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ARTICLE TYPE

Peri-dimethylamino substituent effects on proton transfer at carbon in α-naphthylacetate esters: a model for mandelate racemase

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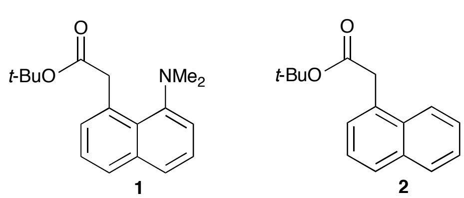
The rate constants for exchange of hydrogen for deuterium at the α-CH_2 positions of 8-(*N,N*-dimethylamino-naphthalen-1-yl)-acetic acid *tert*-butyl ester **1** and naphthalen-1-yl-acetic acid *tert*-butyl ester **2** have been determined in potassium deuteroxide solutions in 1:1 D_2O:CD_3CN, in order to quantify the effect of the neighbouring *peri*-dimethylamino substituent on α-deprotonation. Intramolecular general base catalysis by the (weakly basic) neighbouring group was not detected. Second-order rate constants, k_{DO}, for the deuterium exchange reactions of esters **1** and **2** have been determined as 1.35×10^{-4} $M^{-1}s^{-1}$ and 3.95×10^{-3} $M^{-1}s^{-1}$, respectively. The unexpected 29-fold decrease in the k_{DO} value upon the introduction of a *peri*-dimethylamino group is attributed to an unfavourable steric and/or electronic substituent effect on *intermolecular* deprotonation by deuteroxide ion. From the experimental k_{DO} values, carbon acid pK_a values of 26.8 and 23.1 have been calculated for esters **1** and **2**.

Introduction

Proton transfers are arguably the most abundant and most important processes in biology. Although normally fast, they can become rate determining - and thus need efficient catalysis. This holds especially when the proton is transferred to or from carbon, or when the reaction is concerted with the formation or cleavage of a bond between heavy (i.e. non-hydrogen) atoms. We are interested in the factors that control proton transfer in solution and at enzyme active sites. Small molecule models that incorporate catalytic and substrate functional groups provide an opportunity to study the chemistry in an enzyme-substrate complex, in which functional groups are brought together by an enzyme.[1-5] Mandelate racemase (MR) catalyses a proton transfer reaction, namely the abstraction of a substrate benzylic proton from carbon to an enzyme amine base, Lys-166. MR represents a broader enzyme superfamily that has been postulated to have evolved to catalyze proton abstraction from carbon as a common part of more complex, diverse reaction schemes.[6-8]



We present a synthetic small molecule model **1** designed to mimic the enzyme-substrate complex in MR by juxtaposing a naphthylamino-group *peri* to a benzylic C-H bond. This geometric arrangement had been shown to be unusually efficient for the reverse proton transfer reaction, in enolether hydrolysis catalysed by a *peri*-dimethylammonium group (Scheme 1).[9]

The efficiency of catalysis can be measured by the effective molarity (*EM*), defined as the ratio of *intra*molecular first-order and *inter*molecular second order rate constants. Small molecule models of intramolecular proton transfer exhibit low *EMs* unless the product, and the transition state that leads to it, are stabilized by a strong intramolecular hydrogen bond.[3, 9-12]

Two examples serve to illustrate this point. Based on the same geometric arrangement as in **1**, the ketonization reaction of enol ether **3** (Scheme 1) is catalyzed extraordinarily efficiently by the neighbouring *peri*-dimethylammonium group with an *EM* above 60000.[9] Its efficiency may be rationalized by the formation of a strong intramolecular hydrogen bond in oxocarbenium ion **4.** A smaller, but still substantial, *EM* of 2000 was determined for catalysis by the *ortho*-carboxyl group of the cyclization of enol ether **5** to acylal **6** (Scheme 2).[12] This efficient general acid catalysis was also attributed to the stabilisation of the transition state for proton transfer by intramolecular hydrogen bonding.

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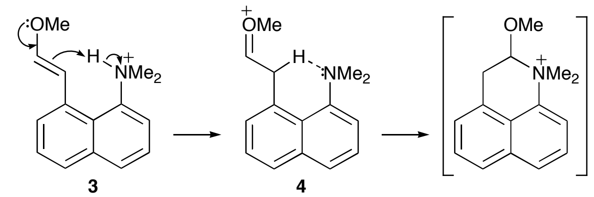
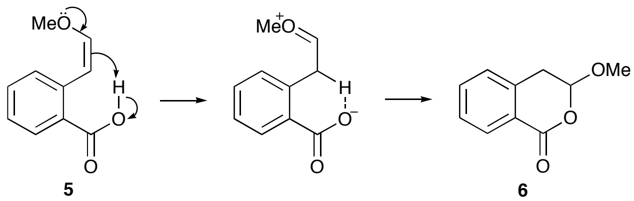


Scheme 1 *Peri*-dimethylammonium catalysis of enol ether protonation.



Scheme 2 Intramolecular catalysis of enol ether protonation.

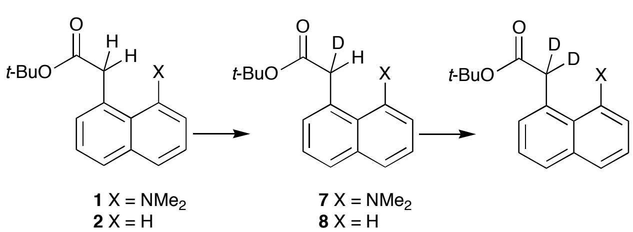
These *EM* values for intramolecular processes involving proton transfer at carbon are the highest reported: the runners-up typically weigh in around 1 M or less.

We report investigations of proton transfer at the α-CH_2 positions of 8-(*N*,*N*-dimethylamino-naphthalen-1-yl)-acetic acid *tert*-butyl ester **1** and**,** for comparison, of naphthalen-1-yl-acetic acid *tert*-butyl ester **2** that is lacking the intramolecular catalytic group . We have employed ^{1}H NMR spectroscopy to follow the exchange of hydrogen for deuterium at the α-CH_2 positions of α-naphthyl esters **1** and **2** in order to probe the effect of the *peri*-dimethylamino substituent on keto-enol tautomerization.

Results

Deuterium exchange experiments

The exchange for deuterium of the α-protons of α-naphthyl esters **1** and **2** (Scheme 3) was followed by monitoring the disappearance of the α-CH_2 groups of the substrates by ^{1}H NMR spectroscopy. Owing to the poor solubilities of both substrates in water, an acetonitrile co-solvent was required. Competing hydrolyses of esters **1** and **2** to the corresponding naphthyl acetic acids were not observed, because of the choice of sterically hindered *tert*-butyl esters as substrates. It was therefore possible to follow the deuterium exchange reaction of both esters for three half-lives in the absence of any significant side reactions.



Scheme 3 Deuterium exchange at α-carbon.

Fig. 1 shows representative partial ^{1}H NMR spectra of α-naphthyl ester **2** obtained during exchange of the α-protons for deuterium in the presence of potassium deuteroxide in 1:1 D_2O:CD_3CN at 25 °C (see supporting information for analogous NMR spectra for ester **1**). The exchange of hydrogen for deuterium led to disappearance of the singlets at 4.71 and 4.49 ppm, and appearance of upfield multiplets at ~ 4.69 and 4.47 ppm

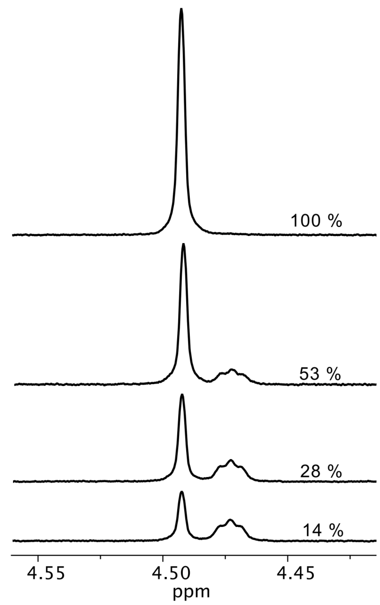


Fig. 1 Representative partial ^{1}H NMR spectra at 400 MHz of ester **2** obtained during exchange of the α-protons for deuterium in the presence of KOD in 1:1 D_2O:CD_3CN at 25 °C and I = 0.1 M (KCl). The percentage of the unexchanged α-CH_2 group of the ester substrate remaining in each sample is indicated above each spectrum.

for esters **1** and **2**, respectively. The upfield multiplets correspond to the α-CHD groups of monodeuteriated α-naphthyl esters **7** and **8** (Scheme 3).

The observed pseudo-first-order rate constants for exchange of the α-protons of esters **1** and **2** for deuterium, k_{obs}, were obtained from the slopes of semilogarithmic plots of reaction progress against time according to eq 1 (all plots are included in the supporting information). The values of *f*(s), the fraction of unexchanged substrate, were calculated from eq 2, where A_{CH2} and A_{std} are the integrated areas of the signals corresponding to the α-CH_2 group of the ester and the twelve methyl hydrogens of the internal standard tetramethylammmonium deuteriosulfate, respectively. Table 1 gives the values of k_{obs} (s^{-1}), which were obtained at different concentrations of potassium deuteroxide.

$$\ln f(\mathrm{s}) = -k_{obs}\mathrm{t} \quad (1)$$

$$f(\mathrm{s}) = \frac{(A_{CH_2}/A_{std})_t}{(A_{CH_2}/A_{std})_0} \quad (2)$$

The observed dependence of values of k_{obs} (s^{-1}) on KOD concentration could be described by eq 3. Plots of k_{obs} values against KOD concentration were linear (Fig. 2) with slopes equivalent to k_{DO} ($M^{-1}s^{-1}$), the second-order rate constants for deuteroxide-catalyzed exchange. The zero intercepts indicate that only the deuteroxide-catalysed reactions are significant. Second-order rate constants, k_{DO}, of 1.35×10^{-4} $M^{-1}s^{-1}$and 3.95×10^{-3} $M^{-1}s^{-1}$ were obtained for the deuterium exchange reactions of esters **1** and **2**, respectively.

$$k_{obs} = k_{DO}[DO^-] \quad (3)$$

Table 1 First and second order rate constants for the exchange of the α-protons of naphthyl esters **1** and **2** for deuterium in KOD solutions in 1:1 D_2O:CD_3CN.[a]

Compound	[KOD]/M	k_{obs}/s^{-1} [b]	k_{DO}/$M^{-1}s^{-1}$ [c]
1	0.023	2.76×10^{-6}	1.34×10^{-4}
	0.046	5.69×10^{-6}	
	0.060	7.90×10^{-6}	
	0.070	9.30×10^{-6}	
	0.083	1.08×10^{-5}	
	0.092	1.18×10^{-5}	
2	0.023	8.28×10^{-5}	3.95×10^{-3}
	0.046	1.77×10^{-4}	
	0.060	2.35×10^{-4}	
	0.070	2.73×10^{-4}	
	0.083	3.20×10^{-4}	
	0.092	3.54×10^{-4}	

[a] At 25 °C and I = 0.1 M (KCl). [b] First order rate constants for deuterium exchange determined from plots of reaction progress against time according to eq 1. [c] Second order rate constants for deuteroxide-catalyzed exchange obtained from the slope of a plot of k_{obs} against [KOD] according to eq 3.

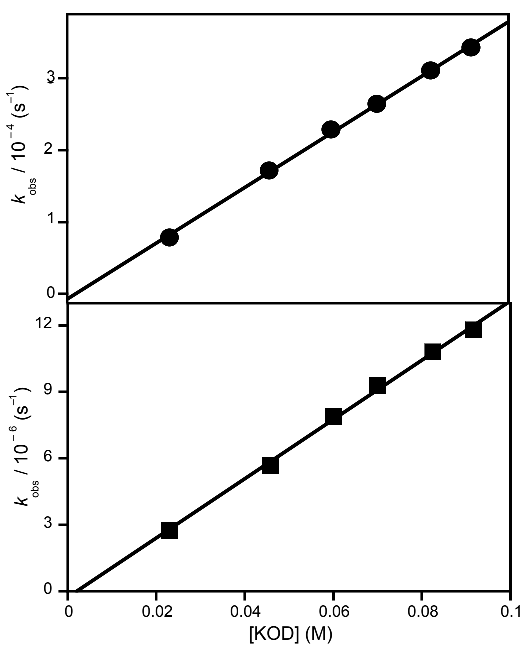


Fig. 2 Plots of first order rate constants, k_{obs}, for exchange of the α-protons of naphthyl esters **1** (■) and **2** (●) for deuterium, against the concentration of potassium deuteroxide (M) in 1:1 D_2O:CD_3CN at 25 °C and I = 0.1 M (KCl).

Determination of the pK_a of the *peri*-dimethylammonium substituent

UV-Visible spectra of ester **1** were acquired in 1:1 H_2O:CH_3CN solutions at a range of pH values. A comparison of spectra obtained in 0.1 M HCl and 0.1 M KOH solutions showed a distinct red shift upon deprotonation of the *peri*-substituent. Spectra acquired in buffered solutions at pH values greater than 2.5 were identical to those obtained in 0.1 M KOH, which shows that the substituent was present as the amino free-base form under these conditions. Fig. 3 shows a range of UV-Vis spectra of ester

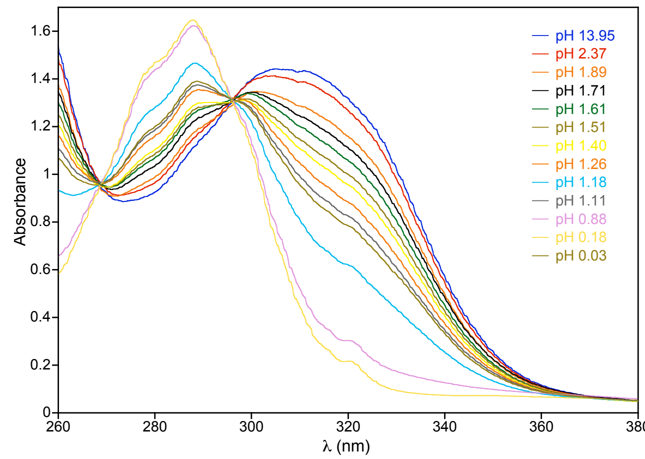


Fig. 3 UV-Visible spectra of ester **1** (0.3 mM) in 1:1 H_2O:CH_3CN solutions at a range of pH values.

1 at different pH values. Non-linear least squares fitting to eq 4 of the changes in absorbance with pH at the chosen analytical wavelength, λ = 325 nm, gives $K_a = 9.61 \times 10^{-2}$ M (pK_a = 1.02 ± 0.03) for the *peri*-dimethylammonium substituent (plot in supporting information). In eq 4, A_{obs} is the observed absorbance at a given pH, A_{max} is the absorbance of the neutral amino substituent and A_{min} is the absorbance of the fully protonated ammonium ion form at λ = 325 nm.

$$A_{obs} = \frac{A_{min} 10^{-pH} + K_a A_{max}}{10^{-pH} + K_a} \quad (4)$$

Discussion

Proton transfer to carbon from the *peri*-dimethylammonium group in **3** is so efficient (*EM* > 60000) that the rate-determining step is the opening of the strong intramolecular hydrogen bond to the oxocarbenium ion intermediate **4** (instead of proton transfer) followed by the rapid addition of the *peri*-dimethylamino group (Scheme 1).[9]

The ester **1** sets up the same geometry as system **4**, with the dimethylamino-group in position vis á vis the α-protons of the ester group to act as an efficient general base. However, only deuteroxide-catalysed exchange is observed. We have determined a pK_a value of 1.02 ± 0.03 for the *peri*-dimethylammonium group of naphthalene ester **1** in 1:1 H_2O: CH_3CN. Under our experimental conditions (pD > 12), this *peri*-substituent will be present in the neutral amino-form and any contribution from an intramolecular reaction will be pD-independent. The absence of a significant positive intercept on the ordinate of the second order plot for ester **1** (Fig. 2) implies that intramolecular general base catalysis by the dimethylamino group is not competitive with the intermolecular reaction of deuteroxide ion present at concentrations of 0.025 – 0.092 M. Reactions at lower pD values, or lower deuteroxide concentrations, were too slow for practical measurements by ^{1}H NMR spectroscopy at 25 ºC.[13] The effect of the *peri*-dimethylamino group on the second order rate constant for deuteroxide-catalyzed exchange at the α-CH_2 position of naphthyl ester **1** is relatively small. The introduction of a *peri*-dimethylamino group suppresses the k_{DO} value by 29.3–fold

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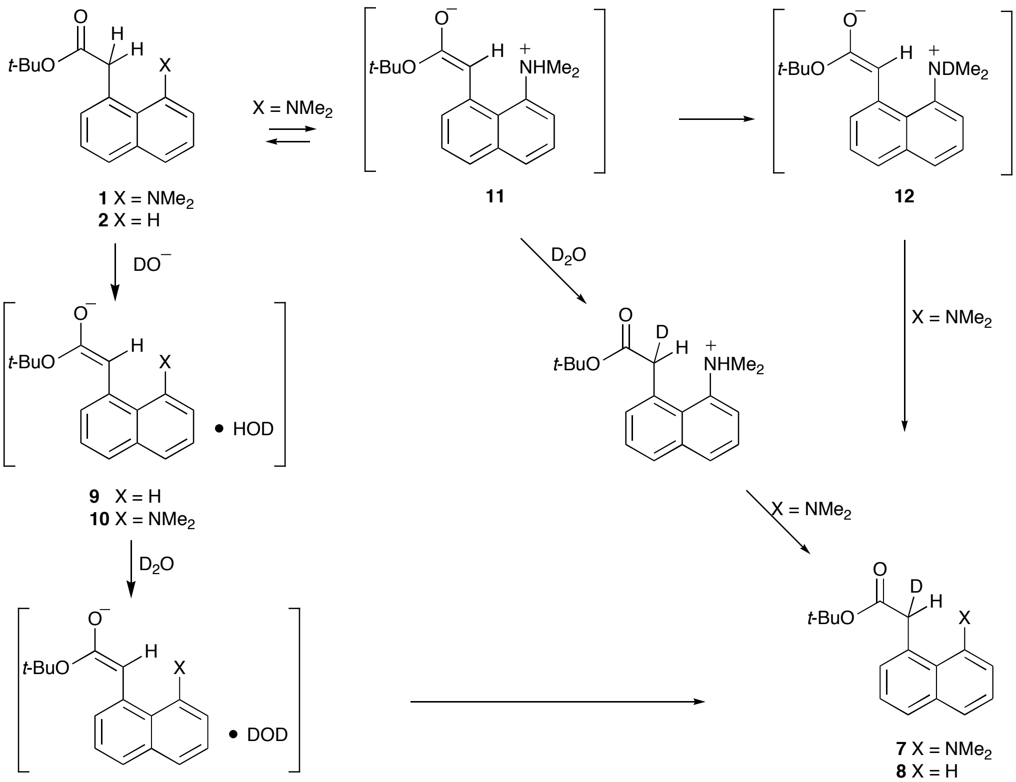


Scheme 4 Potential pathways for deuterium exchange at the α-carbons of naphthyl esters **1** and **2**.

rather than increasing this value.

Intramolecular protonation of enol ether **3** by the peri-dimethylammonium group (pK_a = 4.01), does efficiently outcompete intermolecular protonation by up to 1 M hydronium ion, H_3O^+ (pK_a = −1.74).[9] By contrast, intramolecular deprotonation of the α-CH_2 group of ester **1** by the dimethylamino group (pK_a = 1.02, significantly less basic than might be expected from **3**) does not compete with intermolecular deprotonation by the more basic deuteroxide ion (pK_a (D_2O) = 16.6) present at 0.025 - 0.092 M concentrations. Even though the geometry of ester **1** closely matches that of enol ether system **3**, the complementary requirement for efficient proton transfer of a strong hydrogen bond is not fulfilled. The pK_a of the migrating α-proton of **4**, estimated as less than −3,[12] could match that of the dimethylamino group in the transition state.[12] But the much greater difference between the pK_as of the dimethylammonium group (1.02) and the carbon acid pK_a of ester **1** (26.8, see below) means that similar pK_a matching as the transition state is approached, as invoked as the condition for the efficiency of mandelate racemase (and other enzymes), cannot be achieved.[14-18]

Scheme 4 shows the possible pathways of exchange of hydrogen for deuterium at the α-CH_2 groups of esters **1** and **2**. Formation of the mono-deuteriated product **8** (bottom right in Fig. 4) from **2** can only occur by intermolecular deprotonation by deuteroxide ion to yield an [enolate**.**HOD] complex **9**. The replacement of the initially formed HOD molecule by one of bulk solvent, present in large excess, followed by rapid deuteration by D_2O, then gives initial exchange product **8**.

The formation of monodeuteriated product **7** from ester **1** by an analogous intermolecular pathway will likely occur *via* enolate **10**. Additional routes to exchange product **7** involving intramolecular deprotonation by the *peri*-dimethylamino group are also shown in Scheme 4. Deprotonation of the α-CH_2 proton of **1** by the *peri*-dimethylamino group would generate zwitterionic enolate **11**. Subsequent incorporation of deuterium into enolate **11** could occur by two possible routes. The exchange of the hydrogen of the ammonium group of **11** for deuterium from bulk solvent D_2O would give enolate **12**, and subsequent intramolecular transfer of deuterium to the enolate would yield exchange product **7**. Alternatively, enolate **11** could accept a deuterium atom at α-carbon from a molecule of solvent D_2O followed by the deprotonation of the *peri*-dimethylammonium group.

If intramolecular deprotonation were to occur, the thermodynamically strongly favourable reprotonation of enolate **11** by the acidic ammonium group would be expected to be too fast to permit exchange to occur by either of the two intramolecular routes outlined above. Intermolecular protonation of the enolate of ethyl acetate (pK_a = 25.6) by the conjugate acid ammonium ion of 3-quinuclidinone (pK_a = 7.5) has been estimated to be diffusion limited.[19,20] The *intramolecular* protonation of enolate **11**, by the 6 pK_a unit more acidic *peri*-dimethylammonium ion should be significantly faster. Owing to the proximity of the proton, this protonation reaction will likely outcompete the diffusion of bulk solvent to and from enolate **11**, which is necessary for exchange to occur by either of the two intramolecular routes (Scheme 4).

On the basis of the above discussion, we conclude that the deuterium exchange reactions of esters **1** and **2** both occur by intermolecular routes. The observed 29.3-fold suppression of deuterium exchange by the *peri*-dimethylamino substituent must be due to a steric and/or an electronic substituent effect on intermolecular deprotonation by deuteroxide ion. Electronic and steric effects in *peri*-disubstituted systems have been well-documented.[21-27] X-ray crystal structures of naphthalenes bearing a dimethylamino group and an electron deficient carbonyl substituent in the *peri*-positions show that the pyramidyl dimethylamino group is oriented with its lone pair in the space between the two *peri*-groups as a strategy towards the relief of steric strain.[26] The presence of a lone pair of electrons on the *peri*-nitrogen atom will disfavour the approach of deuteroxide ion and the subsequent formation of the negatively charged enolate intermediate. In addition, the steric bulk of this *peri*-substituent could hinder the approach of deuteroxide ion to the α-CH_2 group of ester **1**. The effective bulk of the *peri* dimethylamino-group will increase on protonation, accounting for its significantly reduced basicity in terms of strain in the conjugate acid in comparison with the analogous group in enol ether **3**. Thus the (smallest tetrahedral pair of) methyl groups of 1,8-dimethylnaphthalene are both splayed out by almost 5° from the trigonal geometry,[28] while systems with larger tetrahedral groups relieve *peri*-strain by ring distortion. [29]

Based on the observed k_{DO} values for intermolecular deuteroxide-catalyzed exchange, carbon acid pK_a values may be estimated for esters **1** and **2**. Using a secondary solvent deuterium isotope effect of $k_{DO}/k_{HO} = 1.4$[19] and the experimental k_{DO} values, second order rate constants for deprotonation of esters **1** and **2** by hydroxide ion at α-carbon can be calculated as $k_{HO} = 9.64 \times 10^{-5}$ $M^{-1}s^{-1}$ and 2.82×10^{-3} $M^{-1}s^{-1}$, respectively. J. P. Richard and co-workers have constructed a correlation of k_{HO} values for deprotonation of neutral α-carbonyl acids with corresponding carbon acid pK_a values in water.[20] An excellent linear relationship has been observed for a broad range of aldehydes, ketones, esters and amides using eq 5, in which both k_{HO} and pK_a are statistically corrected for the number of acidic protons, p, at the carbon acid.

$$\log\left(\frac{k_{HO}}{p}\right) = 6.52 - 0.40(\mathrm{p}K_a + \log p) \qquad (5)$$

Using the k_{HO} values calculated above, and $p = 2$, pK_a values of 26.8 and 23.1 can be estimated for esters **1** and **2**, respectively, which are similar to the value of 25.6 determined for ethylacetate in aqueous solution.[19] The 2.5 unit decrease in pK_a observed in comparing ethyl acetate and ester **2** is similar to the pK_a decrease that occurs upon introduction of an α-phenyl substituent to ethyl acetate: The pK_a for α-phenylethyl acetate in water is 22.7[30], compared to 25.6 in ethylacetate. This suggests that the effects of the 50% acetonitrile co-solvent and the *tert*-butyl functional group on carbon acidity are small relative to that of the α-aryl substituent. The pK_a value for *peri*-substituted ester **1** is 1.2 units higher than for ethyl acetate, thus the *peri*-dimethylamino substituent counteracts the acidifying α-naphthyl substituent effect resulting in an overall decrease in acidity relative to the simple alkyl ester, ethyl acetate.

Implications

Juxtaposition of functional groups is widely accepted as a source of enzymatic catalysis. Evidence from two previous enzyme models[9, 12] predicted that the geometry for proton abstraction in model **1** would be optimal. Though this may indeed be the case, quantification of any effect is impossible because intramolecular reprotonation of the enolate intermediate is faster than the intermolecular exchange reaction. An enzyme such as MR can avoid this scenario by using its flexibility to make the reverse reaction less efficient, e.g. by pulling the protonated amine group away from the reaction centre. These observations highlight a limitation of simple synthetic enzyme models that cannot easily mimic the inherent ability of proteins to effect subtle conformational adjustments as part of catalysis.

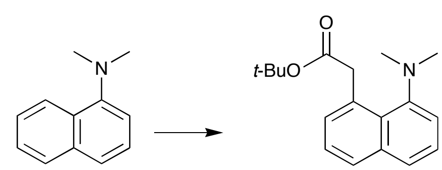
Experimental

Materials.

Deuterium oxide (99.9% D) was purchased from Apollo Scientific Ltd. Deuterium chloride (35% wt, 99.5 % D), potassium deuteroxide (40% wt, 98+% D), deuterated chloroform (99.8% D), 1-naphthylacetic acid (>90%), and *N*,*N*-dimethyl-1-naphthylamine (99%) were purchased from Sigma Aldrich and were recrystallized from ethanol. All other chemicals were reagent grade and were used without further purification. Stock solutions of deuterium chloride and potassium deuteroxide were prepared by dilution of commercial concentrated standards, and titration against volumetric NaOH or HCl using phenolphthalein as indicator.

Synthesis

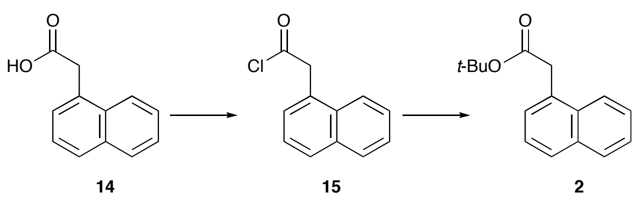
8-(*N*,*N*-dimethylamino-naphthalen-1-yl)-acetic acid *tert*-butyl ester 1.



13 → 1

n-Butyllithium (*ca*. 1.6 M, 10.5 mL in hexane, 16.8 mmol) was added to a stirred solution of *N*,*N*-dimethyl-1-naphthylamine **13** (2.0 mL, 11.2 mmol) in anhydrous diethylether (18.0 mL) under an argon atmosphere. *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (1.94 g, 16.8 mmol) was added to the solution after 15 min of stirring, and the solution was stirred for an additional 14 h. The reaction mixture was then cooled to –78 °C, and a suspension of copper (I) cyanide (1.00 g, 11.2 mmol) in anhydrous diethylether (15 mL) was added. Following the addition of CuCN, the reaction flask was covered in aluminium foil in order to exclude light, and the mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled to –78 °C, and *tert*-butyl bromoacetate (2.18 g, 11.2 mmol) was added. The flask contents were allowed to warm to room temperature and stirred for 1 h. Methanol (150 mL) and diethylether (100 mL) were then added to the reaction flask. The resulting mixture was washed with water (4 × 100 mL) and dried over magnesium sulfate. The crude mixture was concentrated *in vacuo* and purified by column chromatography (cyclohexane to 9:1 cyclohexane:diethylether) to give ester **1** as a colourless oil (1.12 g, 3.91 mmol, 35%). R_f (cyclohexane : diethylether = 9 : 1) = 0.38; $\boldsymbol{\delta_H}$ (700 MHz; $CDCl_3$) 7.75 (d, 1H, *J* 7.2, aromatic-H), 7.59 (d, 1H, *J* 7.2, aromatic-H), 7.40-7.36 (m, 2H, aromatic-H), 7.27 (d, 1H, *J* 6.3, aromatic-H), 7.23 (d, 1H, *J* 6.3, aromatic-H), 4.34 (s, 2H, $ArCH_2CO$), 2.73 (s, 6H, $N(CH_3)_2$) 1.42 (s, 9H, $C(CH_3)_3$). $\boldsymbol{\delta_C}$ (175 MHz; $CDCl_3$) 172.0, 152.4, 136.6, 131.5, 131.1, 129.2, 129.0, 125.8, 125.7, 125.5, 117.9, 80.2, 46.6, 44.2, and 28.7; ***m/z*** (ESI^+) 308.2 (100); HRMS (ESI^+) $C_{16}H_{23}NO_2Na$ requires 308.1626, found 308.1613 (–4.2 ppm).

Naphthalen-1-yl-acetic acid *tert*-butyl ester 2.



Thionyl chloride (3.00 mL, 41.1 mmol) was added under argon to 1-naphthylacetic acid **14** (4.50 g, 24.1 mmol, recrystallised from ethanol). The resulting solution was stirred for 24 h at room temperature. Excess thionyl chloride was then removed *in vacuo* to give the acid chloride **15** as a brown liquid (4.90 g, 23.9 mmol) which was used without further purification. ^1H NMR $\boldsymbol{\delta_H}$ (400 MHz; $CDCl_3$): 7.99-7.21 (m, 7H, aromatic H), 4.62 (s, 2H, CH_2). *Tert*-butanol (1.15 g, 15.4 mmol) and pyridine (8.46 g, 115.4 mmol) were added to a stirred solution of the acid chloride **15** (2.50 g, 11.5 mmol) in anhydrous THF (50 mL). The resulting solution was stirred under argon for 24 h at room temperature. Pentane (150 mL) was added to the mixture, and the solution was filtered to remove the pyridinium chloride salt. The filtrate was washed with saturated sodium chloride solution (2 × 50 mL), saturated sodium bicarbonate solution (2 × 50 mL), and deionised water (2 × 50 mL). The solution was then dried over magnesium sulfate, the solvent was removed in *vacuo*, and subsequent purification by preparative TLC (cyclohexane : diethylether = 9 : 1) gave ester **1 (**1.20 g, 4.9 mmol, 43%) as a colourless oil (found: C, 79.42; H, 7.47. Calc. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%); R_f (cyclohexane:diethylether = 9:1) = 0.80; $\boldsymbol{\nu_{max}}$ (neat)/cm^{-1} 1726 and 1135; $\boldsymbol{\delta_H}$ (700 MHz; $CDCl_3$) 7.99 (d, 1H, *J* 8.5, aromatic-H), 7.85 (d, 1H, *J* 8.1, aromatic-H), 7.77 (d, 1H, *J* 11.5, aromatic-H), 7.49 (m, 2H, aromatic-H), 7.40 (m, 2H, aromatic-H), 3.97 (s, 2H, $ArCH_2CO$), 1.42 (s, 9H, $C(CH_3)_3$); $\boldsymbol{\delta_C}$ (175 MHz; CDCl3) 171.2, 133.8, 132.2, 131.3, 128.7, 128.6, 127.8, 126.1, 125.5, 125.4, 123.9, 81.2, 40.5, and 28.9; *m/z* (ESI^+) 265.1 (100); HRMS (ESI^+) $C_{16}H_{18}O_2Na$ requires 265.1204, found 265.1207 (+1.1 ppm).

Kinetic methods.

Rate constants for exchange for deuterium of the first α-proton of each of the naphthalene esters **1** and **2** in 1:1 D_2O:CD_3CN were determined by monitoring the disappearance of the singlet corresponding to the α-CH_2 group of the substrate by ^1H NMR spectroscopy. Generally, the reactions of each substrate were followed for at least three half-lives. All reactions were carried out in 1:1 D_2O : CD_3CN at 25 °C and a constant ionic strength of 0.1 M maintained with potassium chloride.

In the case of 8-(*N,N*'-dimethylamino-naphthalen-1-yl)-acetic acid *tert*-butyl ester **1**, the progress of isotope exchange was followed directly in the probe of the NMR spectrometer. Reactions in a volume of 800 μL were initiated by the addition of 400 μL of a stock solution of **1** (10 mM in CD_3CN) to a solution of potassium deuteroxide in D_2O (400 μL), containing internal standard, tetramethylammonium deuteriosulfate. NMR samples (750 μL of above solution) were run at 25 °C in a Varian Mercury 500 MHz NMR spectrometer, in which spectra were continuously obtained until ~ 90% of exchange for deuterium of the α-CH_2 had occurred. The progress of isotope exchange of naphthalen-1-yl-acetic acid *tert*-butyl ester **2** was followed using a quench-based method. Reactions in a volume of 12 mL were initiated by the addition of 6 mL of stock solution of **2** (10 mM in CD_3CN) to a solution of potassium deuteroxide in D_2O (6 mL), containing internal standard, tetramethylammonium deuteriosulfate. The progress of isotope exchange was determined by withdrawal of 800 μL aliquots of the reaction mixtures, which were quenched with a 2.5 M DCl solution to pD < 10. The samples were placed in a sealed plastic bag containing calcium chloride and were stored at –18 °C until they could be analyzed by ^1H NMR spectroscopy. For naphthyl esters **1** and **2**, the final substrate and internal standard concentrations in the reaction solutions were 5.0 mM and 2.0 mM, respectively.

^1H NMR spectra were acquired with 64 transients, a delay of 15 s between pulses, an acquisition time of 6 s and a pulse width of 4.8 μs. ^1H NMR spectral baselines were subjected to a first-order drift correction before integration of the peak areas. The estimated error in the observed pseudo-first-order rate constants for exchange (k_{obs}, s^{-1}) is ± 10 % based on the error of the ^1H NMR measurement. Although the measurements of k_{obs} are single determinations, the calculated error in similar measurements for other carbon acids performed by J. P. Richard *et al.* [19, 20] is ± 10 % for k_{obs} and ± 0.5 units for the pK_a.

p$\boldsymbol{K_a}$ Determination

All UV-Vis spectrophotometric measurements were recorded using a Varian Cary 50 UV-Vis spectrophotometer thermostatted at 25 ± 0.1 °C. The same quartz cuvette (1 mL) was used for all measurements. A stock solution of 8-(*N,N'*-dimethylamino-naphthalen-1-yl)-acetic acid *tert*-butyl ester **1** (20.3 mM) was prepared in HLPC-grade acetonitrile. UV-Vis spectra were acquired in 0.01 - 2 M HCl, phosphoric acid buffers, phosphate buffers and 0.1 M KOH in 1:1 H_2O: CH_3CN. With the exception of the 0.5, 1.0 and 2.0 M HCl solutions, the ionic strength of all solutions was maintained at 0.1 M (KCl). In each case, the buffer, HCl or KOH solution (1 mL) was added (via glass bulb pipette) to the quartz cuvette and allowed to equilibrate at 25 ± 0.1 °C for 10 min. The stock solution of **1** (15 μL) was then added via

Hamilton syringe to the cuvette to give a final substrate concentration of 0.3 mM. After mixing, UV-Vis absorbance scans (220-600 nm) were obtained and a fixed wavelength absorbance was subsequently recorded at 325 nm over 10 min. In all cases, the absorbance values were observed to be constant during this time period. The observed absorbance values at 325 nm were corrected for the background absorbance due to buffer, HCl or KOH at the same wavelength. The pH of each solution was determined at 25 ˚C using a MeterLab™ PHM 290 pH-Stat Controller equipped with a radiometer combination electrode.

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