DOI: 10.1002/chem.200600280

Steric Effects in the Uncatalyzed and DMAP-Catalyzed Acylation of Alcohols—Quantifying the Window of Opportunity in Kinetic Resolution Experiments**

Christian B. Fischer, Shangjie Xu, and Hendrik Zipse*[a]

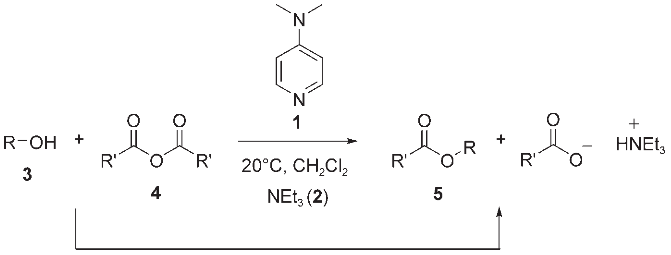
Abstract: The kinetics of the reaction of several alcohols (benzyl alcohol, ethanol, 1-phenylethanol, cyclohexanol, and 1-methyl-1-phenylethanol) with a selection of anhydrides (acetic anyhydride, propionic anhydride, isobutyric anhydride, isovaleric anhydride, and pivalic anhydride) as catalyzed by 4-(*N*,*N*-dimethylamino)pyridine (DMAP)/triethyl amine have been studied in CH_2Cl_2 at 20 °C. In all cases the reaction kinetics can be described by rate laws containing a DMAP-catalyzed term and an uncatalyzed (background) term. The rate constants for the background reaction respond sensitively to changes in the steric demand of the alcohol and the anhydride substrates, making the reaction of cyclohexanol with acetic anhydride 526 times faster than the reaction with pivalic anhydride. Steric effects are even larger for the catalyzed reaction and the reactivity difference between acetic and pivalic anhydride exceeds a factor of 8000 for the reaction of cyclohexanol. There is, however, no linear correlation between the steric effects on the catalyzed and the uncatalyzed part. As a consequence there are substrate combinations with dominating catalytic terms (such as the reaction of benzyl alcohol with isobutyric anhydride), while other substrate combinations (such as the reaction of cyclohexanol with pivalic anhydride) are characterized through a dominating background process. The implications of these findings for the kinetic resolution of alcohols are discussed.

Keywords: acylation · density functional calculations · DMAP · kinetics · nucleophilic catalysis · substituent effects

Introduction

The base-catalyzed acylation of alcohols and amines through reaction with anhydrides plays an important role in the protecting-group chemistry[1] and the kinetic resolution (KR) of these substrates.[2] In both areas the use of sterically hindered anhydrides enjoys widespread application, usually for the sake of reduced reactivity (of the acylation product) or enhanced selectivity (of the acylation process). This type of acylation reaction can be catalyzed efficiently with basic catalysts based on the pyridine[3–5] or imidazole[6–8] motif, but tertiary alkyl amines[9] or phosphines[10] have also been used successfully. In many cases the catalysts are derivatives of 4-(*N*,*N*-dimethylamino)pyridine (**1**, DMAP), whose catalytic potential is exploited widely in acyl- and other group-transfer reactions.[11–22] In situ regeneration of these basic catalysts is typically achieved through addition of a cheap auxiliary base, such as triethyl amine (**2**). The reaction works particularly well in apolar organic solvents[5a,g] and the overall reaction can thus be described as shown in Scheme 1.

In a recent mechanistic study[23] of the DMAP-catalyzed acetylation of cyclohexanol (R = cyclohexyl, R′ = methyl) it was shown that the catalyzed process depicted in Scheme 1



Scheme 1.

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[a] Dr. C. B. Fischer, Dr. S. Xu, Prof. Dr. H. Zipse
Department Chemie und Biochemie, LMU München
Butenandtstrasse 5–13, 81377 München (Germany)
Fax: (+49) 89-2180-77738
E-mail: zipse@cup.uni-muenchen.de

[**] DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

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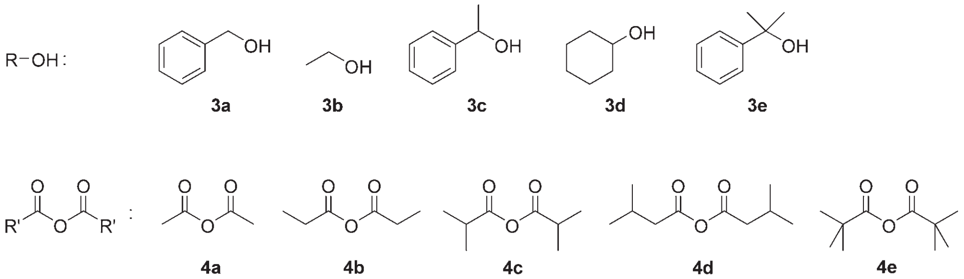
is accompanied by a parallel, uncatalyzed pathway. This is reflected in the rate Equation (1) through the presence of two separate terms:

$$r = k_2[\mathrm{R{-}OH}][(\mathrm{R'CO})_2\mathrm{O}] + k_3[\mathrm{R{-}OH}][(\mathrm{R'CO})_2\mathrm{O}][\mathrm{DMAP}] \quad (1)$$

The uncatalyzed (background) process is characterized through rate constant k_2 and the catalyzed term through rate constant k_3. At millimolar concentrations of the DMAP catalyst the rate of the catalyzed process was found to proceed approximately ten times faster than the background process. Little is known about the influence of the steric bulk of substituents R and R′ on the rate constants k_2 and k_3 (and thus on the ratio of the uncatalyzed and the catalyzed processes). This information is, however, highly relevant for the rationalization of results obtained in the kinetic resolution (KR) of alcohols. A recent review of the nonenzymatic KR of alcohols arrives at the conclusion that secondary alcohols can be resolved effectively with carboxylic acid anhydrides of intermediate steric demand with the aid of a variety of chiral nucleophilic catalysts.[2] Thus, while very good selectivities have been obtained with isobutyric anhydride (R′=*i*Pr) for a variety of secondary benzyl alcohols and catalysts, few examples exist for other classes of alcohols (primary or tertiary) or anhydrides (e.g. R′=*t*Bu). This may at least partially be due to a larger sensitivity of the catalyzed process to steric effects as compared to the uncatalyzed process. To explore this point in a quantitative fashion we have studied here the DMAP-catalyzed acylation of alcohols of different steric demand with anhydrides of equally variable character.

Results

In all cases studied here, the reaction has been performed by using dichloromethane as the solvent and catalyzed by the DMAP/NEt$_3$ combination. Alcohols **3a–e** and anhydrides **4a–e** were selected as substrates.



The rate law described in Equation (1) has been assumed to be valid for all the systems studied here. The linear dependence of the rate of reaction, r, on the catalyst concentration has been confirmed for all cases. To simplify the determination of rate constants k_2 and k_3 we have performed kinetic measurements under pseudo-first-order conditions with the alcohol as the minor component. Under these conditions the rate equation can be simplified to Equation (2) with the pseudo-first-order rate constant $k_{1\psi}$ defined by Equation (3).

$$r = k_{1\psi}[\mathrm{R{-}OH}] \quad (2)$$

$$k_{1\psi} = k_2[(\mathrm{R'CO})_2\mathrm{O}]_0 + k_3[(\mathrm{R'CO})_2\mathrm{O}]_0[\mathrm{DMAP}]_0 \quad (3)$$

The reactions have been followed through gas-chromatographic determination of the alcohol concentration by using *n*-nonane as internal standard.

The results for the acetylation of alcohols **3a–e** with acetic anhydride (**4a**) are given in Table 1. In line with the expectation of increasing steric demand on going from primary to secondary and tertiary alcohols, a general decrease in the rates of the uncatalyzed as well as the catalyzed process can be observed. This is particularly easy to see for the three benzyl alcohols **3a**, **c**, and **d**, whose background rate constants k_2 differ by a factor of 200. The rate constants k_3 describing the catalyzed process vary by a factor 1260 for the same substrates, indicating that steric effects are significantly larger in the catalyzed process. With the rate constants k_2 and k_3 in hand the ratio of the catalyzed and the uncatalyzed (background) process can be expressed quantitatively through Equation (4).

Table 1. Rate constants k_2 [$\mathrm{M^{-1}s^{-1}}$] and k_3 [$\mathrm{M^{-2}s^{-1}}$] in the acylation of alcohols **3a–e** with anhydrides **4a–e** in CH_2Cl_2 at 20°C.

Alcohol	Anhydride	k_2 [$\mathrm{M^{-1}s^{-1}}$][a]	k_3 [$\mathrm{M^{-2}s^{-1}}$][a]
3a	**4a**	$1.77 \pm 0.06 \times 10^{-3}$	$4.06 \pm 0.03 \times 10^{+1}$
3b	**4a**	$7.93 \pm 0.45 \times 10^{-4}$	$1.35 \pm 0.01 \times 10^{+1}$
3c	**4a**	$6.07 \pm 0.28 \times 10^{-4}$	2.80 ± 0.04
3d	**4a**	$1.43 \pm 0.20 \times 10^{-4}$	1.30 ± 0.02
3e	**4a**	$8.74 \pm 0.41 \times 10^{-6}$	$3.22 \pm 0.06 \times 10^{-2}$
3d	**4b**	$2.80 \pm 0.67 \times 10^{-5}$	$7.36 \pm 0.09 \times 10^{-1}$
3d	**4c**	$1.08 \pm 0.20 \times 10^{-5}$	$4.62 \pm 0.03 \times 10^{-1}$
3d	**4d**	$1.27 \pm 0.18 \times 10^{-5}$	$1.56 \pm 0.02 \times 10^{-1}$
3d	**4e**	$2.72 \pm 0.02 \times 10^{-7}$	$1.62 \pm 0.03 \times 10^{-4}$
3a	**4e**	$2.04 \pm 0.03 \times 10^{-6}$	$6.02 \pm 0.04 \times 10^{-3}$
3a	**4c**	$1.51 \pm 0.41 \times 10^{-5}$	$1.99 \pm 0.01 \times 10^{+1}$

[a] Determined according to Equations (2) and (3).

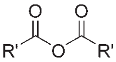
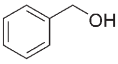
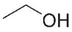
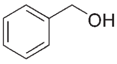
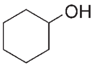
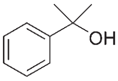
$$r(\mathrm{cat.})/r(\mathrm{uncat.}) = k_3[\mathrm{DMAP}]_0/k_2 \quad (4)$$

$$ce = k_3 \times 10^{-3}/k_2 \quad (5)$$

This ratio depends linearly on the catalyst concentration. Choosing a millimolar concentration for DMAP typical for catalytic transformations the catalytic efficiency (*ce*) can be expressed according to Equation (5). It should be kept in mind, however, that the choice of this catalyst concentration is still arbitrary and that different reaction conditions will also result in different catalytic efficiencies.

The ce data for the acetylation of alcohols **3a**–**e** compiled in Table 2 indeed show that the higher sensitivity of the catalyzed process to steric effects degrades the catalytic efficiency with increasing steric bulk of the alcohol substrate. This is somewhat unfortunate as the acetylation rate of tertiary alcohol **3e** is rather small in absolute terms and thus most deserving of catalytic enhancement. Preliminary experiments with *tert*-butanol as a sterically even more demanding substrate indicate that the reaction rates will be smaller by at least a factor of three relative to those for **3e**. These experiments have therefore not been continued.

Table 2. Catalytic efficiency (*ce*) of DMAP/NEt$_3$ at $[\mathrm{DMAP}]_0 = 1\times10^{-3}\ \mathrm{mol\,L^{-1}}$ in reactions of various alcohols and anhydrides as defined by Equation (5).

 R=	 **3a**	 **3b**	 **3c**	 **3d**	 **3e**
−CH$_3$ (**4a**)	22.9	17.0	4.6	9.1	3.7
−CH$_2$CH$_3$ (**4b**)				26.3	
−CH(CH$_3$)$_2$ (**4c**)	1318			42.7	
−CH$_2$CH(CH$_3$)$_2$ (**4d**)				12.3	
−C(CH$_3$)$_3$ (**4e**)	2.9			0.6	

Increasing the steric bulk of the anhydrides along the series **4a**–**e** also leads to a reduction of the rate constants for the uncatalyzed and the DMAP-catalyzed process, here determined for the acylation of cyclohexanol (**3d**). The background rate constant k_2 varies by a factor of 526 for this substrate, while variations of rate constant k_3 are again larger with a range of 8025. This indicates that the catalyzed process is again more sensitive to steric bulk than the uncatalyzed process. However, the catalytic efficiency does not decrease steadily in this series, but shows a maximum for the anhydrides of intermediate size **4b** and **c** ($ce = 42.7$) and eventually degrades completely for pivalic anhydride **4e** (Table 2). Anhydrides **4b** and **c** thus provide the largest "kinetic distance" between the uncatalyzed and the catalyzed process at a given catalyst concentration.

The additivity of steric effects in the alcohol and anhydride substrates was explored through further measurements including the reaction of benzyl alcohol **3a** with anhydrides **4c** and **e**. Based on the results obtained for the reaction of alcohols **3a** and **d** with acetic anhydride (**4a**), a *ce* value >100 would be expected for the reaction of **3a** with **4c**. The catalytic efficiency values calculated from the k_2 and k_3 rate constants indeed show the effects to be more than additive, predicting a *ce* value >1300 for the combination **3a**/**4c**! However, even for the rather reactive benzyl alcohol **3a** the *ce* values eventually degrade on enlarging the steric bulk of the anhydride as was shown for reaction with **4e**.

All kinetic rate constants determined here must be expected to depend on the reaction conditions and the choice of solvent. One particularly important point concerns the auxiliary base NEt$_3$, for which the concentration was found to have no influence on the reaction rate in earlier measurements on the DMAP-catalyzed reaction of **3d** with **4a**.[23] These measurements have now been repeated for the reaction of **3d** with **4c** at a variety of different DMAP concentrations. At low DMAP concentrations there is essentially no influence of the NEt$_3$ concentration on the reaction rate, while at the highest DMAP concentration studied here ($1.25\times10^{-3}\ \mathrm{mol\,L^{-1}}$) the reaction rate is reduced by 10% on increasing the NEt$_3$ concentration from 0.06 to 0.12 mol L^{-1} (three to six equivalents relative to alcohol **3d**, Figure 1). This observation indicates that the uncatalyzed background reaction is essentially insensitive to the NEt$_3$ concentration, while the catalyzed process responds to the NEt$_3$ concentration in an inverse fashion. This latter observation may most easily be rationalized with a larger sensitivity of the catalyzed process to solvent polarity, higher polarity being detrimental to the overall reaction rate.[24]

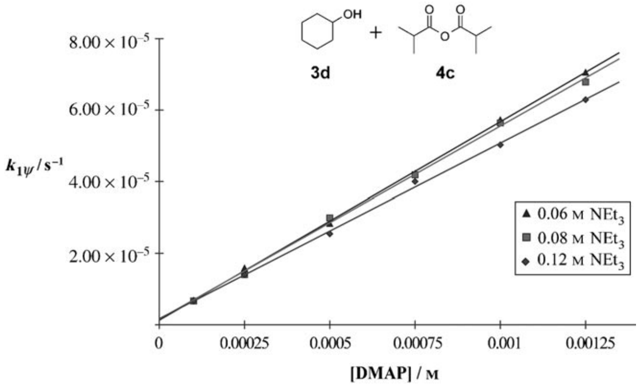
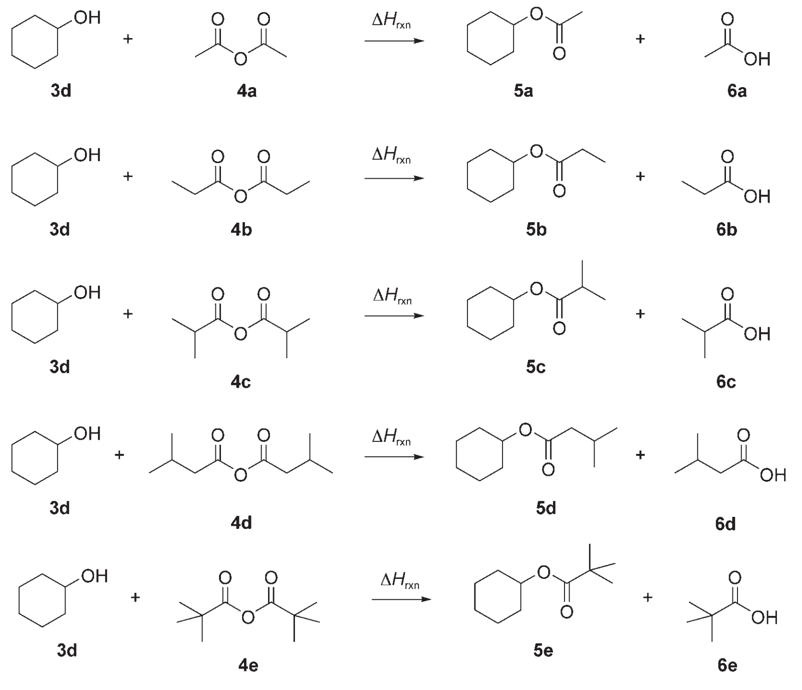


Figure 1. Dependence of the pseudo-first-order rate constant $k_{1\psi}$ on the concentration of DMAP (**1**). The auxiliary base, NEt$_3$ (**2**), is used in 3, 4, or 6 equivalents relative to the minor reaction component cyclohexanol (**3d**).

To explore possible reasons for the largely variable acylation rates compiled in Table 1, we have determined the enthalpies of reaction for the transformations shown in Scheme 2. In the absence of sufficiently detailed experimental data, the gas-phase reaction enthalpies at 298.15 K have been calculated with two different theoretical methods (Table 3). The G3(MP2)B3 compound method used here has been found to reproduce thermochemical values of neutral organic molecules with an average absolute deviation of



Scheme 2.

Table 3. Gas-phase reaction enthalpies at 298.15 K [kJ mol^{-1}] for the reaction of cyclohexanol (**3d**) with anhydrides **4a**–**4e** as calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) and G3(MP2)B3 levels of theory.

Reactants	Products	ΔH_{rxn} (B3LYP)[a]	ΔH_{rxn} (G3(MP2)B3)[b]
3d+**4a**	**5a**+**6a**	−61.2	−63.1
3d+**4b**	**5b**+**6b**	−59.0	−61.1
3d+**4c**	**5c**+**6c**	−58.3	−59.2
3d+**4d**	**5d**+**6d**	−59.0	−60.1
3d+**4e**	**5e**+**6e**	−59.4	−58.2

[a] Calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory. [b] Calculated at the G3(MP2)B3 level of theory.

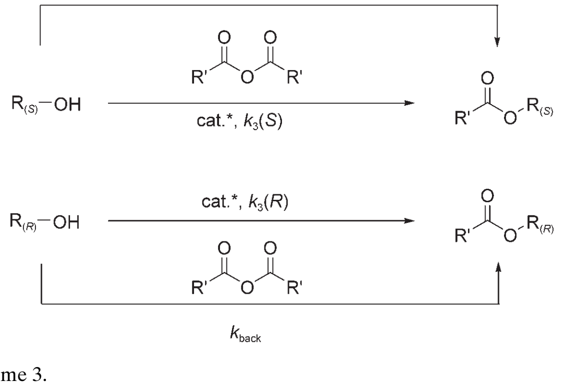
2.2 kJ mol^{-1}, while the B3LYP hybrid functional in combination with large basis sets reproduces the same thermochemical data with an average absolute deviation of 11.5 kJ mol^{-1}.[25–27]

Both methods predict largely similar enthalpies of reaction for the acylation reactions described in Table 3, making the predictions quite reliable. Both methods also agree on the fact that the enthalpies of reaction are more or less independent of the choice of anhydride, the reaction enthalpy for the most reactive anhydride (**4a**) being only 5 kJ mol^{-1} larger than that for the least reactive anhydride **4e** (−63.1 versus −58.2 kJ mol^{-1}). These theoretical estimates differ from the corresponding reaction under experimental conditions in that the neutral carboxylic acids are generated as products. Deprotonation of the latter through reaction with NEt_3 will make the reaction more exothermic under our experimental conditions. As the acidities of the acids generated from the most reactive anhydride **4a** and the least reactive anhydride **4e** are hardly different in water (4.75 versus 5.03), we can expect the reaction exothermicity to be largely similar under experimental conditions. Under the assumption that these reaction energies are representative for the rate-limiting step, the source of the largely different reaction rates must be found in the different intrinsic reaction barriers.

Discussion

The large dependence of reaction rates on the steric bulk of anhydrides found here is by no means the first quantitative assessment of these effects.[28] Previous examples include the acylation of 3-nitrophenol in CCl_4 at 25 °C catalyzed by various bases.[29] Relative rates for the anhydrides **4a**, **b**, **c**, and **e** have been determined for 3-picoline (k_{rel}=29.5:14.8:11.9:1.0) and for 4-picoline (k_{rel}=12.9:8.1:5.2:1.0) as the catalysts. The spontaneous hydrolysis of this series of anhydrides in dilute aqueous solution has been studied previously and relative rates of reaction of 33.3:17.3:10.7:1 have been determined at 25 °C.[30] While the rate variations in k_2 and k_3 found here for cyclohexanol follow the same relative order, the absolute range of reactivities is significantly larger (Table 1). However, one point observed in all studies is the large rate decrease on passing from isobutyric anhydride **4c** to pivalic anhydride **4e**. For cyclohexanol (**3d**) the rate decrease in k_2 and k_3 amounts to a factor of 40 and 2852, respectively!

The fact that the background and the catalyzed reaction respond differently to steric effects has some implications for the kinetic resolution of alcohols, which can most easily be discussed with respect to the general reaction scheme shown in Scheme 3. Here a racemic mixture of alcohols $R_{(R)}$–OH and $R_{(S)}$–OH react with the anhyride $(R'CO)_2O$ as



Scheme 3.

the resolving reagent under the influence of a chiral catalyst, cat.*. In favorable cases the rate constants $k_3(R)$ and $k_3(S)$ for conversion of the alcohols are significantly different, resulting in the preferred conversion of one of the alcohols. The selectivity of the catalyst is defined by the ratio of the two rate constants $s = k_3(R)/k_3(S)$. Kagan et al. have shown in very elegant studies that the *s*-factor can be determined indirectly without the necessity of measuring individual rate constants.[31] In practice, however, the catalyzed processes are accompanied by uncatalyzed (and unselective) background processes characterized through the rate constant k_{back}.

For cases in which the kinetic resolution experiment can be performed with high selectivity, the uncatalyzed background process is obviously of little significance. However, there may be two rather different reasons for an unsuccessful KR experiment: (1) The difference in $k_3(R)$ and $k_3(S)$ is simply too small to provide a kinetic advantage of one process over the other or (2) the background process is so fast that it competes efficiently with the faster of the two catalyzed processes. It is only in this latter case that the rate constants reported in Table 1 provide a guideline for a reasonable choice of reaction partners and reaction conditions. Under the condition that the chiral nucleophilic catalysts used in kinetic resolution experiments are not significantly faster than DMAP (**1**),[32] the window of opportunity for the kinetic resolution of a given set of reactants can be approximated by the *ce* values in Table 2. The best chances for successful kinetic resolution experiments with secondary alcohols thus exist for the reaction with $(i\mathrm{PrCO})_2\mathrm{O}$. With respect to the alcohol substrates it appears that primary alcohols enjoy a particularly large window of opportunity, while the very low absolute reactivity of tertiary alcohols in combination with the small *ce* values poses a severe challenge to successful kinetic resolution processes. The definition of *ce* in Equations (4) and (5) also shows that the window of opportunity depends on the catalyst concentration as one of the key experimental variables. The variation of the absolute catalyst concentration is thus of critical importance in reactions with overly large background rates. How the window of opportunity, defined through the catalyst concentration and the ratio of the catalyzed and uncatalyzed rate constants, is used depends, of course, ultimately on the ratio of $k_3(R)$ and $k_3(S)$.

Experimental Section

General: Dichloromethane was vigorously stirred over concentrated H_2SO_4 to remove traces of olefins (3 d) and further washed with concentrated H_2SO_4 until the acidic phase remained colorless. This mixture was then washed with water, 5% aqueous K_2CO_3 solution, and again with water. After drying over $CaCl_2$ for two days it was distilled from CaH_2 under a nitrogen atmosphere. 4-(*N,N*-Dimethylamino)pyridine (**1**, DMAP) was purchased from Fluka Chemical Company and used without further purification. Cyclohexanol and *n*-nonane (used as internal standards) were purchased from Acros Corporation and distilled from sodium before use. Triethylamine (**2**, NEt_3) was distilled from CaH_2 under a nitrogen atmosphere; acetic anhydride (**4a**, Ac_2O) was refluxed with coarse Mg filings at 80–90 °C for five days and then distilled.

Kinetic measurements: Reaction solutions were prepared through mixing stock solutions of DMAP with a calibrated solution containing cyclohexanol, anhydride, and triethylamine. Reactions have been performed under a nitrogen atmosphere at 20 °C. All kinetic measurements have been performed by using gas chromatography (FISONS 8130, column: SE30) with *n*-nonane as the internal standard. Rate measurements have been performed by following the disappearance of the minor reaction component under pseudo-first-order conditions. In order to maintain first-order conditions throughout all measurements, the conversion of the minor component was limited to below 80% in all cases.

Theoretical calculations: All structures have been optimized at the Becke3LYP/6-31G(d) level of theory. The conformational space of each system has been explored with the MM3 force field as implemented in the Tinker program suite.[33] The energetically most favorable structures have then been reoptimized at the Becke3LYP/6-31G(d) level of theory. The nature of all stationary points has been verified through calculation of the vibrational frequency spectrum. Thermochemical corrections to calculate enthalpies at 298.15 K have been obtained by using the rigid rotor/harmonic oscillator model and the force constants calculated at Becke3LYP/6-31G(d) level. Single point calculations have subsequently been performed at the Becke3LYP/6-311+G(d,p) level of theory. Combination of the single point energies with thermochemical corrections calculated at Becke3LYP/6-31G(d) level yields the "H_{298}" values cited in the text. Based on the Becke3LYP/6-31G(d) structures relative enthalpies at 298.15 K have also been determined by using the G3(MP2)B3 compound method.[20,21] All calculations have been performed by using Gaussian 03, Rev. B.03.[34]

Acknowledgements

This work has been supported financially by the Deutsche Forschungsgemeinschaft (DFG Zi 436/10-1). We also thank Prof. Wolfgang Steglich and Prof. Herbert Mayr for helpful comments and inspiring discussions.

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Received: February 28, 2006