sufficiently different spectra). In the NMR experiment, one "average" environment for the ketone was found due to exchange of the ketone between the two media, one with water and one without. In the infrared the two environments are separable.

The results presented here give a picture of micelles which is compatible with current views.[3,4] Water penetrates *almost* everywhere into micelles; there is a region (assumed to be the central core) completely devoid of water. Probe molecules are able to move in and out of the different environments. Further work is in progress using this methodology to probe the structure of other systems.

Acknowledgment. Thanks are due to Dr. U. Köhler for his advice on the synthesis of 7-oxo-octanoic acid and to Dr. J. Villalain for a preprint of his work.[8]

The Influence of a Carboxylate Group on the Rate of O-Acylation of 2-Hydroxymethylimidazoles by a Strained Amide

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During the course of all serine protease[1] catalyzed ester and amide hydrolyses, the Ser–OH group of the catalytic triad (Asp CO_2^-–HisIm–SerOH) becomes transiently acylated. Although this suggests common hydrolytic pathways, continuing studies with serine proteases (SPases) indicate subtle substrate-dependent diversities. These include differing sites of initial acylation[2] and different numbers of protons in flight in the rate-limiting step.[3] The role of the essential Asp CO_2^- component has not been generally resolved. Two possibilities, general base enhancement of the imidazole basicity and electrostatic stabilization of imidazolium, have been favored.[1] Evidence exists that enzymes inhibited with species approximating the initial tetrahedral intermediate maintain an Asp CO_2^-–H-Im^+-His H-bond, thus supporting the electrostatic role.[4] Even so, it is possible that different substrates may recruit different levels of involvement of the various catalytic components. Nevertheless, the wide-spread occurrence of this catalytic triad suggests a considerable mechanistic advantage to the enzymes that employ it.

If such an arrangement leads to obvious acceleration, it is surprising how few studies have directly addressed the ability of a triad to facilitate O-acylation in a small molecule. A number of reports deal with the reaction of amino alcohols with esters[5] or reactive amides.[5b,1,6] A smaller number deal with the interaction of CO_2^- and imidazole during acyl transfer to H_2O[7] (which is more properly a model for the deacylation of SPases). Apparently the preliminary reports of Bender et al.[8] are the only published ones employing a model of the triad in acylation, in this case by *m*- and *p-tert*-butylphenylacetate.

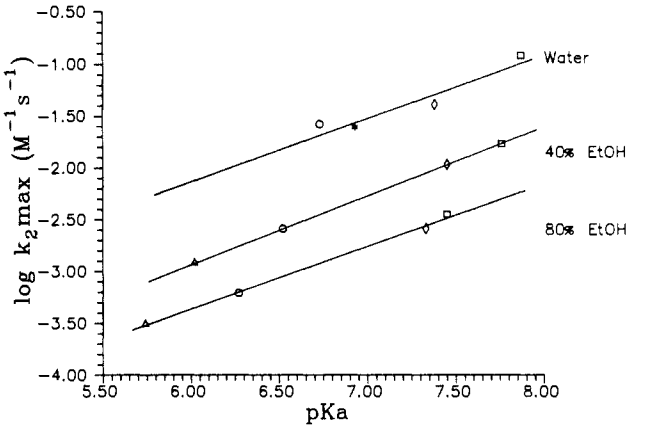

Figure 1. Brønsted plots of the maximal second-order rate constant (k_2^{max}) versus pK_a^{Im} for **1a** (◇), **1b** (△), **1c** (○), **1d** (*), and **1e** (□) with twisted amide **2** in H_2O ($\beta = 0.6 \pm 0.1$), 40% ($\beta = 0.66 \pm 0.03$) and 80% (0.60 ± 0.02) (v/v) EtOH/H_2O, T = 25 °C, μ = 0.2 (KCl).

Table I. pK_a^{Im} Values for **1a–c,e** Determined by Potentiometric Titration at 25 °C, μ = 0.2 (KCl) in H_2O, 40% and 80% (v/v) EtOH/H_2O[a]

		pK_a^{Im}	
compd	H_2O	40% EtOH/H_2O[b]	80% EtOH/H_2O[b]
1a	7.38 ± 0.05	7.45 ± 0.02	7.33 ± 0.02
1b	6.18 ± 0.02	6.02 ± 0.02	5.74 ± 0.02
1c	6.73[c]	6.52 ± 0.02	6.27 ± 0.02
1e	7.88 ± 0.03	7.76 ± 0.02	7.45 ± 0.02

[a] Averages of duplicate measurements. [b] Adjusted pK_a values according to pH = (meter reading) −0.09 (40% EtOH/H_2O) or pH = (meter reading) −0.2 (80% EtOH/H_2O): Bates, R. G.; Paabo, M.; Robinson, R. A. *J. Phys. Chem.* **1963**, *67*, 1833. [c] Eiki, T.; Kawada, S.; Matsushima, K.; Mori, M.; Tagaki, W. *Chem. Lett.* **1980**, 997.

We have shown that the direct O-acylation of **1c** and **d** by **2**[9] proceeds to **3** via the process shown in eq 1.[6] Herein we report an incremental study of the effect of the remote carboxylate in **1a** on the analogous process.

Shown in Figure 1 are Brønsted plots (log k_2^{max} versus imidazole pK_a^{Im})[11] for reaction of **1a–e** with **2** in H_2O, 40% and 80% v/v EtOH/H_2O. (pK_a^{Im} and k_2^{max} values are given as Supplementary Material.) Several common features are of note. (1) The log k_2 values[11] plateau above pK_a^{Im} indicating the basic form is active. (2) The reaction product in all cases is CH_2-O-acylated as judged by ^{1}H NMR, IR, and mass spectral data (see Supplementary Material). (3) With no CH_2OH group present, the k_2^{max} values

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(11) Second-order rate constants (k_2) for **1a–e** with **2** were evaluated from slopes of the k_{obsd} versus [**1a–e**] plots at different pH values. The maximal second-order rate constant (k_2^{max}) was calculated from $k_2 = k_2^{max}K_a^{Im}/([H^+] + K_a^{Im})$.

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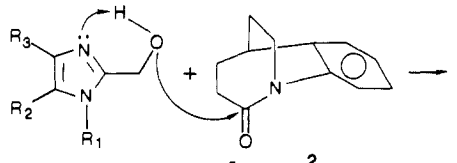
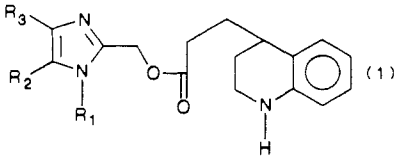


2

1a; $R_1 = R_2 = H$, $R_3 = C(CH_3)_2CO_2^-$
b; $R_1 = R_2 = H$, $R_3 = C(CH_3)_2CO_2Me$
c; $R_1 = R_2 = R_3 = H$
d; $R_1 = CH_3$, $R_2 = R_3 = H$
e; $R_1 = H$, $R_2 = R_3 = CH_3$



(1)

3a-e

lie ~8-100 fold (depending on the example[6]) below the Brønsted line indicating this group is required for maximal activity.[6] For example, if the CH_2OH unit in **1a** is replaced by CH_2OCH_3, the k_2^{max} value drops from (4.06 ± 0.05) × 10^{-2} to (5.90 ± 0.45) × 10^{-3} M^{-1} s^{-1}.

Since **1a** lies on the same Brønsted lines as defined by **1b-e**, the CO_2^- unit in this system is incapable of providing another mechanism for O-acylation[12] other than that simply dependent upon imidazole basicity. A fundamentally different or enhanced pathway such as CO_2^- acting as a general base (on N-H) in concert with the imidazole-HO interaction is expected to produce an upward deviation from the line.

Since this is not observed, at first glance one might suggest there is no positive benefit of attachment of the CO_2^- in **1a**, but we believe the situation is more subtle. The pK_a^{Im} values in Table I show the N basicity of **1a** is greater than that of comparison ester **1b**, and a corresponding increase in k_2^{max} is observed. In $EtOH/H_2O$ media of reduced polarity,[13] activity of all the imidazole alcohols is reduced as expected, and there is a noticeable drop in the pK_a^{Im} of **1b-e**. However, the electrostatic and/or H-bonding stabilization in the zwitterionic form of **1a** counteracts the general medium-induced reduction in N basicity[14] thereby enhancing the CH_2OH nucleophilicity in relation to that of **1b-e**.

In summary, the main benefit of the anionic pendant in **1a** is an electrostatic one which is manifested more prominently in media of reduced polarity. To term this system a "model" for the acylation of SPases invites comparison with the enzyme which may not be justified given the unorthodox structure of the acylating agent[6] and perhaps nonoptimal orientation of the functional groups in **1a**.[15] Rather, we prefer to view the system as a small molecule demonstration of an electrostatic role for CO_2^--Im in direct CH_2OH acylation. Nevertheless we note that in addition to other possibilities,[1] a similar electrostatic role has been suggested for the Asp CO_2^--His section of the triad in the SPases.[4,16]

Acknowledgment. We thank the University of Alberta and Natural Sciences and Engineering Research Council of Canada for financial support.

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Supplementary Material Available: Tables of thermodynamic pK_a^{Im} and k_2^{max} values for **1a-e** reacting with **2** and product study data (^1H NMR, IR, mass spectral) (3 pages). Ordering information is given on any current masthead page.

Solvent-Induced Mechanism Change in Charge-Transfer Molecules. Inversion versus Rotation Paths for the *Z* → *E* Isomerization of Donor-Acceptor Substituted Azobenzenes

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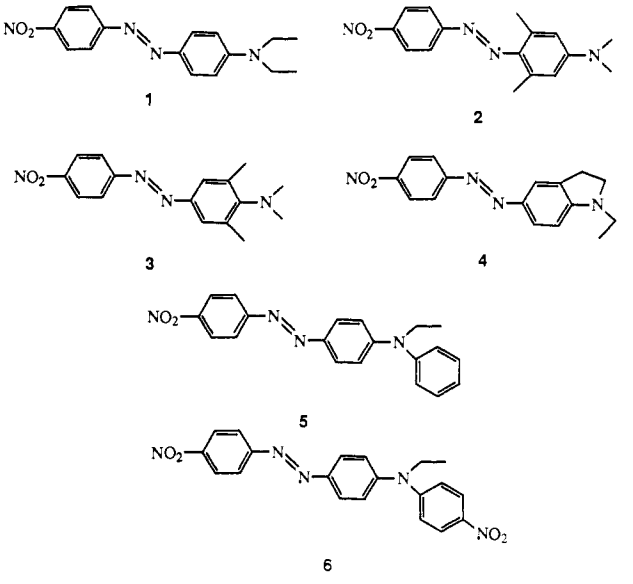
The mechanism for the thermal *Z* → *E* isomerization of p-donor-p'-acceptor ("push-pull") azobenzenes has generated considerable controversy.[1-9] While reaction of azobenzene is generally accepted to proceed by an inversion mechanism, in which sp^2-sp rehybridization of an azobenzene nitrogen affords isomerization via a semilinear transition state,[10-15] we and others have noted coupling of donor and acceptor substituents in compounds such as 4-(diethylamino)-4'-nitroazobenzene (DENAB) (**1**) can



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