Table II. Products from the Solvolysis of 2,7,7-Trimethyl-2-norbornyl *p*-Nitrobenzoate in 80% Aqueous Acetone at 100°

Isomer	Buffer	Products, %[a] 2-Methylene-7,7-dimethylnorbornane	2,7,7-Trimethylnorbornene	ROH[b]
exo	None	82	12	6[c]
exo	NaOAc	79	16	5[d]
endo	None	87	8	5[e]
endo	NaOAc	84	10	6[f]

[a] Normalized. [b] 2,7,7-Trimethyl-2-norbornanol. [c] *exo*:*endo*, 92:8. [d] *exo*:*endo*, 92:8. [e] *exo*:*endo*, 87:13. [f] *exo*:*endo*, 90:10.

of the two transition states of 1.6 ± 0.2 kcal/mol. Clearly steric effects can have major effects in the norbornyl system on both the *exo*:*endo* rate ratio and the *exo*:*endo* product ratio.

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An Unusually High *exo*:*endo* Rate Ratio in the Solvolysis of the 2,6,6-Trimethyl-2-norbornyl *p*-Nitrobenzoates. Further Evidence for Steric Effects as a Major Factor in the *exo*:*endo* Rate Ratios of Norbornyl Derivatives

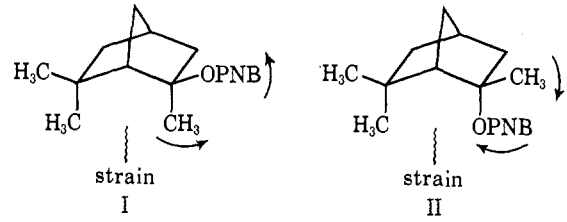
Sir:

The introduction of methyl substituents in the 7 position of the norbornyl structure results in a major increase in the rate of solvolysis of 2-methyl-*endo*-norbornyl *p*-nitrobenzoate. Indeed, the rate at 25° of 2,7,7-trimethyl-*endo*-norbornyl is faster than that of the parent compound by a factor of 580. This enhanced rate is attributed to relief of steric strain accompanying rotation of the *exo*-2-methyl group away from the crowding *syn*-7-methyl substituent during the ionization process.[1]

This large increase in the rate of the *endo* derivative is largely responsible for a marked change in the *exo*:*endo* rate ratio, from 885 observed in the parent system, 2-methyl-2-norbornyl, to 6.1 for 2,7,7-trimethyl-2-norbornyl.

(1) H. C. Brown and S. Ikegami, *J. Am. Chem. Soc.*, **90**, 7122 (1968).

If this interpretation is valid, it would predict that the presence of *gem*-dimethyls at the 6 position should have a similar rate enhancing effect on the *exo* isomer (I). On the other hand, in the *endo* isomer, the 6,6-dimethyls would be expected to interfere with the ionization of the leaving group (II), possibly resulting in a decrease in rate, in spite of the severe crowding resulting from the steric interaction of the *endo*-6-methyl and the *endo*-2-*p*-nitrobenzoate groups.[2,3] Such changes in the individual rate constants would result in a major increase in the *exo*:*endo* rate ratio.



Indeed, we have observed that the *exo*:*endo* rate ratio in the 2,6,6-trimethyl-2-norbornyl system is 3,630,000!

Addition of methylmagnesium iodide to 6,6-dimethyl-2-norbornanone[2] yielded 2,6,6-trimethyl-*endo*-norborneol, mp 81.5–82.0°. 2-Methylene-6,6-dimethylnorbornane, bp 93.5–94.0° (118 mm), n^{25}D 1.4667, was prepared from the ketone *via* the Wittig reaction. Epoxidation, followed by reductive opening of the epoxide with lithium in ethylenediamine[1] yielded 2,6,6-trimethyl-*exo*-norborneol, mp 50.0–50.5°. The alcohols were converted to the *p*-nitrobenzoates and the latter were solvolyzed in 80% aqueous acetone.[1] The results are summarized in Table I.

It is evident that the data fully support the predictions.

The large rate enhancement observed in 2,7,7-trimethyl-*endo*-norbornyl *p*-nitrobenzoate[1] obviously can have nothing to do with possible σ participation, since such participation has not been proposed for *endo* derivatives. However, in the 2,6,6- derivative the large rate increase (×726) occurs in the *exo* isomer, and it is necessary to consider whether σ participation may be involved.

The evidence from a wide variety of sources is now overwhelming that tertiary norbornyl cations, such as 2-methylnorbornyl, are classical.[4] This conclusion has

Table I. Rates of Solvolysis of 2,6,6-Trimethyl-2-norbornyl *p*-Nitrobenzoates and Related Derivatives in 80% Acetone

p-Nitrobenzoate	Mp, °C	$k_1 \times 10^6$ sec^{-1} 25° [a]	Rel rate	Rate ratio, *exo*:*endo*
1-Methyl-1-cyclopentyl[b]	82–83	2.11×10^{-3}	1.00	
2-Methyl-*exo*-norbornyl[c]	114–115	1.00×10^{-2}	4.74	855
2-Methyl-*endo*-norbornyl[d]	100–100.5	1.13×10^{-5}	0.00536	
2,6,6-Trimethyl-*exo*-norbornyl[e]	90.5–91.5	7.26[g]	3440	3,630,000
2,6,6-Trimethyl-*endo*-norbornyl[f]	119.5–120.5	2.00×10^{-6}	0.000948	

[a] Calculated from rates at higher temperature, except where otherwise indicated. [b] H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, **89**, 6378 (1967). [c] $k_1^{75} = 6.94 \times 10^{-6}$ sec^{-1}; $k_1^{100} = 94.6 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 26.3$ kcal/mol; $\Delta S^{\ddagger} = -7.0$ eu. [d] $k_1^{100} = 0.395 \times 10^{-6}$ sec^{-1}; $k_1^{125} = 5.41 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 30.2$ kcal/mol; $\Delta S^{\ddagger} = -7.5$ eu. [e] $k_1^{50} = 163 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 23.2$ kcal/mol; $\Delta S^{\ddagger} = -4.1$ eu. [f] $k_1^{125} = 1.65 \times 10^{-6}$ sec^{-1}; $k_1^{150} = 18.2 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 31.5$ kcal/mol; $\Delta S^{\ddagger} = -6.4$ eu. [g] Rate constant measured at 25.0°.

(2) P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *ibid.*, 87, 375 (1965).
(3) H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U. S.*, **56**, 1653 (1966).
(4) H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **90**, 6216 (1968).

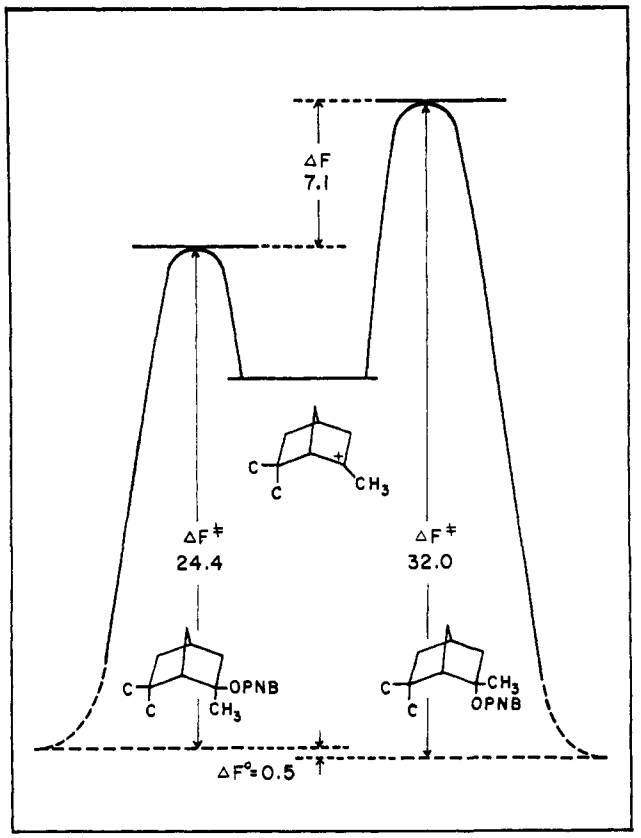


Figure 1. Goering–Schewene diagram for the solvolyses of 2,6,6-trimethyl-*exo*- and -*endo*-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone at 25° (all numbers in kcal/mol).

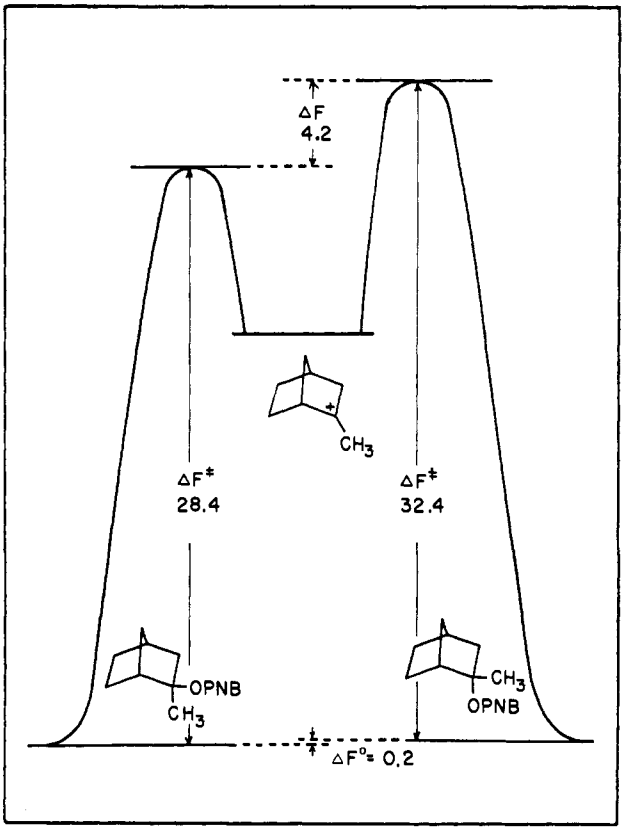


Figure 2. Goering–Schewene diagram for the solvolyses of 2-methyl-*exo*- and -*endo*-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone at 25° (all numbers in kcal/mol).

been elegantly confirmed recently by the successful trapping of the optically active 1,2-dimethyl-2-norbornyl cation or ion pair.[5] Consequently, one can argue from this position that σ participation should not be significant in the 2,6,6-trimethyl-2-norbornyl system. Indeed, Schleyer and his coworkers[2] have observed that 6,6-dimethyl-*exo*-norbornyl tosylate undergoes acetolysis at a rate considerably slower than the parent compound. They therefore concluded that the 6,6-dimethyl substituents should, if anything, decrease the ability of C-6 to participate in the ionization stage.

From both arguments it appears safe to conclude that σ participation cannot be significant in the solvolysis of 2,6,6-trimethyl-*exo*-norbornyl *p*-nitrobenzoate, so that the enhanced rate must result from the decrease in steric strain accompanying the rotation of the *endo*-2-methyl group away from the *endo*-6-methyl substituent.

The decrease in rate of the *endo* isomer as compared to the parent compound ($\times$0.18) is not as great as that observed in the secondary derivative ($\times$0.054), but the decreases in the two systems are of the same order of magnitude and presumably have their origin in the same difficulty of relieving strain during the ionization process.[3]

We must therefore conclude that these major changes in the *exo*:*endo* rate ratio, from 885 in the parent compound to 6.1 in the 7,7-dimethyl derivative[1] to 3,630,000 in the 6,6-dimethyl derivative in this study, can only have their origin in steric effects. Thus a mere shift of methyl substituents from the 7 to the 6 position, both remote from the reaction center, changes the *exo*:*endo* rate ratio by a factor of 600,000. This phenomenon corroborates the belief that the rigid norbornane structure provides an ideal system for the investigation of large steric effects.[6]

Solvolysis of 2,6,6-trimethyl-*exo*-norbornyl *p*-nitrobenzoate at 50° in the presence of sodium acetate gave 58% 2-methylene-6,6-dimethylnorbornane, 32% 2,6,6-trimethylnorbornene, and 10% *exo* alcohol. No trace of the *endo* alcohol (<0.1%) was found.

Dehydration of the alcohols proved to be so rapid that we were unable to equilibrate the epimers. However, we now have data for a considerable number of systems, and we have consistently observed for these systems that methyl and hydroxyl (or acyl) apparently have very similar steric requirements.[1,7] Consequently, if we assume that the ground-state energies are similar,[8] we can construct a Goering–Schewene diagram for the 2,6,6-trimethyl-2-norbornyl system (Figure 1). It is evident that the large difference in the free energies of formation of the two transition states will partition the intermediate cation to the almost exclusive formation of the *exo* product, as was observed.

It is particularly instructive to compare the three diagrams for 2-methyl-2-norbornyl (Figure 2), 2,7,7-trimethyl-2-norbornyl,[1] and 2,6,6-trimethyl-2-norbornyl (Figure 1). Notice that the difference in free ener-

(5) H. L. Goering and K. Humski, *J. Am. Chem. Soc.*, 90, 6213 (1968).

(6) H. C. Brown and J. Muzzio, *ibid.*, 88, 2811 (1966).

(7) M.-H. Rei and H. C. Brown, *ibid.*, 88, 5336 (1966).

(8) The maximum difference we have observed in the ground-state energies of such tertiary epimers is 0.6 kcal/mol, which is negligible in terms of the major differences we have observed for the free energies of activation.

gies of the two transition states varies from 4.2 kcal/mol for the parent tertiary system, down to 1.6 kcal/mol for 2,7,7-trimethyl-2-norbornyl, and up to 7.1 kcal/mol for 2,6,6-trimethyl-2-norbornyl.

These results clearly establish the importance of steric effects as a factor in the *exo*:*endo* rate and product ratios in the norbornyl system.

Acknowledgment. We are deeply indebted to Professor Paul von R. Schleyer of Princeton University for relinquishing his own plans for a closely related study when he learned of our interest in the problem. He generously supplied us with a sample of 6,6-dimethyl-2-norbornanone, which facilitated the initial experiments.

(9) Postdoctorate research associate on a grant (GP 6492 X) supported by the National Science Foundation.
(10) National Science Foundation Cooperative Fellow, 1965–1967.

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Biosynthesis of Tetracyclines. X. Protetrone[1]

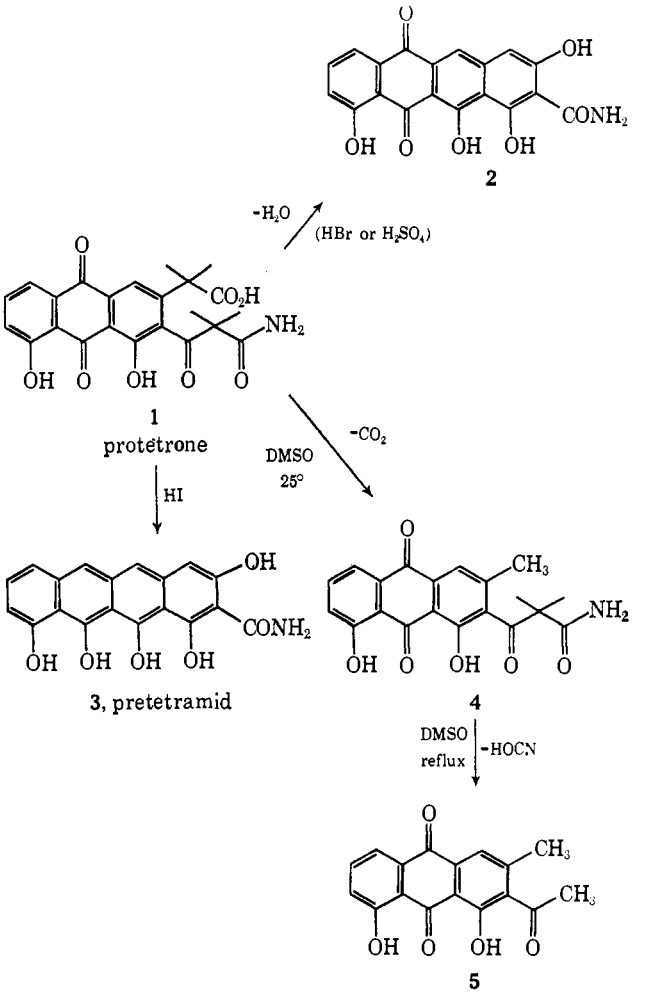
Sir:

A type of mutant frequently encountered in working with the demethyltetracycline-producing strains of *Streptomyces aureofaciens* is characterized by the development of rust-colored pigmentation in colonies on agar plates. These mutants are often low or nonproducers of antibiotic activity but are active in cosynthetic systems with other point-blocked mutants and are efficient converters of biosynthetic intermediates to produce antibiotic activity. One such isolate,[2] ED-1369, is typical of the group. Mutant ED1369 produces less than 1 mμg/ml of antibacterial activity (as demethylchlortetracycline). It is effective in converting to the corresponding antibiotic each of the known tetracycline biosynthetic intermediates, and it shows in mixed fermentations a cosynthetic response[3] with all other noncoincident point-blocked *S. aureofaciens* mutants. The product of each ED1369 cosynthetic system is the particular antibiotic which is characteristic of the other member of the system; therefore we have come to consider ED1369 to be the "universal acceptor" mutant and have long assumed it to be point blocked at a relatively early site in the biosynthetic pathway to the tetracyclines. As pretetramid is among the biologically convertible intermediates,[4] it is evident that ED1369 must be blocked at a point preceding that at which the pretetramids appear.

We wished to determine whether, among the metabolic products of ED1369, there might be substances recognizably related to the tetracyclines. Since much prior experience has indicated that the pigments of *S. aureofaciens* mutants are frequently tetracycline related,[5,6] an investigation of the pigments of ED1369 constituted our starting point. The shaker-flask mash of this mutant is dark maroon and the pigment was found to be almost entirely associated with the mycelial solids.

The isolation of 9,10-dihydro-4,5-dihydroxy-3-malonamoyl-9,10-dioxo-2-anthraceneacetic acid (protetrone, **1**) was accomplished by extraction into acidic tetrahydrofuran and fractional precipitation with hexane. The crude product was further purified by conversion to the sodium salt and back to the free acid, then recrystallized from acidified dimethyl sulfoxide–methylene chloride. After drying over P_2O_5 *in vacuo*, **1** was obtained as an orange crystalline solid:[7] mp 186–190° dec; $C_{19}H_{13}NO_8$; λ_{max} (0.1 *N* HCl–methanol) mμ (ε) 255 (25,200), 276 sh (14,200), 286 sh (11,750), 432 (11,750); ir absorption max, cm^{-1}: 1700 (CO_2H), 1670 (quinone C=O), 1630 (amide C=O); δ_{TMS} (DMSO), ppm: 3.80 (benzylic methylene), 3.89 (methylene of β-keto amide), 5.28 (enol vinyl), 7.0–8.0 (complex of amide and aryl), 11.70 (carboxyl), 12.32 (enol hydroxyl).

Zinc dust distillation of **1** yielded anthracene; solution in sulfuric–boric acid initially showed a characteristic absorption spectrum [λ_{max} mμ (ε): 246 (23,800), 274 (26,600), 295 (23,600), 510 (16,800), 538 (16,500)] which slowly changed (24 hr at 25°) to essentially the spectrum of the known naphthacenequinone,[5]



(1) Previous paper in this series: J. R. D. McCormick, E. R. Jensen, S. Johnson, and N. O. Sjolander, *J. Am. Chem. Soc.*, **90**, 2201 (1968).
(2) Mutant ED1369 was selected from a demethylchlortetracycline-producing parent by Mr. N. Deduck and Dr. John Growich of these laboratories.
(3) J. R. D. McCormick, U. Hirsch, N. O. Sjolander, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **82**, 5006 (1960).
(4) J. R. D. McCormick, S. Johnson, and N. O. Sjolander, *ibid.*, **85**, 1692 (1963).
(5) J. R. D. McCormick and W. E. Gardner, U. S. Patent 3,074,975 (1963).
(6) J. R. D. McCormick and E. R. Jensen, *J. Am. Chem. Soc.*, **87**, 1794 (1965).
(7) Satisfactory microanalyses were obtained for all compounds where the composition is indicated.