential factors A for the two mechanisms are assumed to be identical.

Table 2. Amounts of the components of the transesterification reaction, considering $pK_{eq} = -0.5$

	MeOH	HONa	MeONa	H_2O
t_0	941.609	1.000	0	0
t_{equil}	940.611	0.0003	0.9997	0.9997

The thus obtained equilibrium values allow determining the effective molar ratio α between MeONa and HONa, which are the catalysts of the two competing mechanisms:

$$\alpha = \frac{n_{MeONa}}{n_{NaOH}} = 2962$$

Taking into account the relative amounts of the species in solution, allows us to obtain the ratio between the reaction rates:

$$\frac{r_a}{r_c} = \alpha \frac{k_a}{k_c} = 2962 \cdot 0.08 = 237$$

Thus, in the transesterification reaction according to the protocol proposed by Dong and co-workers (large scale experiment), the classical Zemplén mechanism a) turns out to run over 200 times faster than the proposed hydroxyl-anion assisted mechanism c).
Taking into account the uncertainties of the used pK_a values, the borderline pK_{eq} values were estimated as 0.8 and -1.8. The corresponding ratios r_a/r_c are 12 and 4726, respectively.

Repeating the calculation for the other mechanisms, using mechanism c) as a common reference, yields:

$$\frac{r_b}{r_c} = \alpha^{-1} \frac{k_b}{k_c} = \alpha^{-1} e^{\frac{(-20.8 + 18.4)\ kcal/mol}{0.593\ kcal/mol}} = \alpha^{-1} e^{-4.05} = \frac{0.017}{2962} = 6 \cdot 10^{-6}$$

$$\frac{r_d}{r_c} = \frac{k_d}{k_c} = e^{\frac{(-21.1 + 18.4)\ kcal/mol}{0.593\ kcal/mol}} = e^{-4.55} = 0.010$$

From these results, it follows that both the proposed mechanisms for saponification [b) and d)] are much slower than those proposed for transesterification [a) and c)]. Comparing now the fastest transesterification mechanism with the fastest saponification mechanism, respectively a) and d), we obtain:

$$\frac{r_a}{r_d} = \frac{237}{0.01} = 23700$$

This indicates that transesterification is about $24 \cdot 10^3$ times as fast as saponification.

2. Role of water in the transesterification reaction

Chosen conditions: experiment with 10% (v/v) of water in methanol, employing 1 mL of solution and 0.1 equiv. of base (we choose NaOH) related to the 100 mg of penta-acetyl glucoside.
Performing the same calculations as before, we find:

$$MeOH{:}0.9\ mL \Rightarrow 22.25\ mmol$$

$$H_2O{:}0.1\ mL \Rightarrow 5.56\ mmol$$

$$NaOH{:}0.1\ equiv.\ of\ 100\ mg\ (0.256\ mmol)\ of\ substrate \Rightarrow 2.625 \cdot 10^{-2}\ mmol$$

$$\frac{n_{MeOH}}{n_{NaOH}} = 847.555 \qquad \frac{n_{H_2O}}{n_{NaOH}} = 211.448$$

	MeOH	NaOH	MeONa	H_2O
t_0	847.555	1	0	211.448
t_{equil}	847.555-x	1-x	x	211.448+x

The pK_{eq} value in methanol-water solution (volume fraction of methanol 0.9, molar fraction 0.8) was estimated as -0.3 ± 0.7. Therefore:

$$10^{0.3} = \frac{x(211.448 + x)}{(847.555 - x)(1 - x)}$$

$$x = 0.897$$

	MeOH	NaOH	MeONa	H_2O
t_0	847.555	1	0	211.448
t_{eq}	846.658	0.103	0.897	212.345

$$\alpha = \frac{n_{MeONa}}{n_{NaOH}} = 9$$

$$\frac{r_a}{r_c} = \alpha\frac{k_a}{k_c} = 9 \cdot 0.08 = 0.7$$

$$\frac{r_b}{r_c} = \alpha^{-1}\frac{k_b}{k_c} = \frac{0.017}{9} = 0.002$$

$$\frac{r_d}{r_c} = \frac{k_d}{k_c} = 0.010$$

Considering the uncertainty of the pK_{eq}, the borderline values of r_a/r_c are 0.1 and 3.5.
Thus, mechanism a) is very likely slower than mechanism c), making in this case the new proposed mechanism actually competitive with the classical one. On the other hand, saponification remains always slower than transesterification, although the difference between the two pathways becomes less important.