does not react with DPIBF under our reaction conditions in the absence of base, and dimethylaniline **4** is not deuterated by our reaction mixture. We therefore conclude that the conversion of **3** to **4** and **5** is initiated by base-promoted elimination of HCl to generate butalene. This could then undergo a 1,4 addition of dimethylamine to generate Dewar dimethylaniline **6**, which would isomerize to (*p*-deuterio)-**4**. However, this simple sequence does not explain all the data, in particular the observed deuteration of **4** in the ortho, as well as para, positions. The conversion of butalene to dimethylaniline may well involve more complex mechanisms, including for instance some initial 1,2 addition of dimethylamine.[8]

The conversion of butalene to adduct **5** also could result from at least two pathways. Thus, if 1,4 addition of dimethylamine generates **6**, this could then be trapped to form **5**. However, one would have to invoke spiroconjugative[9] activation of **6** by the dimethylamino group, since the analogous **3** does not react with DPIBF. An alternative pathway involves edge reaction of DPIBF with butalene to form an initial adduct which is then trapped by addition of dimethylamine. Either path could explain the clean deuteration results in **5**.

Although some ambiguity thus remains in the precise reaction pathway, it seems clear that butalene must be an intermediate in both these reactions. Furthermore, judging from the typical free radical reactions[3] of **2** in the gas phase, it is not an intermediate in either of our observed processes. Thus, the prediction[5] that **1** and **2** can have a separate existence, and different chemistry, is confirmed. The vigorous conditions required to generate butalene from **3** also support our previous conclusion[1a,b] that such fused-ring systems are not strongly stabilized by their overall content of $4n + 2\ \pi$ electrons.

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Evidence for a Remote Secondary Deuterium Kinetic Isotope Effect Arising from a Sterically Congested Ground State

Sir:

We wish to report a substantial secondary deuterium kinetic isotope effect whose origin may be attributed principally to relief of nonbonded repulsions in passage from a sterically congested tetrahedral initial state to a less congested trigonal carbocationic transition state.

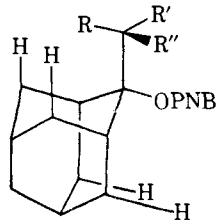
Table I. Comparison of γ-Deuterium Kinetic Isotope Effects

Compound	Solvent[a]	T, °C	k_H/k_D	Ref
1d	95% EtOH	25	1.11	*b*
$CH_3CH{=}C(CD_3)CHClCH_3$	95% EtOH	25	0.965	*c*
$(CH_3)_2CClCH_2CD_3$	80% EtOH	25	0.975	*d*
$(CD_3)_3CCH_2OMes$	H_2O	90	1.017	*e*
$(CD_3)_3CCH(OBs)CH_3$	97% TFE	25	1.011	*f*
	50% EtOH	25	1.003	*f*
	43% EtOH	40	0.979	*g*
	95% TFA	10	0.986	*g*

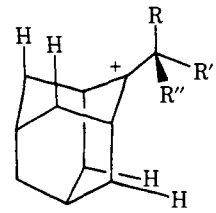
[a] TFE is 2,2,2-trifluoroethanol. TFA is trifluoroacetic acid. [b] This work. [c] R. H. Griffin and J. G. Jewett, *J. Am. Chem. Soc.*, 92, 1104 (1970). [d] Reference 10. [e] M. J. Blandamer and R. E. Robertson, *Can. J. Chem.*, 42, 2137 (1964). [f] V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *J. Am. Chem. Soc.*, 91, 7748 (1969). [g] W. M. Schubert and P. H. LeFevre, *ibid.*, 91, 7746 (1969).

The theoretical basis for understanding secondary deuterium kinetic isotope effects is well established within the context of transition state theory.[1] Briefly stated, a difference in the rates of reaction between the protium- and deuterium-substituted reactants is generally expected if bonds to the light and heavy isotopes experience changes in their vibrational force constants upon passage to the transition state. The rate difference is seen as resulting, in large part, from the inequality in zero point energy differences between the initial and transition states of the protium and deuterium compounds, but *not* to differences in the potential energy surface experienced along the reaction coordinate. The vexing problem of rationalizing kinetic isotope effects in terms relating to reaction mechanisms thus becomes one of ascribing an origin to the vibrational changes taking place as the reaction proceeds. With suitable precautions, the problem may be discussed in terms of the relative importance of inductive, hyperconjugative, and steric intramolecular interactions. The particular question of how adequately the steric origin hypothesis advanced by Bartell[2] explains observed kinetic isotope effects has been the topic of several investigations.[3] However, with few exceptions,[4] studies to date have involved systems in which either the severe steric constraints are incurred at the transition state rather than in the initial state (with $k_H/k_D < 1$)[5] or else the relative importance of inductive and hyperconjugative modes of interaction seems open to question.[6]

In an effort to gain practical information concerning the importance of initial state steric effects in a system in which other modes of intramolecular interaction might be expected to be minimal, we have studied the kinetic isotope effect associated with the solvolysis of 2-*tert*-butyl-2-adamantyl *p*-nitrobenzoate (**1**)[7] deuterated in the *tert*-butyl group. Compound **1h** is one of the most reactive tertiary alkyl substrates known, solvolyzing 459000 times faster than *tert*-butyl *p*-nitrobenzoate and 239000 times faster than 2-methyl-2-adamantyl *p*-nitrobenzoate do under the same conditions.[7] Its extreme reactivity has been ascribed to the serious nonbonded strain interactions in the tetrahedral initial state **1h** which are relieved in the trigonally arranged cation **2**. The source of this strain was seen as arising primarily from the nonbonded repulsions between methyl group R on the axially disposed *tert*-butyl group and the axial hydrogens on the same face of the inflexible chair-form cyclohexane ring. Strain calculations indicated that these repulsive interactions are largely diminished in carbocation **2**. Rate enhancement through methyl participation was deemed unlikely in view of the fact that 16% of the solvolysis products was unrearranged alcohol.[7]



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.

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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).
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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