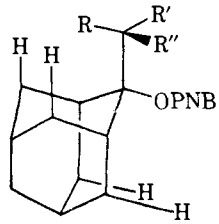
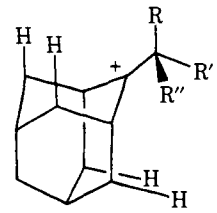


1h, R = R′ = R″ = CH_3
d, R = R′ = R″ = CD_3



2

The first-order rate constants determined for the solvolysis of **1h** and **1d** in 95% ethanol at 25.0° are (3.02 ± 0.01) × 10^{-5} sec^{-1} and (2.71 ± 0.02) × 10^{-5} sec^{-1}, respectively.[8] The resulting kinetic isotope effect, k_H/k_D = 1.11 ± 0.01, may be compared with γ-deuterium kinetic isotope effects summarized in Table I for other substrates undergoing limiting solvolyses in which deuterium is similarly situated in "nonhyperconjugative" positions.

A striking difference is seen between the magnitudes of the isotope effects exhibited by **1** and those substrates in which deuterium is situated in a sterically noncongested environment. In the latter cases, the isotope effects are all centered within a few per cent of unity, indicating that force constant changes in the relatively remote γ-position for similar reactions are quite small in the absence of severe nonbonded interactions. In contrast, the relatively large "normal" effect associated with the solvolysis of **1** is consistent with the view that severe constraints placed upon the vibrational motions of the R methyl C-H (C-D) bonds in **1** result in a greater separation of the zero point energy levels between **1h** and **1d** in the initial state than at the transition state where the nonbonded constraints on vibrational freedom are reduced.[9] This is due to the greater vibrational amplitudes of C-H bonds compared with analogous C-D bonds.[2,11]

Finally, t-Bu/CH_3 rate ratios have recently been used as a diagnostic probe of the sensitivity of various rigid tertiary systems to steric effects.[12] If the t-Bu/CH_3 rate ratio and the t-Bu-d_0/t-Bu-d_9 rate ratio have a common origin in relief of nonbonded repulsions, then one might expect a mechanistically useful linear relationship to exist between the logs of the two ratios, similar to that which exists between α-CH_3/H and α-CH_3/CD_3.[13] We are currently exploring this possibility.

Acknowledgment. We thank Research Corporation for partial support of this work.

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(8) Rate constants were measured through three half-lives by following the decrease in ester absorbance at 260 nm. Error is expressed as average deviations for three runs of **1h** and four runs of **1d**. Essentially the same values were obtained by the conductometric method. The solvent was 0.01 *M* in triethylamine. Temperature was constant to ±0.003° throughout the runs. Compound **1d** was prepared from *tert*-butyl chloride[7] containing 99.11 atom % deuterium (NMR).
(9) Correcting for the presence of R′ and R″ in **1d** using Shiner's suggested[10] inverse inductive effect of 2.5%/CD_3 leads to an isotope effect due solely to R of 1.17.
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(11) See the discussion by W. A. Van Hook in ref 1, pp. 56–63.
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Acetyl Transfer Reaction in Catechol Acetate Malonate. A Model for the Biosynthesis of Polyketides and Fatty Acids

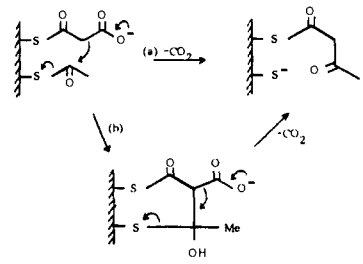
Sir:

Fatty acids and polyketides are built in vivo by successive condensation of C_2 units derived from malonyl CoA with a C_2 unit from acetyl CoA. According to a biosynthetic mechanism proposed by Lynen, the malonyl and the acetyl groups are attached first to a multienzyme complex via thiol ester linkages, and then a decarboxylative, intramolecular acetyl transfer reaction occurs to produce the enzyme bound thiolacetoacetate group (Scheme I).[1] As far as we are aware, none of the existing models for polyketide biosynthesis follows the "natural" sequence, i.e., decarboxylative acylation by malonate of an acetyl starter group.[2] We now describe a chemical model for the acetate-malonate condensation on the multienzyme complex which appears to be in mechanistic accord with Lynen's second mechanism.[3]

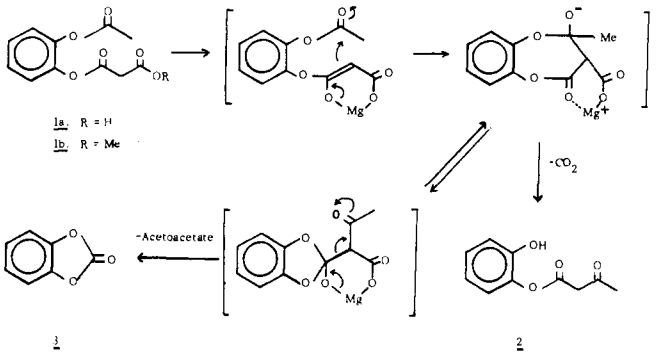
It was envisioned that starting with an appropriate matrix on which an array of contiguous acetate and malonate functionality is attached via easily dissociable ester linkages, one might be able to induce an intramolecular acetyl transfer and subsequent (or concomitant) decarboxylation to give matrix-bound acetoacetate. Protection of the ketone group in acetoacetate followed by malonylation would set the stage for successive decarboxylative acetyl transfer, eventually leading to a protected, long chain polyketide.

After a series of preliminary experiments testing various molecules (e.g., cyclohexanediols, cyclohexanedithiols, etc.) as potential matrices, catechol was found to serve this purpose adequately. Thus, when catechol acetate malonate (**1a**) (mp 103–104°; ir (KBr) 1760, 1700, 1490 cm^{-1}; NMR ($CDCl_3$) δ 2.37 (s, 3 H), 3.80 (s, 2 H), 7.48 (s, 4 H), 10.3 (br, 1 H)),[4] prepared in 53% yield from catechol monoacetate[5] by treatment with the half acid chloride of malonic acid in refluxing ether, was treated with 2 molar equiva-

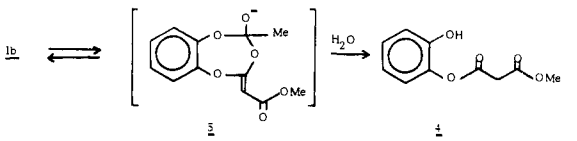
Scheme I



Scheme II



Scheme III



lents of fresh isopropyl magnesium bromide in THF at room temperature for 3 hr, catechol monoacetoacetate (**2**) (30% yield; ir ($CHCl_3$) 3400, 3010, 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.75 (s, 2 H), 6.8–7.2 (m, 4 H))[4] and catechol carbonate (**3**) (40% yield; mp 116–118°, lit. mp[6] 120°; ir (KBr) 1850, 1830, 1480 cm^{-1}) were isolated after acidic aqueous work-up. The catechol monoacetoacetate (**2**) was identified by comparison with an authentic sample synthesized from catechol and diketene in refluxing toluene. The NMR spectrum of the crude product mixture revealed that catechol monoacetoacetate (**2**) and catechol carbonate (**3**) were present in a 1/1 ratio as the only products (Scheme II).

Treatment of **1a** with 1 equiv of isopropyl magnesium bromide over a prolonged period at room temperature gave unchanged starting material upon acidification. Reaction of **1a** with 1 equiv of base, followed by heating at refluxing toluene temperature gave the product of simple decarboxylation, catechol diacetate, indicating that the concerted decarboxylative acetyl transfer[3] did not occur. The intramolecular nature of the condensation was suggested by a control experiment in which magnesium monoethyl malonate failed to condense with catechol monoacetate under identical conditions. Bases other than isopropyl magnesium bromide (e.g., sodium hydride, triethylamine, *n*-butyllithium etc.) failed to convert catechol acetate malonate (**1a**) to catechol monoacetoacetate (**2**). Attempts to trap any intermediate before decarboxylation proved futile, suggesting that decarboxylation was occurring very rapidly upon acidic work-up.

When the methyl ester (**1b**) (oil; ir (neat) 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.60 (s, 2 H), 3.78 (s, 3 H), 7.23 (s, 4 H))[4] was similarly treated with isopropyl magnesium bromide, acetyl transfer did not occur. The product mixture contained only the starting material (**1b**) and a hydrolysis product, catechol monomethylmalonate (**4**) (oil; ir (neat) 3420, 1775, 1730 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (s, 2 H), 3.75 (s, 3 H), 6.9–7.2 (m, 4 H))[4] again in a 1/1 ratio. Most likely, the hydrolysis of **1b** is the consequence of a nucleophilic catalysis involving a species such as **5** (Scheme III).[7]

It is noteworthy that in successful acetyl transfer, magnesium chelation is evidently required not for the catalytic decarboxylation but for the control of the C-acetylation over possible O-acetylation. An extension of this scheme to the synthesis of longer fatty acids and polyketides is in progress.[8]

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(3) The first mechanism (a) involves a concerted, decarboxylative acetyl transfer, and the second possible mechanism (b) involves an intermediate carboxylated species which could be subsequently decarboxylated to give rise to the formation of the enol form of the acetoacetate (see Scheme I).
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(8) Note Added in Proof. An additional control experiment in which resorcinol acetate malonate failed to give resorcinol monoacetoacetate upon treatment with 2 equiv base also supports the *intra*molecular transfer mechanism.

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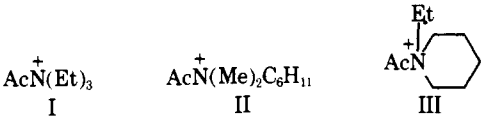
The N-Protonation Route in the Acid-Catalyzed Hydrolysis of Amides

Sir:

Convincing evidence[1] has been reported in favor of the O-protonation mechanism for acid-catalyzed amide hydrolysis. However, only crude *upper* limits for the proportion of the reaction via the N-protonation route result from these methods. In contrast to the predominant O-protonation route for hydrolysis, denitrosation and deamination of nitrosoamides probably occurs with prior N protonation.[2] There is also evidence that other electrophiles complex with amide nitrogen as in some iodine–amide complexes[3] and some metal catalyzed amide hydrolyses.[4] Moreover, N protonation of a peptide substrate has often been postulated in some proteolytic enzymes[5] including carboxypeptidase A where the X-ray crystallographic evidence is convincing.[6a] Since there is some evidence in favor of N protonation in amide hydrolysis[6b] we are interested in the factors controlling the O or N protonation route, and it is the purpose of this work to provide a reliable estimate of the latter's contribution to the overall acid hydrolysis of *N,N*-dialkylacetamides.

Smith and Yates[1b] mentioned the use of nonprotonic *N*-acylammonium salts as models for N-protonated amides; only *N*-acylpyridinium and -imidazolium species were available as stable moieties but these are not sufficiently similar to the intermediate to give reliable estimates. We present here the kinetic and hydrolytic data for the hydrolysis of *N*-acetyl *N,N,N*-trialkylammonium tetrafluoroborates[7] which are good models.



I II III

The hydrolysis of the salts (see Table I) obeys first-order kinetics[8] and is independent of pH up to neutral pH's but is inhibited at high acidities.