The derivative of A_λ with respect to $C^M{}_o$ is 0 when

$$C^M{}_o = (K_{comp})^{-1}\left(1 + \frac{1}{K_T}\right)\left(1 + \frac{[H^+]}{K_1}\right) \qquad \text{(III-3)}$$

Convenient calculations may be performed with data from observations made at 312.5 nm since $\epsilon_{H_2L^-} = \epsilon_{N(1)H} \simeq 0$: $(\epsilon_{N(3)H\cdot M})_{312.5} = 6850$, $(\epsilon_{N(3)H})_{312.5} = 5100$, $K_T = 0.4$, $K_{comp} = 5 \times 10^2\ M^{-1}$ for Mg^{2+}.

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(22) E. R. Tucci et al.[5] have shown that isoorotic acid is complexed by divalent transition metal though to a much smaller extent than orotic acid (four orders of magnitude). Hence, with Mg^{2+} or Ca^{2+} no significant complexation is expected.
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Dependence of Aryl Ether Acylation upon Lewis Acid Stoichiometry

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Received November 13, 1979

Abstract: Acylation of alkyl aryl ethers has been observed to be uniquely dependent on the stoichiometry of the Friedel–Crafts catalyst. With 100 mol % catalyst, acylation proceeds rapidly and in high yield; with large molar excesses of catalyst, the reaction is essentially completely arrested. This inhibition can be reversed by using sterically bulky alkyl groups which effectively prevent complexing between catalyst and aryl ether. Based on these observations, we have developed processes for regioselective intramolecular acylation of either a phenyl or an alkoxylated phenyl ring when both are present.

Introduction

The Friedel–Crafts reaction has been extensively studied and utilized for many years. A prodigious variety of catalysts and reaction conditions have been explored, demonstrating the tremendous scope of this reaction type.[1] Acylation reactions are of particular value owing to the selectivity and ease with which they are usually accomplished, thus providing useful routes to highly functionalized aromatic ring systems. Two comprehensive reviews[2,3] further illustrate and catalog the synthetic utility of this acylation process.

A large variety of Friedel–Crafts acylating agents also has been studied. The two most widely useful systems involve the reactions of acid anhydrides[4-11] and acid chlorides.[2,3,12,13] Accompanying ether cleavage by the Lewis acid catalyst also has been reviewed within the scope of these acylation reactions.[14-17] However, little study has been focused upon the effects of excess catalyst on the acylation reaction itself. The question of Lewis acid catalyst stoichiometry, particularly with respect to the acylation of aryl ethers, has been largely disregarded. For difficult cases, especially those involving simultaneous ether cleavage, the utility of several less common catalysts such as antimony pentachloride, gallium trichloride, and silver trifluoromethanesulfonate has been demonstrated.[18,19] High-temperature acylation conditions have also been invoked using only traces of Lewis acid catalyst;[20] however, such methods are not generally applicable to aromatic ethers. One recent, but unusual, example illustrating the effects which may be associated with catalyst stoichiometry deals with the acylation of phenyl methyl thioether.[21] The observation was made that, by using 100 mol % $AlCl_3$, acylation para to the methylthio group could be maximized. Deviation from this

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Table I. Reaction of Acetyl Chloride and Veratrole in *o*-Dichlorobenzene Catalyzed by $AlBr_3$. Relative Rates of Acylation Based on Product Distribution[a] after 22 h

mol % $AlBr_3$	3,4-dimethoxyacetophenone (1) $k_{rel\ 1}$	3-hydroxy-4-methoxyacetophenone (2) $k_{rel\ 2}$	$k_1 + k_2$	3,4-dichloroacetophenone (3) $k_{rel\ 3}$
50	0.48			
100	1.00[b]	trace	1.00	
125	0.69	0.07	0.76	
150	0.45	0.20	0.65	trace
175	0.14	0.31	0.45	0.01
200	0.07	0.34	0.41	0.03
300	trace	0.08	0.08	0.17
500		0.05	0.05	0.66

[a] All peak areas were normalized to the maximum yield of product **1**, essentially quantitative. [b] Reaction yield quantitative under these conditions.

stoichiometry resulted in lower yields and a diminished para/ortho ratio of acylated products. The relative rates of these acylation reactions were not examined.

The literature is replete with references to successful acylations of aryl ethers under mild conditions, clearly explained by the classical notion of aromatic ring activation by electron donation in electrophilic reactions. In a significant number of cases, however, acylation of aryl ethers has proved difficult and the results have been confusing. Much attention has been focused on solvents, catalysts, and modes of addition. Few direct observations have been made of the relationships between electrophile reactivity and catalyst stoichiometry on the yield and nature of product. In this report we explore these effects in greater detail.

To facilitate this study of Friedel–Crafts acylations, and in particular to examine the effect of stoichiometry, we needed a catalyst that would afford homogeneous reaction mixtures. The polymeric structure of $AlCl_3$[18] renders this catalyst sparingly soluble in many of the common reaction solvents. On the other hand, $AlBr_3$, a slightly more reactive catalyst, is readily prepared and easily purified just before use.[22] Its dimeric structure[18] allows the preparation of catalyst solutions and these can be conveniently and accurately added to reaction systems by syringe. These features allow complete stoichiometric control, thus eliminating the uncertainties which accompany heterogeneous reaction mixtures.

Results and Discussion

Acylation of Some Simple Aryl Ethers with Acetyl Chloride. The reaction chosen for initial investigation was the acetyl chloride acylation of veratrole to form acetoveratrone (**1**).[17,23] 1,2-Dichlorobenzene was the preferred solvent owing to its good solvent properties and its relative inertness to Friedel–Crafts acylations. Reaction progress was monitored by removing aliquots which were washed with dilute aqueous HCl, dried with $MgSO_4$, and then assayed by gas chromatography (GC). By varying only the concentration of Lewis acid catalyst, a direct relationship with product formation was established. These results were normalized with respect to the acylation performed with 100 mol % $AlBr_3$, which was nearly quantitative after 22 h at room temperature, and are presented in Table I. They show the dramatic inhibiting effect of excess catalyst on the acylation of veratrole to the point where the strongly deativated *o*-dichlorobenzene was the major reactant.

Figure 1 shows the relationship between the relative rates of acylation and the mol % $AlBr_3$ after essential completion (4.5 h) of reaction. It clearly demonstrates that the rate of veratrole acylation with acetyl chloride is extremely sensitive

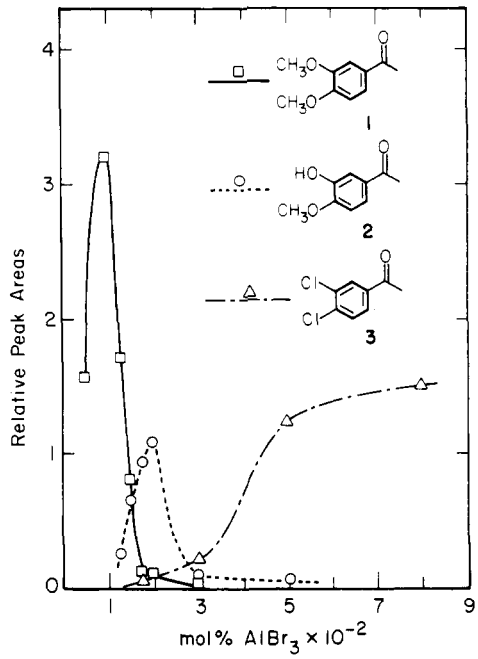
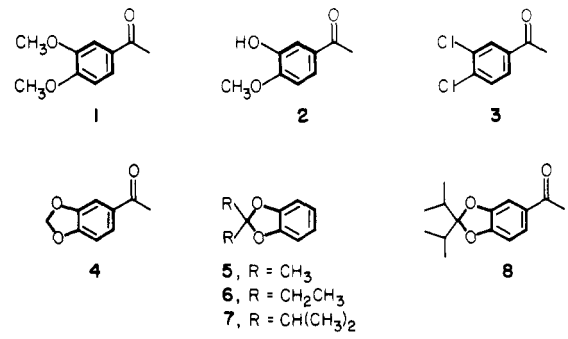


Figure 1. Acylation of veratrole in *o*-dichlorobenzene with acetyl chloride as a function of the mol % of $AlBr_3$ catalyst. Product distribution after 4.5 h among 3,4-dimethoxyacetophenone (**1**), 3-hydroxy-4-methoxyacetophenone (**2**), and 3,4-dichloroacetophenone (**3**).

to $AlBr_3$ stoichiometry. Ether cleavage is also observed under these conditions. However, the appearance of acylated veratrole species ($k_{rel\ 1} + k_{rel\ 2}$) reflects a greatly diminished rate of acylation as soon as the amount of $AlBr_3$ exceeds 100 mol %, for example, even with only 125 mol % Lewis acid catalyst. Beyond this limit, the acylation of veratrole becomes essentially nonexistent as a result of complexation of the veratrole with the catalyst. In addition, 1,2-dichlorobenzene becomes the preferred substrate for acylation when large excesses of Lewis acid are present.

As a further test of this phenomenon of strong complexation of Lewis acid with aryl ethers leading to deactivation, a competition reaction was performed. An equimolar mixture of benzene and veratrole was allowed to react at room temperature with 200 mol % acetyl chloride and 400 mol % $AlBr_3$ in 1,2-dichlorobenzene. After 1 h, greater than 95% of the benzene had been consumed and acetophenone was the sole product. GC analysis established the absence of acetoveratrone and our analytical sensitivity (<0.5% detectable) was confirmed by coinjection of an authentic sample of the veratrole ketone **1**.[14] The corresponding 3-hydroxy-4-methoxyacetophenone (**2**) was also absent by GC analysis. Thus, in the presence of excess Lewis acid, veratrole is an exceedingly poor substrate for acylation.

An additional competition was examined between methylenedioxybenzene and benzene with similar results. With excess $AlBr_3$, 3,4-methylenedioxyacetophenone (**4**) was not de-



tected by GC when reaction aliquots were compared with authentic ketone. Partial decomposition of methylenedioxybenzene was evident; however, the principal product was acetophenone. The instability to cleavage of methylenedioxybenzene compared with veratrole is consistent with the difference expected between acetals and ethers. Differences in the coordinating ability of these two ethers with Lewis acid shall be discussed later.

Acylation of Hindered Catechol Ethers. Under ideal reaction conditions, with 100 mol % Lewis acid, aliphatic acyl chlorides react efficiently with aryl ethers. However, acylation involving less reactive electrophiles is seriously retarded by aryl ether lone pair–Lewis acid complexation. To investigate possible methods for reducing the resulting deactivation, experiments were conducted in which the alkyl portion of the ethers was varied.

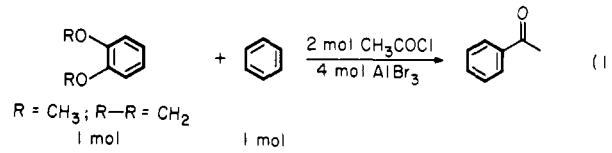
Since the normally high yielding reaction of veratrole with acetyl chloride could be retarded by the presence of excess $AlBr_3$, the preparation and testing of various hindered catechol diethers were undertaken. When catechol diisopropyl ether was treated with acetyl chloride in the presence of 300 mol % $AlBr_3$, acylation was not observed. The only product was catechol diacetate, resulting from the facile cleavage of the starting ether. This result led to an investigation of alternative cyclic catechol ether systems, that is, catechol ketals.

The preparation of several catechol ketals was readily achieved by the azeotropic removal of water from a toluene solution containing the appropriate ketone and catechol, catalyzed by *p*-toluenesulfonic acid. In this manner, the cyclic ketals of catechol and acetone **5**, 3-pentanone **6**, and 2,4-dimethyl-3-pentanone **7** were prepared. The acetone ketal proved to be as unstable as methylenedioxybenzene in the presence of excess Lewis acid. With the 3-pentanone ketal both slow cleavage and acylation were observed. As a result only a small quantity of the anticipated ketone was formed under these reaction conditions.

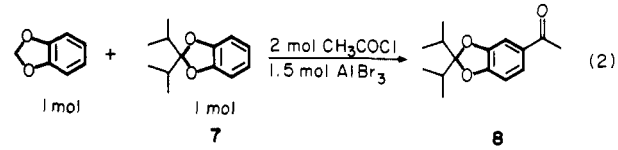
On the other hand, 2,4-dimethyl-3-pentanone catechol ketal (**7**) underwent acylation with unusual ease, forming the expected methyl ketone **8**. It was necessary to add the acid chloride prior to the addition of the Lewis acid solution to prevent ketal decomposition from seriously competing with the desired acylation reaction. Thus, steric congestion about the ether oxygen lone pairs enhances the reactivity of such aryl ethers to acylation, especially in the presence of excess Lewis acid. The increased stability of such aryl ketals to cleavage by Lewis acid gave further evidence of their reduced complexing power, and the net result was little if any deactivation of the aryl substrate.

As a further test of selectivity, competitive studies were made of the reactivity of the catechol ketal **7** of 2,4-dimethyl-3-pentanone with that of methylenedioxybenzene. An equimolar mixture of these aryl ethers was allowed to react with 200 mol % of acetyl chloride in the presence of 100 mol % of $AlBr_3$. After 30 min, an additional 50 mol % of $AlBr_3$ was added to drive the reaction to completion. Upon GC analysis, 3,4-methylenedioxyacetophenone was absent and the principal reaction product was the acylated 2,2-diisopropyl-1,3-dioxolobenzene **8**.

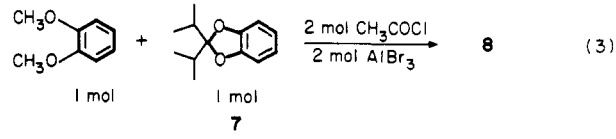
The reactivity of the hindered ketal was then compared with that of veratrole itself. In this case an additional 100 mol % $AlBr_3$ was required to drive the reaction to completion. Presumably veratrole is a more effective Lewis acid coordinating agent than methylenedioxybenzene, thereby reducing the effective concentration of unassociated catalyst. The major reaction product was that resulting from acylation of the sterically bulky catechol ether **7**. A trace of acetoveratrone could be observed by GC analysis. These results are particularly striking in view of the fact that in electrophilic reactions methylenedioxybenzene is nearly 100-fold less reactive than veratrole.[24] The rate enhancement observed in the acylation of hindered dioxybenzenes must be attributable to a reduced tendency to coordinate with the aluminum halide catalyst. Consequently, this aromatic system experiences greater reactivity toward electrophiles. The results of these competitive intermolecular acylations are summarized in eq 1–3.



(1)

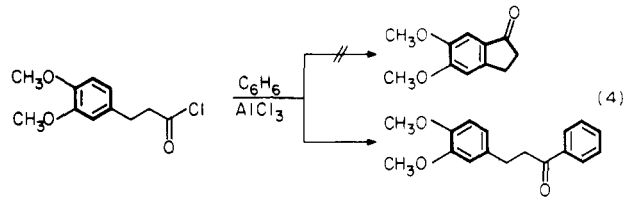


(2)



(3)

Intramolecular Acylation Reactions. The literature provides many examples of ring formation via aryl acylation. However, the record is less clear regarding intramolecular acylation of aryl ethers. Earlier studies[25] illustrate some of the difficulties encountered in the formation of various indanones by acylation. The ring closure of β-(*p*-methoxyphenyl)propionic acid, in which acylation occurs meta to the methoxyl group, is representative of such resistant cyclization reactions.[26,27] A partial solution to this problem was provided by use of the inverse addition technique, thus affording the internal ketone and avoiding self-condensation of the product.[28] However, applying these conditions to the preparation of 5,6-dimethoxy-α-indanone resulted in failure, the major product being the phenyl ketone resulting from intermolecular acylation (eq 4).



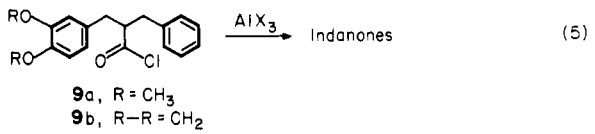
(4)

The explanation offered for the failure of dimethoxyindanone formation is not convincing. Lewis acid–aryl ether coordination was suspected as a contributing cause to the difficulties observed in the cyclization of β-(*p*-methoxyphenyl)propionic acid. Also, a methoxy group meta to the site of the electrophilic substitution is inductively deactivating. However, having overcome the problems caused by a single *m*-methoxy function, the greater difficulty encountered in the acylation of the dimethoxy analogue still remained. Although complexation and thus deactivation were considered, Lewis acid stoichiometry in relation to the reaction result was not discussed.

Subsequently, difficulty was reported[29] in reproducing the earlier[26] success in the internal acylation of β-(*p*-methoxyphenyl)propionic acid. The desired indanone was formed in 20% yield together with 40% of the intermolecular ketone. Later[30] it was observed that slow addition of $AlCl_3$ to a dilute solution of β-(*p*-methoxyphenyl)propionyl chloride produced the indanone in 90% yield. Again, questions relating to the Lewis acid stoichiometry were not addressed directly. The

study[21] dealing with the relationship between the mol % of $AlCl_3$ and regioselectivity in the acylation of thioanisole provides the only recent data on the stoichiometric aspects of the Friedel–Crafts acylation reaction.

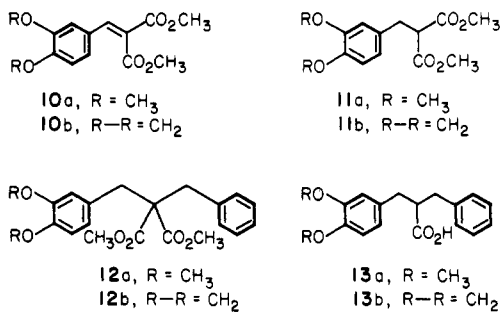
The β,β'-diphenylisobutyric acid model system shown in eq 5 was designed to facilitate further examination of the effect



(5)

9a, R = CH_3
9b, R–R = CH_2

of stoichiometry on the direction of competitive intramolecular indanone formation. A similar intramolecular competition study[31] involved the effect of alkyl groups in a β,β-diphenylpropionic acid reaction system. The desired bis-substituted isobutyric acids were prepared by condensation of the appropriate aldehydes with dimethyl malonate. Catalytic hydrogenation of the benzylidenemalonates **10** to the corresponding benzylmalonates **11** proceeded with 10% Pd/C in dioxane/CH_3OH. Subsequent alkylation with benzyl bromide was best achieved in two steps. Preparation of the sodiomalonate with CH_3O^-/CH_3OH followed by alkylation in a DMF/Et_2O mixture afforded the bisbenzylmalonates. Ester hydrolysis and decarboxylation gave the desired propionic acids **13** for the Friedel–Crafts acylation studies.



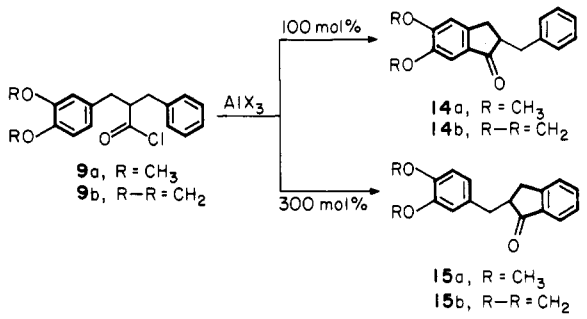
10a, R = CH_3
10b, R–R = CH_2

11a, R = CH_3
11b, R–R = CH_2

12a, R = CH_3
12b, R–R = CH_2

13a, R = CH_3
13b, R–R = CH_2

Dependence of Indanone Formation on Catalyst Stoichiometry. Competitive intramolecular acylation to form indanones was studied in a manner similar to that described for the intermolecular studies and the results are summarized in eq 6. Acid chloride formation proceeded normally by the action



9a, R = CH_3
9b, R–R = CH_2

14a, R = CH_3
14b, R–R = CH_2

(6)

15a, R = CH_3
15b, R–R = CH_2

of oxalyl chloride/DMF. In each case, $AlBr_3/CH_2Br_2$ was quickly added in one portion to preformed solutions of the acid chloride in CH_2Br_2. When only 100 mol % catalyst was added, the exclusive product formed was 2-benzyl-5,6-dimethoxy-α-indanone (**14a**). However, the addition of 300 mol % Lewis acid led to ether cleavage and hydroxymethoxyindanone, which was isolated in good yield. Dimethyl sulfate methylation then afforded 2-(3,4-dimethoxybenzyl)-α-indanone (**15a**). These indanone products were readily distinguished by UV analysis (Figure 2). The absence of a strong n–π^* transition (λ_{max} 290–310 nm) clearly indicated that excess Lewis acid resulted in the abnormal mode of cyclization, that is, cyclization into the phenyl, rather than dimethoxyphenyl or hydroxymethoxyphenyl, ring.

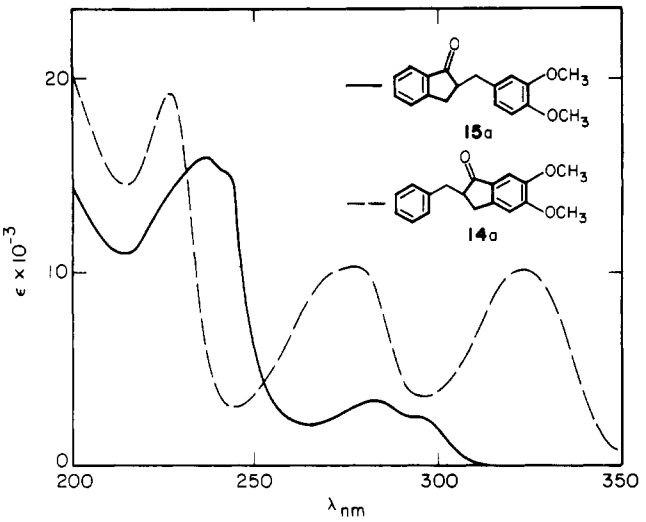


Figure 2. Ultraviolet absorption spectra in methanol of the α-indanones **14a** and **15a**.

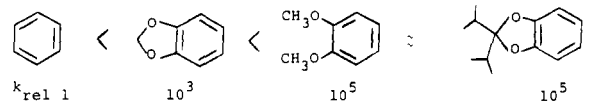
Similar results were achieved when $AlCl_3$ was used as catalyst suspended in CH_2Cl_2. In this case the acid chloride solution was quickly added to the Lewis acid in one portion. Again, excess Lewis acid afforded the dimethoxybenzyl-α-indanone **15a,** the result of acylation of the less activated aromatic ring. Ether cleavage, however, was not observed with the chloride catalyst. As expected, the normal course of acylation to form **14a** was observed when only 100 mol % $AlCl_3$ was utilized.

A similar competition study was examined for the methylenedioxy substrate **9b** using $AlCl_3$; $AlBr_3$ could not be used because accelerated acetal cleavage was unavoidable. Cyclization into the oxygenated phenyl ring yielding **14b** was observed when using only 100 mol % of $AlCl_3$. However, in the presence of excess $AlCl_3$, 2-(3,4-methylenedioxybenzyl)-α-indanone (**15b**) was the major product. Variable amounts of the 5,6-methylenedioxy-α-indanone **14b** also were observed in this case. This mixture probably resulted from a decreased tendency of the Lewis acid to coordinate with the methylenedioxyphenyl system relative to veratrole. As a result, the deactivation experienced by the methylenedioxyphenyl moiety was reduced slightly and the normal mode of acylation could proceed at an observable rate. Thus we find that, in all cases involving oxygenated arenes, the stoichiometry of the Lewis acid has a profound influence upon the ease and direction of acylation.

Relative Order of Reactivity of Some Aryl Ethers toward Acylation. The results of our studies suggest some modification of the usual classical notions of aromatic ring activation with respect to acylation reactions. With 100 mol % AlX_3 catalysts, the common generalizations hold, and the oxygenated aromatics react much more rapidly. However, with large excesses of catalyst, as frequently used, the oxygenated aromatics are deactivated relative to benzene. The one exception arises when the oxygen is substituted by a highly branched group. Qualitatively, the relative reactivities we have found in the two cases are summarized below.

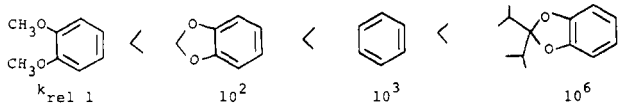
The most likely explanation for these effects in both the inter- and intramolecular cases studied is a total reversal of the electron-donating ability of an aryl ether oxygen in the presence of excess Lewis acid. This results from the essentially complete complexing of the oxygen lone pair with the Lewis acid in solution. When this Lewis acid–oxygenated aromatic complexing is prevented by the steric bulk of an attached highly branched group, the greater electron density and greater reactivity of the oxygenated aromatic nucleus are restored.

With 100 mol % AlX_3



k_{rel} 1 10^3 10^5 10^5

With excess AlX_3



k_{rel} 1 10^2 10^3 10^6

From a synthetic viewpoint, these differences in acylation reactivity can be quite useful. By careful selection of reaction conditions, primarily the stoichiometry of the catalyst, the potential to discriminate between two arene systems clearly exists. Even more interesting is the possibility to exploit selectivity in the acylation of one alkyl aryl ether in the presence of another aromatic ether in the same molecule by invoking steric bulk in the alkyl group.

Experimental Section

General Procedures. Infrared spectra were obtained using a Perkin-Elmer 137 spectrophotometer. All NMR spectra were recorded with a Varian T-60 NMR; samples were prepared in $CDCl_3$ unless otherwise stated. UV spectra were determined in CH_3OH using a Varian Cary 219 spectrophotometer. Gas chromatographic data were obtained with a Hewlett-Packard 402 chromatograph; micro sample collection was achieved using an Aerograph Autoprep Model A-700. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All reactions were carried out in a nitrogen atmosphere and organic solutions were dried over $MgSO_4$ and evaporated in vacuo using a Berkeley rotatory evaporator.

Acylation of Veratrole with Acetyl Chloride and $AlBr_3$. General reaction conditions were as follows. To a magnetically stirred solution of 127 μL (1.0 mmol) of veratrole in 10 mL of *o*-dichlorobenzene (DCB) was added 71 μL (100 mol %) of acetyl chloride. The desired amount of 2 M $AlBr_3$ in DCB was then added dropwise over 5 s at room temperature. Samples for analysis were prepared by removing by syringe at periodic intervals a 0.5-mL reaction aliquot which was shaken with 1.0 mL of dilute HCl. The organic phase was removed by pipet and passed through a small plug of $MgSO_4$ by gravity filtration. The clear filtrate was then analyzed by GC (5 μL; 10-ft column of 5% SE-30 on Chromosorb W) to determine relative reaction yields. In this manner, product development could be directly correlated with the concentration of $AlBr_3$ in the reaction solutions studied. The GC data were normalized relative to the maximum yield of **1**, which was essentially quantitative.

Competitive Acylation of Veratrole, Methylenedioxybenzene, and Benzene. To a magnetically stirred solution of DCB (26 mL) containing benzene (0.078 g, 89 μL, 100 mol %) and veratole (0.138 g, 128 μL, 100 mol %) was added 142 μL (200 mol %) of acetyl chloride. This was followed by a solution of $AlBr_3$ (1.068 g, 400 mol %) in 10 mL of DCB. After 1 h, an aliquot was removed from the homogeneous reaction mixture and analyzed as described. Authentic samples of acetophenone and acetoveratrone (**1**) were used in the GC assay by coinjection. A sample of 3-hydroxy-4-methoxyacetophenone (**2**) was obtained by preparative GC from the previous acylation study.

The competitive acylations of methylenedioxybenzene and benzene were conducted similarly.

Preparation and Acylation of Catechol Diisopropyl Ether. To a magnetically stirred solution of KOH (61.6 g, 200 mol %) and catechol (60.5 g, 100 mol %) in 700 mL of CH_3OH was added isopropyl iodide (200 g, 237 mol %) in one portion. The dark brown solution was refluxed for 24 h, solvent was evaporated, and the residue was diluted with ether (300 mL) and 0.5 N NaOH (300 mL). The organic layer was separated, washed successively with 0.5 N NaOH (2 × 250 mL), 0.1 N HCl (250 mL), and brine (200 mL), and dried. Evaporation and Kugelrohr distillation afforded catechol diisopropyl ether as a light yellow oil: 69 g, 71% yield; bp 55–60 °C (0.3 mm); IR (neat) 3150 (s), 1620 (m), 1510 (s), 1480 (m), 1470 (m), 1395 (s), 1255 (s), 1215 (m), 1120 (s), 1040 (w) cm^{-1}; NMR δ 1.4 (12 H, d, J = 6 Hz), 4.41 (2 H, h, J = 6 Hz), 6.83 (4 H, s).

Attempts were made to prepare 3,4-diisopropoxyacetophenone by adding acetyl chloride (79 μL, 110 mol %) followed by $AlCl_3$ (134 mg, 100 mol %) to a solution of catechol diisopropyl ether (0.182 g, 1.0 mmol) and CH_2Cl_2 (35 mL) at −30 °C. The reaction was monitored by GC and, when the starting ether was >95% consumed (2 h), two major products were observed. The reaction was quenched with 1 N HCl (30 mL) and the phases were separated. The organic layer was washed successively with cold 0.5 N NaOH (1 × 20 mL), 0.1 N HCl (1 × 20 mL), and brine, then dried and evaporated to afford a crude yellow oil. Kugelrohr distillation afforded a partially decomposed residue (81 mg) of unidentifiable composition and a colorless oil (48 mg): bp 70–75 °C (0.4 mm); IR (neat) 3050 (s), 1760 (s), 1610 (m), 1485 (s), 1450 (m) cm^{-1}; NMR δ 1.22 (6 H, d, J = 6 Hz), 2.17 (3 H, s), 4.42 (1 H, h, J = 6 Hz), 6.87 (4 H, m); UV λ_{max} nm (ε) 271 (2180), 278 (1815). These spectral data are consistent with a monoacetate monoisopropyl ether of catechol; no ketone could be isolated.

When the above reaction was repeated with excess $AlCl_3$ or $AlBr_3$ (200–300 mol % in CH_2Br_2), the principal neutral reaction product was catechol diacetate, identified by GC coinjection with an authentic sample prepared from catechol, acetyl chloride, and triethylamine: NMR δ 2.2 (6 H, s), 7.5 (4 H, s).

Preparation and Acylation of Hindered Catechol Ketals. Catechol ketals were prepared with acetone, diethyl ketone, and diisopropyl ketone by the following general method.

A magnetically stirred solution of catechol (11.0 g, 0.1 mol) in benzene (200 mL) containing 2.5 g of *p*-toluenesulfonic acid and the specified quantity of ketone was refluxed for 24 h with solvent cycling through 3-Å sieves. The reaction mixture was evaporated, and the residue redissolved in ether (100 mL) and extracted with 2 N NaOH (3 × 25 mL). The organic phase was washed (brine), dried, evaporated, and Kugelrohr distilled to afford the desired ketals as colorless oils.

ketone (mol %)	yield, g, %	bp (0.02 mm)
acetone (1000)	8.0, 51	50 °C, **5**
diethyl ketone (400)	8.7, 47	50 °C, **6**
diisopropyl ketone (300)	9.9, 47	55 °C, **7**

The diisopropyl ketone ketal **7** exhibited the following properties: IR (neat) 3065 (w), 2965 (s), 1485 (s), 1380 (m), 1365 (m) cm^{-1}; NMR δ 1.01 (12 H, d, J = 7 Hz), 2.12 (2 H, s, J = 7 Hz), 6.72 (4 H, s). Anal. ($C_{13}H_{18}O_2$) C, H.

The following procedure was used for acylation of these catechol ketals. To a magenetically stirred solution of the diisopropyl ketal **7** (0.103 g, 0.5 mmol) in 5 mL of DCB at 0 °C containing 0.035 mL (100 mol %) of acetyl chloride was added 0.400 g (300 mol %) of $AlBr_3$ in 2 mL of DCB. The reaction mixture was allowed to warm to room temperature and analyzed by GC. The ketal was completely consumed forming a single product which was isolated by GC and identified spectrally as the desired ketone **8**: MS m/e 248 (M^+, 1.7), 205 ($M^+ - COCH_3$, 20), 162 (0.7), 43 (100); UV λ_{max} nm 276, 314.

Competitive Acetylation of Various Catechol Ketals. The competitive acetylation of methylenedioxybenzene and each hindered ketal was performed as described for the competitive acetylation of veratrole and benzene except that only 100 mol % $AlBr_3$ was used. After 1 h, starting ketal could still be detected by GC; consequently, an additional 50 mol % $AlBr_3$ was used to drive the acetylation to completion. This reaction afforded the 3,4-dihydroxyacetophenone ketal of diisopropyl ketone (**8**) as the major product. A small quantity of catechol diacetate was also detected.

An authentic sample of ketone **8** was obtained by adding 160 μL (110 mol %) of acetyl chloride to diisopropyl ketone catechol ketal (**7**, 0.408 g, 2 mmol) in CH_2Cl_2 (60 mL) at room temperature. Then $AlCl_3$ (0.270 g, 101 mol %) was added in one portion, the reaction mixture was stirred for 1 h, 50 mL of 0.5 N HCl was added, and the layers were separated. The organic phase was washed successively with 0.5 N NaOH (1 × 30 mL), 0.1 N HCl (1 × 30 mL), and brine, and the solvent was dried and evaporated to yield an oil. Kugelrohr distillation afforded 31 mg of catechol diacetate and 360 mg (74% yield) of ketone **8**: IR (neat) 2990 (s), 1665 (s), 1580 (m), 1470 (s), 1420 (s), 1345 (m), 1255 (s), 1240 (s), 1180 (m) cm^{-1}; NMR δ 1.01 (12 H, d, J = 7 Hz), 2.26 (2 H, h, J = 7 Hz), 2.50 (3 H, s), 6.68 (1 H, d, J = 8 Hz), 7.42 (2 H, m); UV λ_{max} nm (ε) 223 (19 000), 277 (5570), 314 (8890); GC (6 ft, 5% SE-30 on Chromosorb W, 180 °C) t_R 2.85 min (t_R for 3,4-methylenedioxyacetophenone, 4.60 min). Anal. ($C_{15}H_{20}O_3$) C, H.

The competitive acetylations of veratrole and catechol ketal **7** were

performed in a manner identical with that described above. The acetylated catechol ketal **8** was the sole reaction product.

Dimethyl 3,4-Dimethoxybenzylidenemalonate (10a). To a mixture of 16.6 g (0.1 mol) of veratraldehyde, 14.5 g (110 mol %) of dimethyl malonate, and 0.4 g of 3,4-dimethoxybenzoic acid was added 0.8 g (10 mol %) of piperidine and the mixture was heated in an oil bath (85–90 °C) for 1 h with periodic swirling. The melt was cooled in an ice bath while the flask was swirled vigorously and the crystalline mass was then triturated with CH_3OH (75 mL) and collected by suction filtration, washing with a small volume of cold CH_3OH followed by hexane (100 mL). Air drying afforded pure **10a:** 25.8 g, 92% yield; mp 127–128 °C (lit.[32] mp 130–131 °C); IR (mull, nujol) 1720, 1620 (m), 1595 (s), 1510 (s), 1260 (s), 1225 (s), cm^{-1}; NMR δ 3.86 (12 H, m), 6.55–7.33 (3 H, m), 7.63 (1 H, s); UV λ_{max} nm (ϵ) 241 (11 060), 302 (12 940), 327 (18 350).

Dimethyl 3,4-Dimethoxybenzylmalonate (11a). The benzylidenemalonate **10a** (25.8 g, 0.092 mol) was dissolved in warm CH_3OH/dioxane (1:2) and degassed (N_2 stream) for 5 min. The solution was then hydrogenated using 5 g of 10% Pd/C and 55 psi of H_2 for 6 h followed by filtration and evaporation to afford a heavy oil. This residue was warmed at 50 °C for 1 h under high vacuum, giving **11a** as a white solid: 25.6 g, 99% yield; mp 69–70 °C from hexane (lit.[32] mp 70–71 °C); IR (neat) 3025 (m), 1740 (s), 1595 (m), 1505 (s), 1240 (s, b) cm^{-1}; NMR δ 3.10 (2 H, d, J = 8 Hz), 3.65 (6 H, s), 3.78 (6 H, s), 3.46–3.83 (1 H, m), 6.67 (3 H, s); UV λ_{max} nm (ϵ) 230 (7140), 280 (2050), 285 (sh).

Dimethyl Benzyl-3,4-dimethoxybenzylmalonate (12a). To a stirred solution of $NaOCH_3$ (110 mol % Na) in CH_3OH was added a CH_3OH solution (50 mL) of the malonate **11a** (25.6 g, 0.09 mol) in one portion. After the mixture was stirred for 30 min, the solvent was evaporated and the glassy residue was dried further under high vacuum (30 min). Then the glass was dissolved in 50 mL of DMF followed by 300 mL of dry Et_2O, benzyl bromide (16.1 g, 110 mol %) was added dropwise (5 min), and the reaction mixture was allowed to stir for an additional 2 h. It was then diluted with H_2O (300 mL), the phases were separated, and the organic layer was washed with H_2O (2 × 100 mL), dried, and evaporated to afford an oil. Further drying under high vacuum (90 °C) removed excess benzyl bromide and cooling gave **12a** as a solid: 30.5 g, 95% yield; mp 72.5–73 °C; IR 3030 (m), 1760 (s), 1510 (s), 1440 (s, b), 1250 (s, b) cm^{-1}; NMR δ 3.16 (2 H, s), 3.23 (3 H, s), 3.65 (6 H, s), 3.85 (6 H, s), 6.68 (3 H, m), 7.18 (5 H, m). Anal. ($C_{21}H_{24}O_6$) C, H.

2-(3,4-Dimethoxybenzyl)-3-phenylpropionic Acid (13a). A mixture of aqueous 2 N NaOH (250 mL) and a solution of the disubstituted malonate **12a** (30.0 g) in CH_3OH (50 mL) was refluxed for 2 h, cooled, and extracted with CH_2Cl_2 (2 × 100 mL). The aqueous phase was acidified with 6 N HCl (160 mL) and refluxed for an additional 2 h. Cooling, extracting with CH_2Cl_2 (4 × 100 mL), drying, and evaporating, finally under high vacuum (60 °C), yielded a white solid which was recrystallized from CH_2Cl_2/hexane: 21.2 g, 86% yield; mp 100–102 °C; IR (mull, Nujol) 3400–2600 (m, b), 3025 (m), 1740 (s), 1700 (s), 1595 (w), 1505 (s), 1250 (s), 1220 s), 1140 (s), 1125 (s) cm^{-1}; NMR δ 2.53–3.25 (5 H, m), 3.78 (6 H, s), 6.67 (3 H, s), 7.17 (5 H, s), 10.93 (1 H, s). Anal. ($C_{18}H_{20}O_4$) C, H.

The competitive intramolecular acylation experiment was performed in the following manner. To a magnetically stirred solution of 2-(3,4-dimethoxybenzyl)-3-phenylpropionic acid (**13a**, 1.2 g, 4.0 mmol) in CH_2Br_2 (80 mL) were added 20 μL of DMF and oxalyl chloride (400 μL, 113 mol %). The reaction mixture was allowed to stir for 1 h, at which time the homogeneous light yellow solution was divided into two equal volumes. Each portion was then cooled to −15 °C; to one portion of acid chloride was added 534 mg (100 mol %) of $AlBr_3$ in CH_2Br_2 in one portion; to the other was added 1.602 g (300 mol %) of $AlBr_3$ in CH_2Br_2, again in one portion.

The two homogeneous reaction mixtures were allowed to stir at −15 °C for 24 h. At this point, TLC examination revealed the presence of unreacted acid chloride in the reaction mixture containing excess Lewis acid. Consequently, an additional 24 h was allowed for this reaction to go to completion. Isolation entailed quenching each reaction with 1 N HCl (40 mL) and separating the layers. The individual organic phases were washed successively with 5% $NaHCO_3$ (2 × 30 mL) and brine, dried, filtered, and evaporated to afford a solid in the one case and a light yellow liquid in the other.

From the reaction with 100 mol % $AlBr_3$ was obtained 437 mg, 78% yield, of **2-benzyl-5,6-dimethoxy-α-indanone (14a):** mp 125–126 °C from EtOAc/hexane; IR (mull, Nujol) 1690 (s), 1600 (m), 1580 (m), 1485 (s), 1290 (s, b), 1230 (s) cm^{-1}; NMR δ 2.33–3.50 (5 H, m), 3.86 (6 H, s), 6.86 (1 H, s), 7.08 (1 H, s), 7.17 (5 H, s); UV λ_{max} nm (ϵ) 230 (19 830), 268 (11 210), 314 (10 140). Anal. ($C_{18}H_{18}O_3$) C, H.

From the reaction with 300 mol % $AlBr_3$ was obtained 519 mg, 97% yield, of a mixture of **2-(3-hydroxy-4-methoxybenzyl)-α-indanone** and **2-(4-hydroxy-3-methoxybenzyl)-α-indanone:** IR (neat) 3200 (w), 3015 (m), 1705 (s), 1605 (s), 1505 (s), 1455 (s), 1420 (s), 1260 (s, b), 1225 (s), 1195 (s), 1140 (s) cm^{-1}; NMR δ 2.40–3.42 (5 H, m), 3.80 (3 H, s), 5.82 (0.4 H, s), 5.92 (0.6 H, s), 6.67 (3 H, m), 7.02–7.78 (4 H, m); UV λ_{max} nm (ϵ) 241 (13 020), 285 (4800). Anal. ($C_{17}H_{16}O_3$) C, H.

The NMR data clearly indicated that indiscriminate methyl ether cleavage occurred in the presence of excess $AlBr_3$. To remethylate these phenols, a solution of 530 mg (0.99 mmol) of the 300 mol % $AlBr_3$ product in methyl ethyl ketone was treated with K_2CO_3 (0.7 g, 105 mol %) and dimethyl sulfate (0.504 g, 200 mol %). The resulting suspension was vigorously stirred and refluxed for 14 h, then cooled, diluted with water (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed successively with 1 N NaOH (1 × 50 mL), water (1 × 50 mL), and brine, dried, and evaporated to afford crystalline **2-(3,4-dimethoxybenzyl)-α-indanone (15a):** 461 mg, 86% yield; mp 116–117 °C; IR (mull, Nujol) 1695 (s), 1615 (w), 1595 (m), 1505 (s), 1250 (s), 1230 (s), 1140 (s) cm^{-1}; NMR δ 2.38–3.33 (5 H, m), 3.81 (6 H, s), 6.73 (3 H, s), 7.08–7.86 (4 H, m); UV λ_{max} nm (ϵ) 238 (14 540), 245 (sh), 285 (4440), 294 (sh). Anal. ($C_{18}H_{18}O_3$) C, H.

2-(3,4-Dimethoxybenzyl)-α-indanone (15a) also could be prepared directly from the corresponding propionic acid chloride **9a** in good yield using $AlCl_3$ (300 mol %) by adding the acid chloride to a stirred suspension of the Lewis acid in CH_2Cl_2. After 24 h at 0 °C, the product was isolated in the usual fashion (60% yield when reaction concentration was 0.11 M; yields improved when performed under more dilute conditions).

Dimethyl 3,4-methylenedioxybenzylidenemalonate (10b) was prepared using the same procedure as for the dimethoxy analogue **10a**: mp 75–76 °C (lit.[33] mp 63 °C); IR (mull, Nujol) 1735 (s), 1720 (s), 1605 (s), 1480 (s), 1335 (s), 1230 (s, b) cm^{-1}; NMR δ 3.80 (3 H, s), 3.85 (3 H, s), 5.92 (2 H, s), 6.76 (1 H, s), 6.84 (2 H, s), 7.22 (1 H, s).

Dimethyl 3,4-Methylenedioxybenzylmalonate (11b). To a solution of 114.5 g (0.43 mol) of the methylenedioxybenzylidenemalonate **10b** in 500 mL of dioxane/CH_3OH (1/1) was added 6.5 g of 10% Pd/C. The solution was then hydrogenated for 5 h at 55 psi of H_2 and the resulting malonate **11b,** 114.2 g, 99% yield, was an oil with bp 110–120 °C (0.01 mm): IR (neat) 3040 (m), 1755 (s), 1735 (s), 1480 (s), 1435 (s), 1330 (m, b), 1240 (s, b), 1135 (s, b) cm^{-1}; NMR δ 3.06 (2 H, d, J = 7 Hz), 3.60 (1 H, t, J = 7 Hz), 3.65 (6 H, s), 5.81 (2 H, s), 6.6 (3 H, s). Anal. ($C_{13}H_{14}O_6$) C, H.

Dimethyl Benzyl-3,4-methylenedioxybenzylmalonate (12b). To $NaOCH_3$ (10.9 g of Na, 111 mol %) in CH_3OH (200 mL) was added 114 g (0.43 mol) of dimethyl 3,4-methylenedioxybenzylmalonate (**11b**) in CH_3OH (100 mL) in one portion. After 30 min, the solution was evaporated and dried under high vacuum for 1 h (60 °C). The residue was then dissolved in DMF (100 mL), Et_2O (400 mL) was added, and benzyl bromide (73.35 g, 100 mol %) was added dropwise over 30 min followed by stirring for an additional 3 h. Solvent was then evaporated, and the slurry diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were combined, washed with brine, dried, and evaporated under high vacuum to afford malonate **12b** as a white solid: 143.5 g, 94% yield; mp 81–82 °C from hexane; IR (mull, Nujol) 1730 (s), 1495 (s), 1475 (m), 1225 (s), 1160 (s) cm^{-1}; NMR δ 3.10 (2 H, s), 3.18 (2 H, s), 3.60 (6 H, s), 4.78 (2 H, s), 6.57 (3 H, s), 7.12 (5 H, s). Anal. ($C_{20}H_{20}O_6$) C, H.

2-(3,4-Methylenedioxybenzyl)-3-phenylpropionic Acid (13b). Hydrolysis and decarboxylation proceeded identically with that previously described for the corresponding 3,4-dimethoxy analogue. In this manner 35.6 g (0.1 mol) of the methylenedioxybenzylmalonate **12b** was converted to propionic acid **13b:** 25.2 g, 89% yield; mp 115–116 °C from CH_2Cl_2/hexane; IR (mull, Nujol), 1700 (s), 1495 (s), 1280 (s), 1224 (s), 1185 (m) cm^{-1}; NMR δ 2.47–3.20 (1 H, m), 2.83 (4 H, b, s), 5.80 (2 H, s), 6.6 (3 H, s), 7.13 (5 H, s), 11.23 (1 H, s). Anal. ($C_{17}H_{16}O_4$) C, H.

2-Benzyl-5,6-methylenedioxy-α-indanone (14b) was readily prepared in the same manner as described for the preparation of the corresponding 5,6-dimethoxy analogue **14a,** using $AlCl_3$ in CH_2Cl_2. Thus 0.568 g (2.0 mmol) of the methylenedioxypropionic acid **13b**

afforded 479 mg (87% yield) of ketone **14b** after recrystallization from CH_2Cl_2/hexane: mp 125–126 °C; IR (mull, Nujol), 1695 (s), 1610 (m), 1495 (m), 1245 (s), 1025 (m) cm^{-1}; NMR δ 2.37–3.56 (5 H, m), 6.02 (2 H, s), 6.72 (1 H, s), 7.10 (1 H, s), 7.22 (5 H, s); UV λ_{max} nm (ϵ) 231 (22 320), 267 (9280), 319 (11 070). Anal. ($C_{17}H_{14}O_3$) C, H.

2-(3,4-Methylenedioxybenzyl)-α-indanone (**15b**) was prepared in a manner identical with that described for 2-(3,4-dimethoxybenzyl)-indanone (**15a**) using $AlCl_3$ (300 mol %) in CH_2Cl_2. From 0.568 g (2.0 mmol) of the methylenedioxypropionic acid **13b** was obtained a 3/2 mixture of the ketones **15b** and **14b**. The desired product **15b** was isolated by chromatography (SiO_2, CH_2Cl_2/EtOAc) and recrystallized from CH_2Cl_2/hexane: mp 118–119 °C; IR (mull, Nujol) 1695 (s), 1525 (s), 1250 (s, b), 1160 (s), 1045 (m) cm^{-1}; NMR δ 2.35–3.52 (5 H, m), 5.78 (2 H, s), 6.77 (3 H, s), 6.60–7.75 (4 H, m); UV λ_{max} nm (ϵ) 252 (12 950), 277 (sh). Anal. ($C_{17}H_{14}O_3$) C, H.

Acknowledgments. This research was supported in part by the National Institute on Drug Abuse.

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General-Acid-Catalyzed Imidazolidine Ring Opening. Hydrolysis of Symmetrical and Unsymmetrical 1,3-Imidazolidines of *p*-Dimethylaminocinnamaldehyde

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Abstract: Rate constants have been obtained for ring opening of a series of symmetrical and unsymmetrical 1,3-imidazolidines of *p*-dimethylaminocinnamaldehyde in H_2O at 30 °C. Ring opening of the *N,N'*-diphenyl derivative is catalyzed by hydronium ion (k_H = 2290 M^{-1} s^{-1}), and gives rise to a cationic Schiff base with λ_{max} 505 nm. The reaction is considerably slower in D_2O than in H_2O, k_H/k_D = 3.0. At pH greater than 6 ring opening is pH independent (k_0' = 1.8 × 10^{-2} s^{-1}). Ring opening of the *N,N'*-dimethylimidazolidine to a species with λ_{max} 480 nm is hydronium ion catalyzed (k_H = 2 × 10^9 M^{-1} s^{-1}) and pH independent at pH values above 11.5. The unsymmetrical *N*-isopropyl-*N'*-phenyl derivative opens to give a species with λ_{max} 480 nm and with rate constants that are similar to those for the *N,N'*-dimethyl substituted compound (k_H = 4 × 10^7 M^{-1} s^{-1}). Consequently, this species must be the *N*-isopropyl Schiff base resulting from breaking of the C–N phenyl bond. General acid catalysis of ring opening was observed in trimethylamine buffer. Only at pH values less than 6 does C–N isopropyl bond breaking become competitive, giving the *N*-phenyl Schiff base (λ_{max} 512 nm). The interconversion of Schiff bases (480 → 512 nm) is general acid catalyzed by buffer acids or a kinetic equivalent. Thus, ring-opening reactions of imidazolidines have been directly monitored, and general acid catalysis has been observed. It can be concluded that, in reactions of the neutral species and hydronium ion, or a general acid, the imidazolidine ring opens preferentially to give the most stable carbonium ion with expulsion of the least basic nitrogen. In the reaction of the unsymmetrical imidazolidine at low pH when there are two protons in the transition state, either C–N bond may break, and the C–N phenyl Schiff base is the favored product. These results are discussed in relation to reactions of N^5,N^{10}-methylenetetrahydrofolic acid.

In reactions of the important enzyme cofactor N^5,N^{10}-methylenetetrahydrofolic acid, the imidazolidine ring must open,[1] possibly with general acid catalysis by an appropriate functional group in the active site of the enzyme. Knowledge of the manner in which imidazolidines may be cleaved is therefore crucial in understanding the mechanism of action of the cofactor. There have been several kinetic studies of the formation of an imidazolidine ring from formaldehyde and various diamines,[2-5] and buffer catalysis is observed in this reaction.[2] The hydrolysis of 2-(aryl or alkyl)-N,N'-disubstituted 1,3-imidazolidines to the corresponding aldehyde proceeds with ring opening followed by rate-determining hydrolysis of a cationic Schiff-base intermediate.[6,7] With 2-(*p*-methoxyphenyl)-1,3-imidazolidines this Schiff base can be observed spectrophotometrically at pH values less than 4.7.

A question of considerable theoretical interest is whether concerted general-acid-catalyzed reactions will occur when basicity of the substrate is high.[6,8] Since ease of bond breaking is a critical feature in giving rise to such reactions in acetal hydrolysis,[9,10] it might be expected that general acid catalysis will occur in the hydrolysis of acetal analogues of high basicity

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