Relative Rates of Transesterification vis-à-vis Newman's Rule of Six

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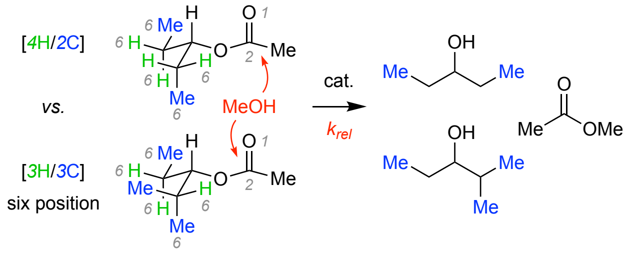
Supporting Information Placeholder

ABSTRACT: The relative reactivity of a systematic series of simple aliphatic acetate esters has been measured. Exposure of pairs of esters of increasing remote steric hindrance (by altering the degree of branching of the ester alkyl group) to a methanolic solution of Cs_2CO_3 proved to be a reliable (and general) method for quantitating the rate differences in these base-catalyzed transesterification reactions. The trends in relative rates are in accordance with the qualitative "Rule of Six" put forward by Melvin S. Newman in 1950, as deduced then from interpretation of earlier reports of ease of Fischer esterification reactions.



INTRODUCTION

In 1950 M. S. Newman proposed an empirical rule for analyzing reactions that involved additions to carbon-containing unsaturated functional groups (C_{sp2}=X).[1] As stated there:

> *In reactions involving addition to an unsaturated function, the greater number of atoms in the six position the greater will be the steric effect. For convenience this will be referred to as the rule of six and the number of atoms in the six position will be called the six-number* (cf. [*n*H/*m*C] in **1**, Figure 1a).

Newman presented this in the specific context of analysis of three earlier literature reports[2] of the rates of acid-catalyzed esterification reactions of ca. two dozen aliphatic carboxylic acids that differed in the types and number of alkyl groups near the carboxyl functionality (cf., e.g., **2a-c**). These reactions proceed, of course, through a tetrahedral intermediate in which the carbonyl carbon has become sp^3-hydridized. Several specific examples that serve to demonstrate the categorization of some of these simple aliphatic acids are shown in Figure 1b. The number of hydrogen atoms and/or carbon atoms (here, always methyl groups) in the six-position are indicated by the convention [*n*H/*m*C]. (A methyl carbon atom in the six-position necessarily, of course, carries with it three hydrogen atoms in the seven-position.) The relative rates of Fischer esterification (with methanol) are shown below each of these structures.

Newman followed his initial report with a more extensive discussion in a chapter titled "Additions to Unsaturated Functions" in his book on steric effects in organic chemistry.[3] He limited his analyses to the identification of qualitative (rather than quantitative) trends because of the added complexity of the conformational landscape as well as the fact that substituents in the 5-postion also contribute to differential reactivities, albeit to a lesser extent.[4] Most of the (relatively few) subsequent citations to the rule of six refer to it in only a passing comment,[5] likely a reflection of its qualitative nature. Nonetheless, we felt that gaining a sense for the magnitude of this kind of remote steric effect would still be of value.

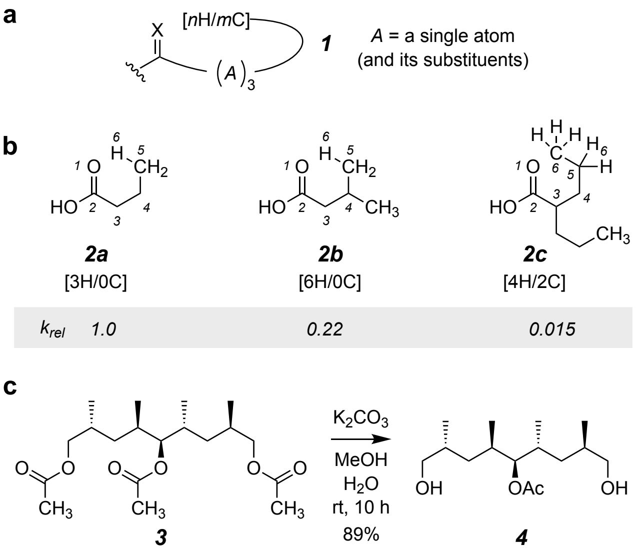


Figure 1. (a) A generic structure in which the rule of six can be considered for the reactivity of addition reactions to the C=X moiety. (b) Three (of the dozens) of Fischer esterification reactions that Newman drew upon in developing his empirical rule of six. (c) An example showing the benefit of understanding the role of remote steric hindrance.

In a previous study in our laboratory of a natural product synthesis,[6] we observed the efficient conversion of the triacetate **3** to the monoacetate-diol **4** upon exposure to aqueous methanolic potassium carbonate. No trace of another product was detected. This was very much in accord with Newman's empirical rule of six. We decided to more systematically study the impact of substitution of related transesterification reactions, a type of transformation that also typically proceeds through a tetrahedral intermediate derived from the ester carbonyl in the substrate. The results of these studies are presented here.

RESULTS AND DISCUSSION

Cs_2CO_3 Catalyzed Transesterifications. Using competition experiments, we have measured the relative rates of transesterification of the ten acetate esters **5-11** (Figure 2) in a homogeneous solution of methanol using cesium carbonate as a basic catalyst. Temperatures of 20, 50, and 120 °C were used in order to achieve comparable time scales for analysis. These homologous substrates differ by the orderly change arising from replacement of a six-position hydrogen atom by a six-position methyl group. The systematic nature of structural change across the series is easily seen in the bracketed designations where the sum of the six position atoms is constant (i.e., $n + m = 6$).

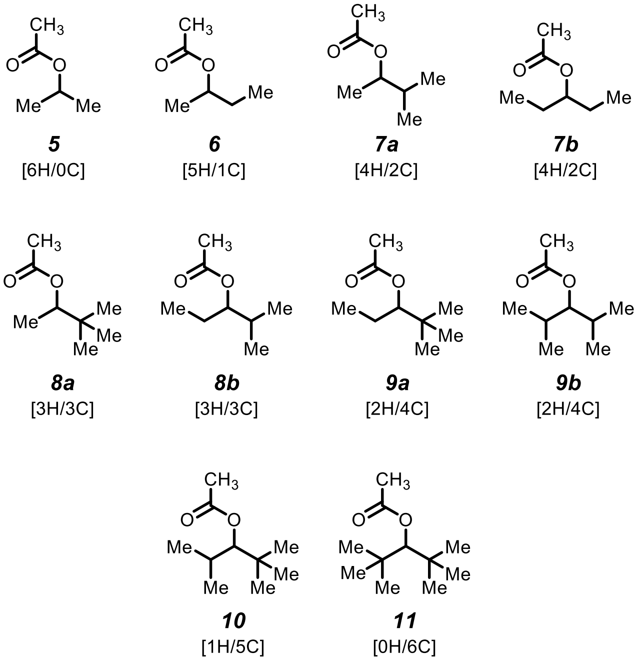


Figure 2. Ten model acetates ranging from zero [6H/0C] to six [0H/6C] carbons in the six-position were studied.

Although we initially used a gas-chromatographic method to assess the relative rates of many of these,[6] we have more recently used a series of pairwise competition studies using ^{1}H NMR analysis. This latter approach ensures that the temperature and catalyst concentration was identical for any one experiment and benefits from the fact that the detector response is more straightforward (^{1}H integration). Mesitylene (ca. 0.5 equiv) was added as an internal standard. Following the addition of a stock solution of Cs_2CO_3 (ca. 0.5 equiv), small aliquots (ca. 20 μL) of the reaction mixture were removed over time and directly added to C_6D_6 (ca. 0.5 mL). The ^{1}H NMR spectrum was recorded soon after; controls showed that there was no significant further change in the ratio of components in the C_6D_6 samples, even days later. The use of C_6D_6 rather than $CDCl_3$ provided superior resolution of the methyl group resonances of the two acetate substrates. Their disappearance could then be monitored over time relative to the aromatic proton resonances of the mesitylene standard. Each of the pairwise competition experiments was performed in duplicate, and the agreement between the relative rates measure in both runs was good.

As an example of this methodology, analysis of the pair of acetates **6** vs. **7b** is shown in Figure 3. The spectrum in panel (b) is for the zero time point. The starting ratio of acetates in this particular experiment is measured to be 1.12 from the relative integrations of each acetate methyl group singlet at ca. 1.7 ppm. The stack plot in panel (c) shows the disappearance of each of the two substrates (blue vs. red) as well as the appearance of the methyl acetate product (δ 1.60 ppm, green) over time. These data are plotted in panel (d) (as ln[acetate]/ln[mesitylene] vs. time). The near linearity is consistent with an expected pseudo first-order reaction mechanism for the transesterification. The ratio of the slopes for the rate of disappearance for this trial was 3.2 (and 3.0 for a second trial). We judged that the data obtained using this approach were sufficiently good to provide the type of semi-quantitative, relative reactivities we were seeking.

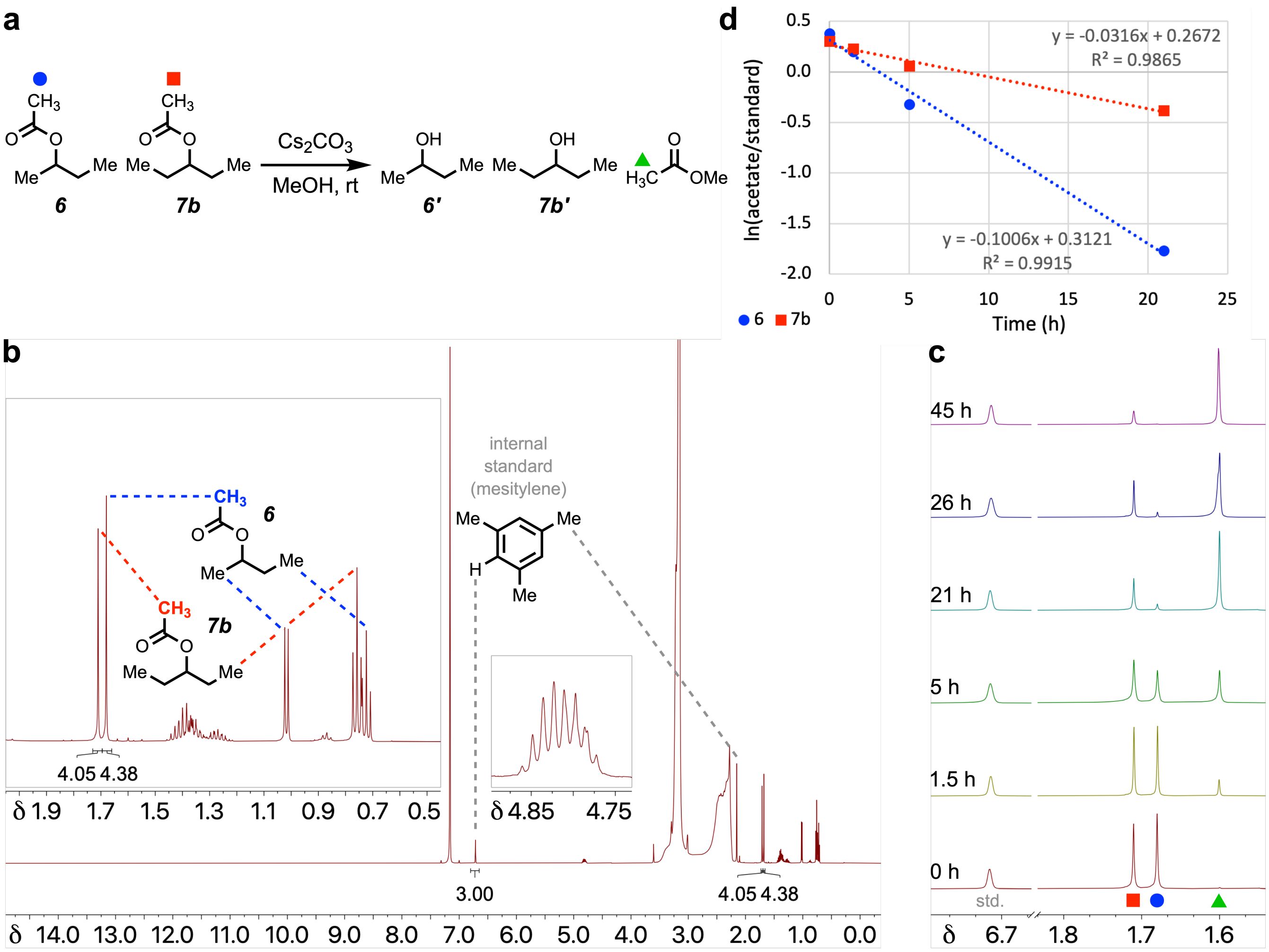
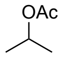
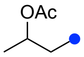
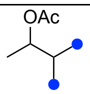
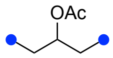
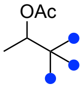
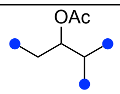
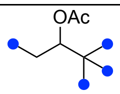
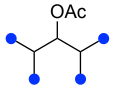
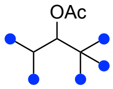
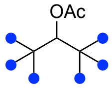


Figure 3. An example of the data collection for one trial (a) of **6** vs. **7b**. (b) Time zero spectrum from which the initial ratios of each acetate vs. the mesitylene standard were measured. (c) Spectra of aliquots taken over time. (d) Plot of the consumption of each of acetates **6** and **7b** over time.

Table 1 presents the relative rate comparisons for the entire complement of acetates. All of the fastest reacting subset (**5-8b**) were measured at ambient temperature. The 3-pentyl acetate (**7b**) was used as the common substrate (i.e., the benchmark compound) in each of these five pairwise competition experiments. As shown in the first column of relative rate data in Table 1, the transesterification rapidity for these six acetates ranged over a factor of 22. The more hindered substrates **9a**–**9b** reacted more slowly, so their methanolyses were carried out at 50 °C (in comparison to **8b** as the benchmark). Similarly, for acetate **10**, we found a reaction temperature of 120 °C to be convenient; it was measured in competition with **9b**. The most hindered substrate, **11**, not surprisingly, reacted extremely slowly. At 150 °C it was only partially cleaved to its corresponding alcohol after 20 h, making it challenging to perform a pairwise comparison under the same conditions. Moreover, there is the possibility that **11** may be giving rise to the alcohol **11'** (di-*tert*-butyl carbinol) by an alternative mechanism – ketene formation from the ester enolate.[7] Consequently, we have not offered any quantitative comparison for this slowest substrate of all.

Several trends can be seen from the information in Table 1. Within the set of the first six acetates, as each additional methyl group is added to the previous homolog (i.e., progressing from [6H/0C] to [5H/1C] to [4H/2C] to [3H/3C]) the transesterification rate slows by a factor of 2-3 with the addition of each new methyl group. Isomers **7a** and **7b** differ only by which side of the ester alkyl moiety has gained the extra methyl group (each is [4H/2C]). They have nearly the same rate ($k_{rel(\mathbf{7a}/\mathbf{7b})} = 1.1$). The same is true for the pair **8a** and **8b** (as well as **9a** and **9b**). Moreover, for each of these pairs the ester with the more balanced degree of branching in the ester alkyl group (i.e., the **b**-isomer) reacted slightly slower than the **a**-isomer. Interestingly, portions of this trend can be gleaned from the experimental data for Fischer esterification (in both MeOH[2c] and in EtOH[2a]) that Newman used when first formulating the rule of six.

Table 1. The full set of acetate ester substrates and their observed relative rates of methanolysis.

ester		# of		relative rates[a]		
#	**structure**	***Six*-Hs**	***Six*-Cs**	**20 °C**	**50 °C**	**120 °C**
5		6	0	22	-	-
6		5	1	10	-	-
7a		4	2	3.7	-	-
7b		4	2	3.3[b]	-	-
8a		3	3	1.1	-	-
8b		3	3	1.0	8.3[b]	-
9a		2	4	-	1.2	-
9b		2	4	-	1.0	2.2[b]
10		1	5	-	-	1.0
11		0	6	-	-	see text

[a]The relative rates at each individual temperature were normalized by assigning the rate of the slowest reacting substate a k_{rel} of 1.0. [b]The benchmark compound used for all experiments at this temperature (i.e., to determine the k_{rel}s within any one column). This benchmark was present in each of the pairwise competition experiments used at this temperature.

Upon adding the fourth methyl group and moving from **8a/b** to **9a/b** (i.e., progressing from [3H/3C] to [2H/4C]), there is more substantial rate retardation that deserves some special consideration. More specifically, the isomers of **9** react ca. 8x slower than the acetate **8b**.[8] Why is this not more like the factor of 2-3 seen for all of the earlier homologs? To explore this we carried out a multiconformational search and full set of density functional theory (DFT) calculations to find the conformational preferences for each acetate (see Supporting Information for details).

For **9a** and **9b**, the lowest energy conformer for each is shown in Figure 4.[9] Notice that each has an extended, anti-anti arrangement of its parent pentane backbone. The terminal methyl groups (i.e., C1 and C5 of the pentane) serve to dissuade tetrahedral intermediate formation arising from any nucleophilic addition to the acetate carbonyl group. Regardless of whether the rate limiting step in the mechanism for base-catalyzed transesterification under the conditions used in this study is formation of the tetrahedral intermediate or its subsequent collapse to release methyl acetate, steric congestion near that tetrahedral intermediate would both slow its rate of formation as well as diminish its equilibrium concentration. The conformer for each of **9a** and **9b** that allows access for methanol to engage the acetate carbonyl was computed to be 3.0 and 3.5 kcal mol^{-1} higher in energy, respectively. Each is created by rotation about the C3–C4 pentane bond (i.e., is an anti-gauche conformer) but is greatly destabilized by the syn-pentane interaction that accompanies that geometric change. Thus, each of these conformers, which are more conducive to participating in the transesterification, is populated to only <1% of the equilibrium ensemble of conformers. In contrast, the same analysis of the [3H/3C] homolog **8b**, shows, again, its lowest energy conformer to have the anti-anti pentane geometry; however, an anti-gauche conformer with freer access for tetrahedral intermediate formation is only 1.0 kcal mol^{-1} higher in energy than the global minimum and comprises 8% of the full conformational ensemble for **8b**. Said another way, a reasonably large portion of the **8b** molecules can adopt a conformation that avoids a syn-pentane interaction, yet still allows access for attack at the carbonyl carbon. The larger rate retardation for **9a/b** relative to all the earlier progressions from **5** through **8b** can be attributed to the significantly reduced population of the more reactive conformers **9a/b**.

The relative rate ratio of **9b** vs. **10** was measured to be 2.2 (at 120 °C, last column in Table 1). The acetate in the latter is flanked by one *tert*-butyl and one *iso*-propyl group. As with **9b**, the most reactive (accessible) conformer of **10**, which has its *iso*-propyl methine proton oriented toward the acetate carbonyl group, is ca. 3 kcal mol^{-1} higher in energy than the most stable conformer. A simple argument that can account for the reactivity difference (of 2.2) in this **9b**/**10** pair is that the former has two *iso*-propyl groups that can orient so as to more readily accommodate the tetrahedral intermediate while **10** has only one. The mole fractions of those conformations that have a Me_2C–H oriented toward the carbonyl group in **9b** vs. **10** are computed to be 0.43% vs. 0.28%, respectively.

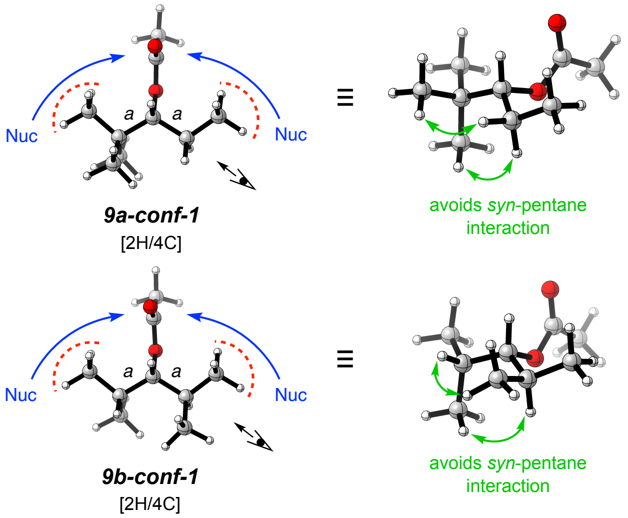
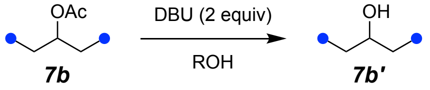


Figure 4. Conformational analysis of the lowest energy conformers of **9a** (2,2-dimethyl-3-pentyl acetate) and **9b** (2,4-dimethyl-3-pentyl acetate).

The overall range of rate differences between the most and least reactive acetates, i.e., **5** vs. **10**, was estimated in the following way. The steric factor: Acetate **5** reacts 22 times faster than **8b**, which reacts 8.3 times faster than **9b**, which reacts 2.2 times faster than **10**. If these were all being measured at the same temperature, the steric factor alone would then account for a factor of 400 in relative rates. The temperature correction: Using the half-life of the transesterification at 20 °C for **7b** of 21 h and i) assuming a pseudo first-order reaction (the methanol solvent was in large excess in all reactions), ii) assuming a pre-exponential factor of 10^{12}, and iii) ignoring the concentration of the Cs_2CO_3 catalyst (which was similar in all experiments), we deduce an activation energy of 22.8 kcal mol^{-1}. The impact of the temperature change from 20 to 120 °C is a factor of 21,500 ($k = Ae^{(-Eact/RT)}$). Assuming that all of the transesterification reactions are subject to the same temperature dependence, we estimate an overall difference in reactivity of $k_{rel(\mathbf{5}/\mathbf{10})}$ = 8,600,000.

Related transesterification experiments. *Transesterifications of 7g with different alcohols*. We compared the rates of alcoholysis in the series of increasing sterically hindered (and less polar) solvents MeOH, EtOH, and ^{i}PrOH for the single acetate **7b** (Table 2). We used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.0 equiv) as the basic catalyst because the solubility of Cs_2CO_3 was limited in the higher alcohols. In MeOH more than half of **7b** was consumed over 24 h at 20 °C. The bulkier EtOH required heating the reaction mixture to 50 °C and ^{i}PrOH necessitated extended heating at 120 °C to achieve convenient rates of reaction. From the observed precipitous drop in reactivity, one can see that the hindrance of the nucleophilic agent forming the tetrahedral intermediate impacts the transesterification rate significantly. Thus (and not surprisingly), the choice of the solvent contemplated for use in a deprotection of a complex substrate is a factor to be considered.

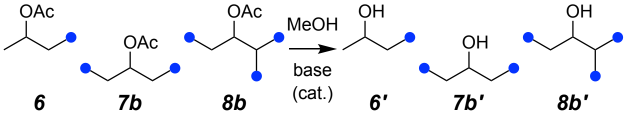
Table 2. Transesterification reaction of 7b with alcohols of increasing steric bulk, catalyzed by DBU (2.0 equiv).



ROH solvent	Temp	Time	Consumption of 7b
MeOH	20 °C	24 h	62%
EtOH	50 °C	48 h	25%
^{i}PrOH	120 °C	168 h	23%

Cs_2CO_3 vs. DBU as the (base) catalyst. The acetates **6**, **7b**, and **8b** (ranging from [5H/1C] to [4H/2C] to [3H/3C]) displayed a three-fold decrease in reactivity for each successive carbon in the six-position when using 0.5 equiv of Cs_2CO_3 as the base (Table 3, first column of relative rates). Use of DBU (1.0 equiv) led to essentially the same relative rates of acetate cleavage among **6**, **7b**, and **8b**, suggestive of a similar mechanism (e.g., both general base catalysis) for each of the two different bases.

Table 3. Relative rates of transesterification for acetates 6, 7b, and 8b using Cs_2CO_3 vs. DBU in MeOH.



	relative rates[a]	
#	Cs_2CO_3 (cat.)[b,c]	DBU (cat.)[d]
6	3.1	3.0
7b	1.0	1.0
8b	0.30	0.29

[a] Normalized to that of **7b** for each set of conditions. [b] From Table 1. [c] MeOH, 20 °C, Cs_2CO_3 (0.5 equiv). [d] MeOH, 20 °C, DBU (1.0 equiv, which gave similar absolute rates of the methanolysis as did use of 0.5 equiv of Cs_2CO_3, thus allowing for the same array of timepoints to be taken during the NMR monitoring).

H_2SO_4 as the (acid) catalyst. We briefly examined a Brønsted acid-catalyzed variant of the methanolysis using the same set of acetate esters **6**, **7b**, and **8b**. In MeOH containing ~0.5 equiv of H_2SO_4 the relative rate ratios were 2.0:1.0:0.43, respectively (Figure 5). Thus, the acid-catalyzed methanolyses showed a slightly lower level of selectivity compared to the analogous base-catalyzed reactions (i.e., difference of ca. 2x vs. 3x). This suggests that a base-catalyzed

ester cleavage would likely be more selective in a structurally complex molecule containing more than one ester (cf. **3** to **4**, Figure 1).

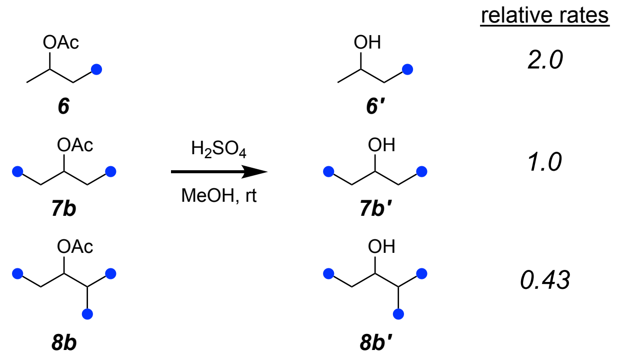


Figure 5. Relative rates of Brønsted acid-catalyzed methanolysis for the acetates **6**, **7b**, and **8b**.

CONCLUSIONS

We have systematically examined the relative rates of base-catalyzed transesterification for ten model acetates containing, in total, a combination of six hydrogen and/or methyl groups in the six position relative to the acetate carbonyl oxygen atom. The observed drop in reactivity for each successive carbon in the six position reaffirms Newman's qualitative, empirical rule of six. Computation (DFT) of the ground state conformational populations of the acetates was used to rationalize an observed discontinuity (**8a/b** vs. **9a/b**) in the rate depression resulting from systematic replacement of six-Hs by six-Cs. Of the two bookend acetates studied, [6H/0C] (**5**) vs. [1H/5C] (**10**), an overall difference in the rate of transesterification of seven orders of magnitude was approximated. Increasing the steric bulk of the solvent was shown to significantly slow the rate of base-catalyzed transesterification. Finally, the rates of analogous Brønsted acid-catalyzed methanolysis was shown to be slightly less sensitive to the degree of hindrance in the acetate relative to the base-catalyzed reaction.

EXPERIMENTAL SECTION

General Procedures for Kinetic Experiments.

a) Cs_2CO_3 or H_2SO_4 or DBU as catalyst in MeOH. To a screw cap culture tube was added i) 0.2 mL each of a 0.5 M stock solution in methanol of each of the two acetates being compared, ii) 0.1 mL of an ca. 0.5 M solution of mesitylene in methanol, and iii) 0.5 mL of a 0.1 M stock solution of either Cs_2CO_3 or H_2SO_4 or 0.5 mL of a 0.2 M stock solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). An aliquot (20 mL) was taken and immediately diluted into ca. 0.5 mL of C_6D_6; the NMR spectrum was recorded to determine the initial (t = 0) ratio of the two acetates relative to the mesitylene internal standard. Additional aliquots were removed and analyzed at multiple timepoints over two days. The reactions were performed at ambient temperature or in an oil bath equilibrated to either 50, 120, or 150 °C.

b) DBU as catalyst in MeOH, EtOH, or ^{i}PrOH. To a screw-cap culture tube was added **7b** (0.1 mmol, 0.013 g), mesitylene (0.05 mmol, 0.006 g), DBU (0.2 mmol, 0.0304 g), and alcohol solvent (1 mL). An aliquot (20 mL) was taken and immediately diluted into ca. 0.5 mL of C_6D_6 or $CDCl_3$ to record the initial amount of **7b** in the mixture relative to the mesitylene standard. Additional aliquots were removed and analyzed at multiple timepoints over two days. The reactions were performed at ambient temperature or in an oil bath equilibrated to either 50 or 120 °C.

Spectral Data for Acetates 3, 4, and 6–11.

(±)-(2R,4R,6R,8R)-2,4,6,8-Tetramethylnonane-1,5,9-triyl Triacetate (**3**) *and (±)-(2R,4R,6R,8R)-1,9-Dihydroxy-2,4,6,8-tetramethylnonan-5-yl Acetate* (**4**). To a suspension of potassium carbonate (1.49 g, 10.8 mmol) in aq MeOH ($MeOH:H_2O$ = 3 : 1, v/v, 100 mL) was added the triacetate **3**[6] (1.76 g, 4.9 mmol). After 10 h of stirring at RT, the complete consumption of the starting material was confirmed by TLC analysis. The mixture was extracted (CH_2Cl_2 x 4), washed (saturated NH_4Cl), and dried ($MgSO_4$). Concentration followed by MPLC (1 : 1.5 hexane/EtOAc, containing 5% isopropanol) yielded the diol monoacetate **4** (1.20 g, 4.3 mmol, 89 %). *For triacetate* **3**. ${}^1H$ NMR ($CDCl_3$, 200 MHz): δ 4.64 (dd, *J* = 7.0, 7.0 Hz, $CH_3CO_2C\underline{H}$), 3.92–3.74 (m, 2 x $CH_3CO_2C\underline{H}_2$), 2.03 (s, $C\underline{H}_3CO_2CH$), 2.01 (s, 2 x $C\underline{H}_3CO_2CH_2$), 1.94–1.68 (m, 4 x $CH_3C\underline{H}$), 1.21–1.03 (m, 2 x $CHC\underline{H}_2CH$), 0.85 (d, J = 6.5 Hz, $C\underline{H}_3CH$), 0.84 (d, J = 7.0 Hz, $C\underline{H}_3CH$), 0.82 (d, J = 6.4 Hz, $C\underline{H}_3CH$), and 0.80 (d, J = 7.2 Hz, $C\underline{H}_3CH$). ${}^{13}C\{{}^1H\}$ NMR ($CDCl_3$, 50.3 MHz): δ 170.5 (2x), 170.5, 81.3, 69.5, 69.2, 36.8, 34.5, 31.0, 30.7, 29.4, 29.3, 20.3 (2x), 20.3, 16.0, 15.5, 15.4, and 13.1. IR ($CDCl_3$) 3000, 2850, 1710, 1250, and 1030 cm^{-1}. HRMS (Cl) Calcd for $C_{19}H_{34}O_6 + NH_4^+$: 376.2694. Found: 376.2685. *For acetate* **4**. ${}^1H$ NMR ($CDCl_3$, 300 MHz): δ 4.67 (dd, *J* = 7.0, 4.9 Hz, $C\underline{H}OAc$), 3.47 (dd, *J* = 11.1, 4.0 Hz, $C\underline{H}_aH_bOH$), 3.46 (dd, *J* = 10.2, 5.6 Hz, $C\underline{H}_bH_aOH$), 3.42 (dd, *J* = 10.6, 6.6 Hz, $C\underline{H}_aH_bOH$), 3.41 (dd, J = 11.1, 6.2 Hz, $C\underline{H}_bH_aOH$), 2.08 (s, OAc), 1.95–1.80 (m, $CH_3C\underline{H}CHOAc$), 1.75–1.60 (m, $CH_3C\underline{H}CH_2OH$), 1.21 (ddd, *J* = 13.5, 9.9, 4.5 Hz, $\underline{H}CH$), 1.20 (ddd, *J* = 13.2, 10.9, 3.3 Hz, $\underline{H}CH'$), 1.06 (ddd, *J* = ~13.0, 10.9, 3.0 Hz, $\underline{H}CH''$), 1.05 (ddd, *J* = 13.7, 9.5, 4.6 Hz, $\underline{H}CH''''$), 0.89 (d, *J* = 6.6 Hz, $CHC\underline{H}_3$), 0.88 (two overlapping d's, *J* = 6.6 Hz, $CHC\underline{H}_3'/''$), and 0.86 (d, *J* = 6.6 Hz, $CHC\underline{H}_3'''$). ${}^{13}C\{{}^1H\}$ NMR ($CDCl_3$, 50.3 MHz): δ 170.7, 81.2, 68.6, 68.2, 36.7, 34.5, 32.6, 32.4, 31.1, 30.7, 20.4, 15.6, 15.5, 15.3, and 13.0. IR (neat) 3400, 2980, 2960, 2890, 1730, 1460, 1380, 1240, 1040, and 960 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.49; H, 10.88.

NMR Spectral Data for Acetates 6–11.

Because the NMR spectral data in the literature for **6**–**10** are of variable quality, the line listings for the ${}^1H$ and ${}^{13}C$ NMR spectra of those acetates are provided here. Full characterization data for **11** are provided here for this reported[10] but uncharacterized acetate.

6: (0.36 g, 62%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.83 (nfom, 1H), 2.03 (s, 3H), 1.59 (dqd, *J* = 13.7, 7.5, 6.9 Hz, 1H), 1.53 (dqd, *J* = 13.7, 7.5, 5.9 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), and 0.90 (dd, *J* = 7.5, 7.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.1, 72.4, 28.9, 21.5, 19.6, and 9.8.

7a: (0.43 g, 66%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.72 (dq, *J* = 6.7, 6.3 Hz, 1H), 2.04 (s, 3H), 1.77 (qqd, *J* = 6.8, 6.8, 5.8 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.902 (d, *J* = 6.8 Hz, 3H), and 0.901 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.0, 75.4, 32.8, 21.5, 18.2, 18.1, and 16.8.

7b: (0.43 g, 66%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.75 (tt, *J* = 6.8, 5.5 Hz, 1H), 2.05 (s, 3H), 1.57 (dqd, *J* = 14.0, 7.5, 5.5 Hz, 2H, $CH_3C\underline{H_a}H_b$), 1.55 (dqd, *J* = 14.0, 7.1, 7.1 Hz, 2H, $CH_3CH_a\underline{H_b}$), and 0.88 (dd, *J* = 7.3, 7.3 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.3, 76.9, 26.6, 21.4, and 9.7.

8a: (0.54 g, 75%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.68 (q, *J* = 6.5 Hz, 1H), 2.04 (s, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), and 0.90 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.0, 77.8, 34.2, 25.8, 21.4, and 15.0.

8b: (0.47 g, 65%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.67 (ddd, *J* = 8.2, 5.8, 4.6 Hz, 1H), 2.06 (s, 3H), 1.83 (qqd, *J* = 6.8, 6.8, 5.8 Hz, 1H), 1.58 (dqd, *J* = 13.9, 7.4, 4.4 Hz, 1H, $C\underline{H_a}H_b$), 1.52 (ddq, *J* = 14.3, 8.2, 7.2 Hz, 1H, $CH_a\underline{H_b}$), 0.894 (dd, *J* = 6.8 Hz, 3H), 0.888 (d, *J* = 6.9 Hz, 3H, $HCCH_3$), and 0.87 (t, *J* = 7.5, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.3, 80.0, 31.1, 24.2, 21.2, 18.7, 17.7, and 10.0.

9a: (0.67 g, 84%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.66 (dd, *J* = 2.5, 10.6 Hz, 1H), 2.08 (s, 3H), 1.62 (dqd, *J* = 14.0, 7.4, 2.5 Hz, 1H, $CH_3C\mathit{H_a}H_b$), 1.44 (ddq, *J* = 14.2, 10.7, 7.1 Hz, 1H, $CH_3C\mathit{H_a}H_b$), 0.89 (s, 9H), and 0.86 (dd, *J* = 7.4, 7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.4, 82.5, 34.7, 26.1, 22.6, 21.1, and 11.1.

9b: (0.62 g, 79%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.58 (t, *J* = 6.0 Hz, 1H), 2.07 (s, 3H), 1.89 (qqd, *J* = 6.9, 6.9, 6.1 Hz, 2H), 0.90 (d, *J* = 6.9 Hz, 6H), and 0.90 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.4, 82.8, 29.5, 21.0, 19.7, and 17.3.

10: (0.76 g, 85%, pale yellow oil) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.55 (d, *J* = 3.3 Hz, 1H), 2.08 (s, 3H), 2.01 (qqd, *J* = 6.8, 6.8, 3.3 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), and 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): δ 171.3, 84.2, 35.5, 28.6, 26.8, 23.3, 21.0, and 18.1.

11: (0.56 g, 60%, clear crystalline solid) ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.58 (s, 1H), 2.08 (s, 3H), and 1.00 (s, 18 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 Hz): 171.1, 85.9, 37.2, 28.8, and 21.1. IR (neat): 2959 (C_{sp3}-H), 1733 (C=O), and 1240 (C-O st as) cm^{-1}. HRMS (EI-TOF) *m/z*: [M^+-tBu•] Calcd for $C_7H_{13}O_2^+$ 129.0910, Found 129.0913 (10 %); [tBuC(H)=O^+H] Calcd for $C_5H_{11}O^+$ 87.0804, Found 87.0808 (100%); [tBu^+] Calcd for $C_4H_9^+$ 57.0699, Found 57.0705 (50%). mp: 27.6–30.3 °C.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

> PDF containing the experimental procedure for preparing compound **4**, graphs of the data from all pairwise competition reactions between acetates, description of DFT computational methods and energies and co-ordinates for all conformers of acetates **5**–**11**, and the static copies of the proton and carbon spectra for each of acetates **6**–**11**.
>
> A .zip file of the .xyz files of all computed conformers. A .zip file of the folders of raw NMR data for **6**–**11** titles FID for Publication.

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Notes

None of the authors have a competing financial interest in this work.

ACKNOWLEDGMENT

This work was supported by a grant from the National Science Foundation (NSF, CHE-2155042). A.M.H.W. was supported by a Heisig-Gleysteen Summer Fellowship. Partial support for NMR instrumentation came from an NIH Shared Instrumentation Grant (NIH S10 OD011952). Mass spectrometry data were obtained with instrumentation in the University of Minnesota Department of Chemistry Mass Spectrometry Laboratory (MSL), obtained with an NSF instrumentation grant (CHE-1336940). The DFT computational studies were made possible by the Minnesota Supercomputing Institute (MSI).

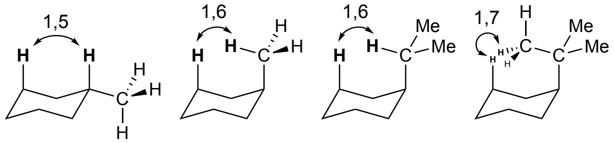
REFERENCES

[1] Newman, M. S. Some observations concerning steric factors. *J. Am. Chem. Soc.* **1950**, *72*, 4783–4786.

[2] (a) Bhide, B. V.; Sudborough J. J. Studies in transesterification. *J. Ind. Inst. Sci.* **1925**, *8*, 89–128. (b) von Braun, J.; Fischer, F. Beiträge zur Kenntnis der sterischen Hinderung, VII. Mitteil.: Veresterung und Verseifung vom Standpunkt der elektronischen Theorie der Bindung. *Chem. Ber.* **1933**, *66*, 101–104. (c) Smith, H. A.; Burn, J. Kinetics of the acid-catalyzed esterification of phenyl- and cyclohexyl-substituted aliphatic acids in methanol. *J. Am. Chem. Soc.* **1944**, *66*, 1494–1497.

[3] Newman, M. S. Additions to unsaturated functions. In *Steric Effects in Organic Chemistry*; John Wiley & Sons, 1956; pp 201–248.

[4] (a) This type of longer-range steric effect (or wrap-around effect) is similar to what is learned from the A-values in the monoalkylcyclohexanes (i.e., 1.7 Me to 1.8 Et to 2.2 ^{i}Pr to ~5 ^{t}Bu kcal mol^{-1}); Anslyn, E. V.; Dougherty, D. A. Strain and stability. In *Modern Physical Organic Chemistry*; University Science, 2005; pp 65–143. (b) The change of ^{i}Pr to ^{t}Bu introduces, perforce, a methyl carbon in place of a hydrogen that is six atoms removed from the axial hydrogen atoms at C3 and C5 of the cyclohexane ring.



increasing number of intervening bonds between Hs, yet closer in space

[5] A Google Scholar search (6-27-24) for "rule of six" within the 196 articles that cite reference #1 resulted in 61 hits, of which approximately half are in the context of polymer chemistry.

[6] Ahn, S.-C. Studies toward the total synthesis of the venturicidin aglycone. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, 1991.

[7] (a) Tidwell, T. T. Preparation of ketenes. In *Ketenes*, 2nd ed.; Wiley-Interscience, 2006; pp 76–86. (b) Pratt, R. F.; Bruice, T. C. The carbanion mechanism (E1cB) of ester hydrolysis. III. Some structure–reactivity studies and the ketene intermediate. *J. Am. Chem. Soc.* **1970**, *92*, 5956–5964. (c) Inoue, M.; Bruice, T. C. Influence of steric effects upon the rate constants for competing B$_{AC}$2 and E1cB ester hydrolyses. *J. Org. Chem.* **1983**, *48*, 3559–3561.

[8] This trend of a non-linear increase in the relative energetics of a set of substrates containing substituents changing in the steric bulk of substituents (e.g., Me to Et to ^{i}Pr to ^{t}Bu) is, again, reminiscent of the change in A-values for the alkylcyclohexanes.[4a]

[9] The conformers were visualized using *CYLView*. Legault, C. Y. *CYLView20*; Université de Sherbrooke, 2020 (http://www.cylview.org; accessed 6-20-24).

[10] Newman, M. S.; Hishida, S. Alkaline hydrolysis of normal and pseudo methyl esters of *o*-benzoylbenzoates and of hindered alkyl acetates. *J. Am. Chem. Soc.* **1962**, *84*, 3582–3584.