any sampling was begun. For the kinetic analyses carried out in the range of 43.4–44.0 °C, 1-μL aliquots were withdrawn every 12–15 min and analyzed directly by GC/MS. For the analyses carried out at other temperatures, 150-μL aliquots were withdrawn at various time intervals and placed in cooled (0–4 °C) sample vials, which had been rinsed with distilled water and oven dried. These vials were then capped, wrapped with parafilm, and stored in a freezer at −20 °C. Once all the samples had been accumulated, they were immediately subjected to GC/MS analysis. The GC/MS analyses for a given kinetic run were carried out in one sitting over the shortest possible period of time to prevent inherent instabilities in the performance of the MS system from biasing the data. The mass spectra for the kinetic runs were acquired in the single ion monitoring (SIM) mode.

Acknowledgment. We thank the National Science Foundation for supporting our studies on hydrocarbon isomerizations and Syracuse University for Graduate Fellowship awards to N.D.G. in 1985–1987.

Registry No. 3, 4125-18-2; **3**-$^{13}C_2$, 119787-48-3; **3**-d_1, 104309-53-7; **3**-d_3, 119770-93-3; **3**-d_4, 119770-96-6; **4**, 74503-34-7; **4**-d_1, 104309-51-5; **4**-d_3, 119771-03-8; **4**-d_4, 119771-04-9; **4**-$^{13}C_2$, 119771-05-0; **5**, 17804-59-0; **5**-$^{13}C_2$, 119770-99-9; **6**, 119770-89-7; **7**, 119770-90-0; **8**, 119770-91-1; **9**, 119770-92-2; **9**-d_0, 68757-99-3; **9**-d_1, 119770-94-4; **9**-d_5, 119770-95-5; **9**-$^{13}C_2$, 119771-02-7; **10**, 119770-97-7; **11**, 56267-17-5; **12**, 119787-47-2; **13**, 119770-98-8; D_2, 7782-39-0; 4,4-dimethylcyclopent-2-en-1-one, 22748-16-9; 1,2-bis(trimethylsiloxy)-4,4-dimethylcyclopentene-*2,4*-$^{13}C_2$, 119771-00-5; 1,2-bis(trimethylsiloxy)-4,4-dimethylcyclopentene, 54851-48-8; 4,4-dimethylcyclopent-2-en-1-one-*2,4*-$^{13}C_2$, 119771-01-6.

Circumventive Catalysis: Contrasting Reaction Patterns of Tertiary and Primary Amines with Cyclic Anhydrides and the Avoidance of Intermediates

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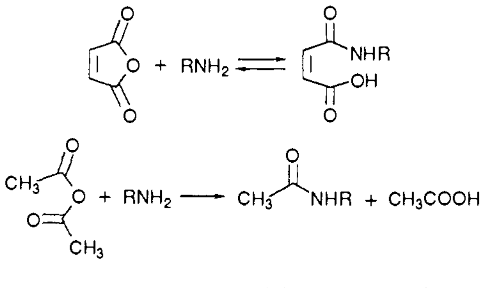
Abstract: The aminolysis of cyclic anhydrides proceeds via initial formation of a zwitterionic tetrahedral intermediate which tautomerizes to an uncharged intermediate. The aminolysis of acyclic anhydrides does not involve formation of the uncharged tautomer. The dichotomy of the reaction patterns was investigated by examining the reaction of tertiary amines with cyclic anhydrides. These amines catalyze the hydrolysis of acyclic anhydrides through the formation of reactive acylammonium ions. Pyridine, which reacts with acyclic anhydrides, does not promote the hydrolysis of maleic anhydride and does not form detectable intermediates (pH 7.3, 25 °C). 4-(Dimethylamino)pyridine does not promote the hydrolysis of succinic anhydride (the reaction with pyridine was not observed due to spectral overlap) but does produce the succinyl 4-(dimethylamino)pyridinium ion (pH 7.3, 7.8, 8.3, 9.0). The divergence in reactivity patterns between the cyclic and acyclic species is consistent with the function of the tautomerization step being the circumvention of an O-protonated amide carboxylate species. Presumably, these are generated from the cyclic anhydrides but are reconverted too fast for hydrolysis to compete. Tautomerization permits the less reactive N-protonated amide to form and this reacts with water. Catalysis by added acids permits the reaction to circumvent the O-protonated amide with a neighboring carboxylate group. Such circumventive catalysis permits release of products where their departure would normally be hindered by their affinity.

A primary or secondary amine reacts readily with an anhydride in water to produce an amide and a carboxylic acid.[1-3] The reverse of this exergonic process, acylolysis of an amide, is observed only for intramolecular reactions[4-6] where the cyclic anhydride which is produced is in favorable equilibrium with the corresponding diacid.[7] Such diacids also must have carboxyl groups in a *synperiplanar* conformation, as in derivatives of maleic acid.[8]



Intramolecular acylolysis reactions (and aminolysis of the related cyclic anhydrides) are subject to specific-acid catalysis and/or general-acid catalysis.[5-9] In contrast, the reactions of acyclic anhydrides with amines are not subject to acid catalysis. These observations require that a catalytic mechanism be available uniquely to the cyclic compounds and also implies that proton-transfer steps are kinetically significant. Kinetic studies in the cyclic series support a mechanism in which acid catalysis promotes proton transfer between nitrogen and oxygen centers of a tetrahedral intermediate (see Scheme I).[1-10] The initially formed tetrahedral intermediate is zwitterionic and the transfer of the proton converts it to the uncharged tautomer. The reaction may also be subject to general-acid catalysis (as specific-acid–general-base catalysis) and this catalysis is associated with a similar proton-transfer process.[9,10]

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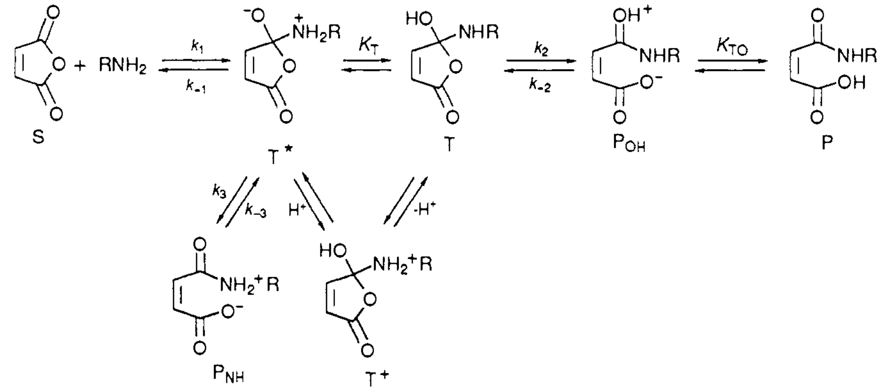
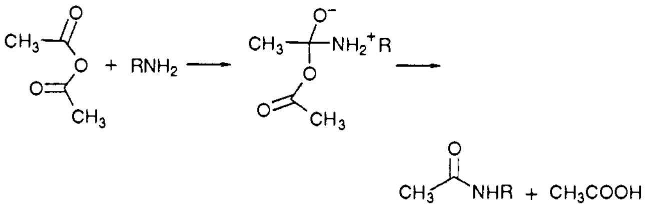
Scheme I



Scheme II



Earlier studies have shown that the water-catalyzed reaction involves the conversion of the zwitterionic intermediate to the uncharged species.[5] If the uncharged intermediate is generated directly from an isoimide, the rate-determining transition states are associated with the proton-transfer process in the intermediates since the amide, rather than the anhydride, is formed as the initial product. This shows that there is a higher barrier to formation of the amine and the rate-determining step is associated with this process. Since the reaction is catalyzed by acids and buffers, proton transfer must be part of the rate-determining process.

Studies of the aminolysis of acyclic anhydrides have been established that the reaction involves addition of an amine to the anhydride to form a zwitterionic intermediate which decomposes directly to the amide and carboxylic acid (Scheme II).[11-13] There are no proton-transfer steps of any kinetic or mechanistic significance. Thus the uncatalyzed aminolysis of acyclic anhydrides involves only the zwitterionic intermediate T* (Scheme I). Reaction via the neutral intermediate T circumvents the N-protonated amide and diverts the reaction through the lower energy O-protonated species.[9] However, since these protonated amides are certainly more stable than tetrahedral intermediates and associated transition states, there is no advantage in proceeding through the more stable species (if it requires going through a less efficient mechanism) unless there are additional consequences that affect the rate of the reaction. Through the study of a related reaction which does not involve proton transfer, the reaction of cyclic anhydrides with tertiary amines, we have been able to deduce the function of catalysis of proton transfer in the cyclic series and also to understand the relationship between the various reaction pathways. While a catalyst normally is expected to promote a reaction by reducing barriers in a mechanism which parallels the uncatalyzed route, an alternative possibility is that the catalyst avoids diversion to an unproductive route. Because the path is less direct but more efficient, we characterize such a pattern as *circumventive catalysis*.

Experimental Section

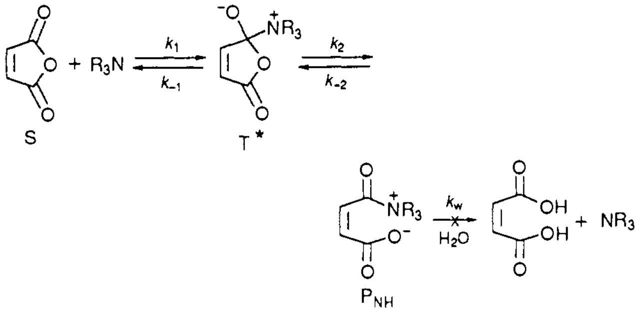
Measurements. UV-visible absorptions were recorded with a Varian Cary 210 spectrophotometer. Kinetic data were collected through a microprocessor-controlled interface built by Comspec Ltd., Downsview, Ontario. The spectrophotometer interface was connected through an IEEE-488 interface to a Commodore 2001 microcomputer. The temperature of the cell compartment was maintained at 25.0 °C by a circulating-water bath controlled within a 0.1 °C range by a Neslab Exacal 1000 circulator. The temperature inside the cell compartment was monitored with a thermistor connected to a Fisher 119 combination meter. Measurements of pH were taken with a Radiometer pH Meter 26 equipped with a Canlab combination pH electrode. Proton NMR were obtained on a Varian T60 spectrometer.

Table I. Lack of Effect of Added Pyridine on the Rate of Hydrolysis of Maleic Anhydride

pH	[pyridine] total, M	[pyridine] free, M[a]	k_{obsd}, s^{-1}	no. of runs	std dev
5.00	0.01	0.0011	0.029	3	0.006
6.00	0.10	0.0560	0.030	7	0.010
6.00	0.25	0.1400	0.023	11	0.007

[a] pK_a of pyridinium = 5.51. Free pyridine concentration from Henderson-Hasselbach equation.

Scheme III



Kinetic Methods. Kinetic data from the spectrophotometer were collected through the microcomputer and stored on floppy disks for calculations. Up to 650 points could be collected at a rate of about 11 points/s. Within these constraints, the maximum number of data points was collected for a given kinetic experiment. Reactions were carried out under the conditions specified in the tables cited in the Results section. The ionic strength of solutions was maintained at 1.0 with added potassium chloride. Reactions were initiated by injection of 5-12 μL of the reactant dissolved in acetonitrile. Phosphate buffers (pH 5.0-8.2) were prepared by weight from KH_2PO_4 (BDH, analytical grade). Borate buffers (pH 7.8-10.0) were prepared with $Na_2B_4O_7 \cdot 10H_2O$ (Fisher Certified, ACS). First-order rate constants were obtained from the kinetic data to a best fit of the first-order rate law. Standard deviations for series of runs are listed in the tables. All reported results fit the first-order rate equation with correlation coefficients of 0.999 or better.

Results

It has previously been shown that pyridines promote the hydrolysis of acetic anhydride through the intermediate formation of *N*-acetylpyridinium ions.[11,12] As a first test of the possibility of a reaction of a tertiary amine with a cyclic anhydride, we examined the reaction of maleic anhydride with water in the presence of pyridine. We found that the rate of the reaction is independent of the concentration of pyridine (Table I). Therefore, if an intermediate acylammonium ions forms, it must revert to

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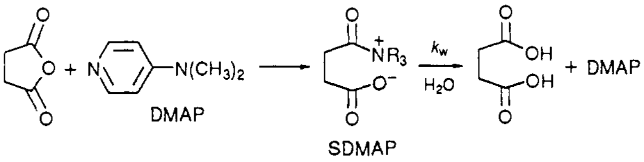
Scheme IV



reactants faster than it can react with water (Scheme III). (There is a relatively large standard deviation in the data although the correlation coefficient for the fit of each set of data to the first-order rate expression is greater than 0.999.)

A more basic tertiary amine than pyridine (but of comparable steric bulk) should react more rapidly with the anhydride. The resulting acylammonium ion also should be more stable than that derived from pyridine and might be detected since it is known that the 1-acetyl-4-(dimethylamino)pyridinium ion forms from the addition of 4-(dimethylamino)pyridine to acetic anhydride.[13] The reaction of maleic anhydride and 4-(dimethylamino)pyridine was monitored by scanning the absorbance of the reaction solution in the 280–330-nm region, where such ions are expected to absorb (conditions: pH 7.0; 0.1 M phosphate buffer; total concentration of 4-(dimethylamino)pyridine (DMAP), 0.1 M; concentration of maleic anhydride, 10^{-5} to 10^{-4} M). The solution was monitored immediately after mixing but no spectral change was observed, indicating that no significant formation of a complex occurs.

These results suggested that it is likely that the reactions of maleic anhydride and pyridines are readily reversed. This is likely to be the result of the high effective molarity of the intramolecular carboxylate nucleophile produced in the reaction and is consistent with the observed rate suppression by common ions in reactions involving acylammonium ion intermediates.[14,15] If this interpretation is correct, a system with an adjacent carboxylate of lower effective molarity would provide a better opportunity for the complex to exist in higher concentration. Since succinic acid is known to cyclize more slowly and to a lesser extent than maleic anhydride,[16,17] it was used for the next set of experiments.

The hydrolysis of succinic anhydride in the presence of pyridine could not be studied due to the high background absorbance of pyridine in the region in which the spectral change of the anhydride would be observed (220–230 nm). The formation of an acylpyridinium ion is expected to be observed as an increase in absorption in the 280–330-nm range. However, no production of such a species was observed with concentrations of pyridine ranging from 10^{-4} to 1.0 M.

The reaction of succinic anhydride with 4-(dimethylamino)pyridine in water was also examined for the reasons stated earlier with regard to maleic anhydride. In this case, we observe the formation of a species which absorbs with a maximum at about 330 nm. The rate of decomposition was measured directly since the products (succinic acid and 4-(dimethylamino)pyridine) do not absorb in this region (Table II). The spectroscopic properties and reaction products of the complex are consistent with those expected for the succinyl 4-(dimethylamino)pyridinium carboxylate (SDMAP in Scheme IV). The rate of decomposition of the species was determined, and rate constants for the hydrolysis of succinyl 4-(dimethylamino)pyridinium ion at pH 7.3 and 7.8 in the presence of phosphate buffers are listed in Table II. For comparison, rate constants for the hydrolysis of succinic anhydride as a function of phosphate buffer concentration at pH 7.3 are also given. The data indicate that the rate of decomposition of the ion depends upon buffer concentration, but is independent of the concentration (within the ranges used) of added 4-(dimethylamino)pyridine.

The substituted succinylpyridinium species and succinic anhydride have similar hydrolytic reactivity. A value of 5×10^{-2} s^{-1} for the observed first-order rate constant for pH-independent hydrolysis of the corresponding acetylpyridinium ion is obtained from an extrapolation of the work of Fersht and Jencks.[12] This is comparable to the value of 2.5×10^{-3} s^{-1} for the pH-independent rate constant for the hydrolysis of succinic anhydride. The reaction rate of water with the acetylammonium ion is about 20 times that with succinic anhydride.

Table II. Kinetic Data for the Hydrolysis of SDMAP in the Presence of DMAP and Phosphate Buffer (pH 7.3, 7.8) or Borate Buffer (pH 8.3, 9.0)[a]

pH	[buffer] total	[DMAP] total	[DMAP] free[b]	k_{obsd}	no. of runs	std dev
7.3	75	72.80	0.41	0.066	19	0.001
7.3	100	72.80	0.41	0.085	9	0.001
7.3	150	91.10	0.51	0.119	4	0.002
7.3	200	91.10	0.51	0.154	12	0.002
7.8	75	27.00	0.47	0.092	10	0.002
7.8	100	27.00	0.47	0.111	9	0.002
7.8	150	51.00	0.89	0.160	10	0.002
7.8	200	51.00	0.89	0.210	9	0.002
7.3	100	succinic anhydride		0.065	5	0.004
7.3	140	succinic anhydride		0.110	5	0.004
7.3	180	succinic anhydride		0.146	5	0.006
8.3	200	19.30	1.03	0.045	8	0.001
8.3	300	19.30	1.03	0.05	10	0.0004
8.3	480	9.66	0.51	0.061	6	0.001
8.3	560	19.30	1.03	0.065	8	0.0002
9.0	200	8.65	1.91	0.151	5	0.001
9.0	300	8.65	1.91	0.173	5	0.0005
9.0	400	8.65	1.91	0.192	4	0.001
9.0	480	8.65	1.91	0.210	5	0.001

[a] Observed at 327 nm and for succinic anhydride (where indicated), observed at 220 nm without added DMAP. Concentrations are in mM and first-order rate constants are in s^{-1}. [b] pK_a of DMAP = 9.55.

The rate constant for the reaction of acetate ion with acetyl-4-(dimethylamino)pyridinium ion to form 4-(dimethylamino)pyridine and acetic anhydride is 7.7×10^{-5} M^{-1} s^{-1}. The rate constant for the formation of acetyl-4-(dimethylamino)pyridinium acetate from acetic anhydride and 4-(dimethylamino)pyridine is 3.2×10^2 M^{-1} s^{-1}.[13] Thus, the equilibrium constant for formation of acetyl-4-(dimethylamino)pyridinium acetate from acetic anhydride and 4-(dimethylamino)pyridine is 4.2×10^7. The ratio of this equilibrium constant to that obtained for the intramolecular reaction (1.78×10^2 M^{-1}) is 2.3×10^5 M. This is close to the effective molarity of 5×10^4 M for the carboxyl group in the hydrolysis of succinanilic acid[18] and also near the effective molarity of the carboxyl group in the equilibrium between succinic anhydride and succinic acid (1.9×10^5).[17] The similarity between the kinetic and thermodynamic ratios indicates that the same factors are responsible for the differences in reaction patterns associated with inter- and intramolecular reactions of the carboxyl group.

Discussion

The reaction of maleic anhydride with primary and secondary amines is subject to acid catalysis. We find that the reaction of tertiary amines with this anhydride appears not to occur, presumably because the intermediate which forms reverts too readily to the reactants. The reaction of maleic anhydride with water is sufficiently rapid to compete with any hydrolysis which might involve the intermediacy of the acylammonium ion. Studies of the forward and reverse reactions of substituted maleic anhydrides with primary and secondary amines indicate that the intermediate zwitterion undergoes transfer of a proton from nitrogen to oxygen to produce the uncharged intermediate which reverts more slowly (Scheme I).[6,9] Thus, the route provides circumventive catalysis.

The failure of pyridine to catalyze the hydrolysis of maleic anhydride can be understood quantitatively in terms of the mechanism in Scheme III. The rate constant for the hydrolysis of maleic anhydride is about 0.03 s^{-1} and therefore any reaction via the maleylammonium ion must occur at a faster rate in order to have an observable effect. The rate constant for the hydrolysis of the maleylpyridinium ion should be about the same as that for

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the hydrolysis of the acetylpyridinium ion, 0.10 s^{-1}, which is about 4 times faster than for the hydrolysis of maleic anhydride. We know that primary amines with p*K*s the same as pyridine react successfully with maleic anhydride at concentrations as low as 8×10^{-5} M. Therefore, if this reaction did not involve proton transfer, we would expect that moderate concentrations of pyridine should produce the maleylpyridinium ion, which would cleave at a rate which would lead to catalysis. From our earlier studies of the aminolysis of maleic anhydride,[1] we expect an amine with a pK of 5.9 to have a k_1 of about 7.5×10^3 M^{-1} s^{-1}, and a $k_{-1} = 2.0 \times 10^8$ s^{-1}. The equilibrium constant for formation of the intermediate zwitterion is therefore 3.8×10^{-5} M^{-1}. This indicates that the zwitterion is a high-energy intermediate compared to the reactant and it should go on to the maleylpyridinium ion without a significant barrier. The maleylpyridinium ion is expected to be seen in the UV spectrum if it forms or to hydrolyze rapidly and thus serve as a catalytic intermediate. Yet, neither catalysis nor the intermediate is observed. The rate for internal attack of the carboxylate on the acylpyridinium ion must be comparable to the rate of attack of acetate upon the acetylpyridinium ion, corrected for the intramolecular effect. The rate constant for the bimolecular process is 910 M^{-1} s^{-1} [12] and the effective molarity of the carboxylate is certainly greater than 1 M. Since the rate constant for hydrolysis of the acylpyridinium species is 0.1 s^{-1}, the reversion is faster than hydrolysis. Thus, the reaction of pyridine with maleic anhydride is not observed because the reversion competes extremely favorably with the addition of water to the intermediate.

The reactions of succinic anhydride with primary and secondary amines are not subject to acid catalysis[2,3] (the reverse reaction has been the subject of study). However, we observe the formation of the succinyl 4-(dimethylamino)pyridinium ion in the reaction of succinic anhydride with 4-(dimethylamino)pyridine. The hydrolysis of succinic anhydride via the intermediate formation of this ion is not accelerated but is subject to general-base catalysis by added buffers. In this case, the reverse reaction of the succinylpyridinium ion is sufficiently slow to permit accumulation of the intermediate. However, its steady-state concentration is low and thus the rate of reaction via this species does not compete effectively against the direct reaction of succinic anhydride with water or the catalyzed addition of water to the anhydride.

Acyclic anhydrides undergo rapid reaction with tertiary amines and this path accelerates the hydrolysis of the anhydride.[4,12] Thus, for the acyclic series, nucleophilic catalysis is significant. The carboxylate leaving group is not attached to the intermediate and the entropic barrier to recombination prevents reversion to reactants. Thus, a significant steady-state concentration of the intermediate can exist and there is a viable catalytic route for the reaction without any need to circumvent the N-protonated amide in the reaction of the acyclic anhydride.

Suh and Chun observed that Fe(III) and Al(III) ions can function as catalysts in the hydrolysis of acetyl (5-acetyl) salicylates by becoming chelated to the intermediate and to one of the products of the reaction.[19] The added stability induced by the metal complexation shifts the equilibrium about the intermediate and retards the reverse reaction, which normally prevents the product from accumulating. This is an alternative mode of circumvention of an intermediate and these workers suggest that such a pattern may be a general mode of catalysis by metalloenzymes.

Conclusion

The reactions of primary amines with cyclic anhydrides involve a proton transfer within the initially formed zwitterionic intermediate, converting it to the corresponding uncharged species. This route circumvents the O-protonated amide containing an adjacent carboxylate. The results show that the most likely role of acid catalysis in the aminolysis of cyclic anhydrides is the facilitation of proton transfer in the intermediate to produce a species which reverts less readily to reactants. The water- and buffer-catalyzed reactions also permit the reaction to occur via the more stable O-protonated intermediate, circumventing the N-protonated species which reverts more rapidly than it hydrolyzes. O-protonation of amides is favored over N-protonation by several kilocalories. The internal addition of a carboxylate to such a reactive species appears to be faster than the rate of the second-order process by which water adds to the protonated amide, a process which is subject to the limitations of diffusion. If the product formed by an internal proton switch mechanism, then diffusion would be avoided but the molecule would still have to undergo structural reorganization which apparently is slower than reclosure. It is then likely that the intermediate does not even form.

We have shown that circumventive catalysis occurs where an intramolecular-addition process competes with a unimolecular-decomposition process but not with a bimolecular process. If the intramolecular reaction occurs readily, then the bimolecular process occurs at too low a rate. The implications for circumventive catalysis by enzymes are significant. Since enzymes bind reactants and products well, additional steps or intermediates avoid unproductive reactions which would be due to reversion. In the case of the departure of a leaving group which is a good nucleophile, isomerization of the intermediate followed by dissociation of the leaving group involves an extra step, which provides a significant increase in efficiency. While reactions choose a minimum-energy pathway, the creation of a product requires that intermediates develop in concentrations sufficient to permit the overall reaction to occur.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for continuing support through an operating grant.

Registry No. SDMAP, 119820-42-7; 4-(dimethylamino)pyridine, 1122-58-3; succinic anhydride, 108-30-5; pyridine, 110-86-1; maleic anhydride, 108-31-6.

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(19) Suh, J.; Chun, K. H. *J. Am. Chem. Soc.* **1986**, *108*, 3057. We thank Professor O. S. Tee (Concordia University) for calling our attention to the relevance of this work to the context of circumventive catalysis.