value for the pure solvent, indicating the presence of further unrelaxed reactions and/or altered solvent structure.

The data presented here imply that a minimum molecular size of the solvent–macromolecule structure is required before cooperativity is displayed. The requirement of a minimum molecular size has been demonstrated in the case of the helix–coil transition in polypeptides,[15] but not for solute–solvent interactions. The change in cooperativity with molecular weight can be seen in Figure 3, in which the ratio of the relaxation time in 8 *m* urea to that in pure water is plotted against molecular weight. The minimum size of the cooperative unit for polyethylene glycol involves a polymer of about molecular weight 3400; this is also the approximate maximum size of the effective cooperative unit. Thus the size of the cooperative structural unit appears rather precisely fixed and is surprisingly large: approximately 75 monomer units are involved in this unit and if only the first layer of water molecules is of importance, roughly 500–1000 solvent molecules. The fact that a minimum molecular size of solvated macromolecule is required before cooperativity can be exhibited may be of considerable relevance to biological systems.

(15) M. Goodman, M. Langsam, and I. F. Rosen, *Biopolymers*, **4**, 305 (1966), and references therein.

Communications to the Editor

An Unusually Low *exo*:*endo* Rate Ratio in the Solvolysis of the 2,7,7-Trimethyl-2-norbornyl *p*-Nitrobenzoates. Evidence for Steric Effects as a Major Factor in the *exo*:*endo* Rate and Product Ratios of Norbornyl Derivatives

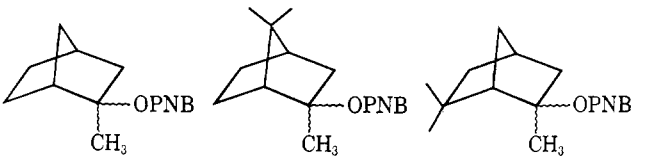
Sir:

The *exo*:*endo* rate ratio at 25° decreases from 885 for 2-methyl-2-norbornyl *p*-nitrobenzoate to 6.1 for the related 2,7,7-trimethyl-2-norbornyl esters (for solvolyses in 80% aqueous acetone). This major decrease in the *exo*:*endo* rate ratio, as compared to the parent compound, arises primarily from a major increase in the rate of solvolysis of the *endo* isomer, 2,7,7-trimethyl-*endo*-norbornyl *p*-nitrobenzoate, attributable to major steric interactions between the 2-*exo*-methyl and the *syn*-7-methyl group, relieved during ionization. This result supports the conclusion that steric effects can be very large in the rigid norbornyl system and can play a major role in the observed *exo*:*endo* rate ratio.[1]

As was recently pointed out, the evidence from a wide variety of approaches is becoming overwhelming in favor of the conclusion that tertiary norbornyl cations, such as 2-methylnorbornyl, are classical in structure.[2,3] Yet this classical system exhibits an *exo*:*endo* rate ratio of 885, easily comparable to the titrimetric ratio of 350 (1600 if we allow for internal return) exhibited by 2-norbornyl brosylate.[4] Since neither σ participation nor torsional effects[5] apparently make a significant contribution to this high *exo*:*endo* rate ratio in the tertiary derivative,[3] we appear to be left with steric hindrance to ionization as the major contributor.

Steric effects in acyclic and alicyclic systems are usually relatively small,[6] unless exceedingly bulky groups are introduced.[7] Consequently, there is a natural reluctance to attribute such a large *exo*:*endo* rate ratio simply to the operation of steric effects in such a simple, relatively uncluttered system. However, it is apparent that the conformational mobility of acyclic and alicyclic systems provides a mechanism for minimization of steric effects, whereas such an escape mechanism is absent in the rigid, three-dimensional norbornane structure.[8] Consequently, it might be anticipated that this system should be capable of exhibiting huge steric effects, even with relatively small substituents. Accordingly, we undertook to examine the *exo*:*endo* rate ratio in 2-methylnorbornyl containing *gem*-dimethyl substituents in appropriate positions.

In this communication we report that the presence of *gem*-dimethyls in the 7 position (II) decreases the *exo*:*endo* rate ratio to 6.1 from the 885 value observed in the parent compound (I). On the other hand, the presence of *gem*-dimethyls in the 6 position (III) increases the *exo*:*endo* rate ratio to 3,630,000![9] Thus the *exo*:*endo* ratio changes by a factor of 600,000 merely by a shift of the methyl substituents from the 7 to the 6 positions—a truly remarkable steric effect.



885 I 6.1 II 3,630,000 III

Apocamphor, treated with a threefold excess of methylmagnesium iodide, gave an *exo*:*endo* alcohol mixture of 97:3, with 20% of recovered ketone. Retreatment of the crude product gave 95% of the tertiary alcohol (with the same *exo*:*endo* ratio as before) with 5% of residual ketone. Purification by chromatography over alumina afforded pure 2,7,7-trimethyl-*exo*-

(1) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964).
(2) H. L. Goering and K. Humski, *ibid.*, **90**, 6213 (1968).
(3) See H. C. Brown and M.-H. Rei, *ibid.*, **90**, 6216 (1968), for pertinent references.
(4) S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952).
(5) P. von R. Schleyer, *ibid.*, **89**, 701 (1967).
(6) H. C. Brown and R. S. Fletcher, *ibid.*, **71**, 1845 (1949).
(7) P. D. Bartlett and M. Stiles, *ibid.*, **77**, 2806 (1955).
(8) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).
(9) S. Ikegami, D. L. Vander Jagt, and H. C. Brown, *ibid.*, **90**, 7124 (1968).

Table I. Rates of Solvolysis of 2,7,7-Trimethyl-2-norbornyl *p*-Nitrobenzoates and Related Derivatives in 80% Acetone

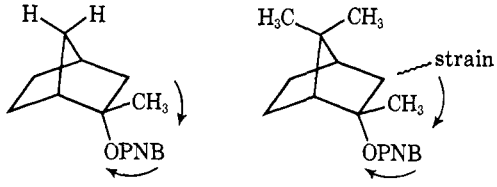
p-Nitrobenzoate	Mp, °C	$k_1 \times 10^6$ sec^{-1} 25.0° [a]	Rel rate	Rate ratio, *exo*:*endo*
1-Methyl-1-cyclopentyl[b]	82–83	2.11×10^{-3}	1.00	
2-Methyl-*exo*-norbornyl[c]	114–115	1.00×10^{-2}	4.74	885
2-Methyl-*endo*-norbornyl[c]	100–100.5	1.13×10^{-5}	0.00536	
2,7,7-Trimethyl-*exo*-norbornyl[d]	95.5–96.5	4.01×10^{-2}	19.0	6.1
2,7,7-Trimethyl-*endo*-norbornyl[e]	115.5–116.5	6.54×10^{-3}	3.1	

[a] Calculated from rates at higher temperatures. [b] H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, **89**, 6378 (1967). [c] Reference 9. [d] $k_1^{75} = 17.6 \times 10^{-6}$ sec^{-1}; $k_1^{100} = 212 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 24.5$ kcal/mol; $\Delta S^{\ddagger} = -10.2$ eu. [e] $k_1^{75} = 3.93 \times 10^{-6}$ sec^{-1}; $k_1^{100} = 53.7 \times 10^{-6}$ sec^{-1}; $\Delta H^{\ddagger} = 25.8$ kcal/mole; $\Delta S^{\ddagger} = -9.5$ eu.

norbornanol, mp 41.5–42.5°.[10] The *endo* alcohol, mp 103.5–104.5°, was obtained by the epoxidation of α-fenchene[11] with *m*-chloroperbenzoic acid, followed by reduction of the epoxide with lithium in ethylenediamine[12] and separation of the *exo*–*endo* alcohols (16:84) by recrystallization from *n*-pentane. The *p*-nitrobenzoates were prepared in the usual manner and solvolyzed in 80% aqueous acetone.[13] The rates are summarized in Table I.

The fact that 2,7,7-trimethyl-*exo*-norbornyl solvolyzes at a moderately faster rate (×4) than the parent compound is consistent with the increase in rate (×8.8) observed in the corresponding secondary derivatives.[14] Presumably, relief of steric strain, occasioned by the *syn*-7-methyl substituent, slightly overbalances any hindrance to ionization afforded by this substituent.

In 2,7,7-trimethyl-*endo*-norbornyl, however, there is observed a major increase in rate (×580) over the parent *endo* derivative. Since the major change in the *exo*:*endo* rate ratio accompanying the introduction of methyl groups in the 7 position has its primary origin in a major change in rate of the *endo* derivative, there can be no question that σ participation is not responsible here for this major change in the *exo*:*endo* rate ratio. We attribute the marked increase in the rate of the *endo* isomer to relief of steric strain accompanying the rotation of the 2-methyl substituent away from the *gem*-dimethyl group during the ionization process.



The solvolysis of the 2,7,7-trimethyl-2-norbornyl epimers gave the same products in almost the same ratios in 95–98% yields, resulting in 95% olefins and 5% alcohols (Table II).

Equilibration of the two alcohols in a heterogeneous system (cyclohexane–2 *M* H_2SO_4)[15] gave the two epimers in the ratio *exo*:*endo* 2.5:1.0, corresponding to a greater ground-state stability of the *exo* alcohol of 0.5 kcal/mol. With the assumption that the steric requirements of HO– and RCO_2– are similar, we can construct a Goering–Schewene diagram for the 2,7,7-trimethylnorbornyl system (Figure 1). In contrast to the related system, 1,2-dimethylnorbornyl,[3] which indicates a free-energy difference of 4.2 kcal/mol for the two transition states, the present diagram reveals a much smaller difference, 1.6 kcal/mol.[16] Actually, the observed isomer distribution for the alcohol product, 8–13% *endo*, corresponds to a difference in the energy

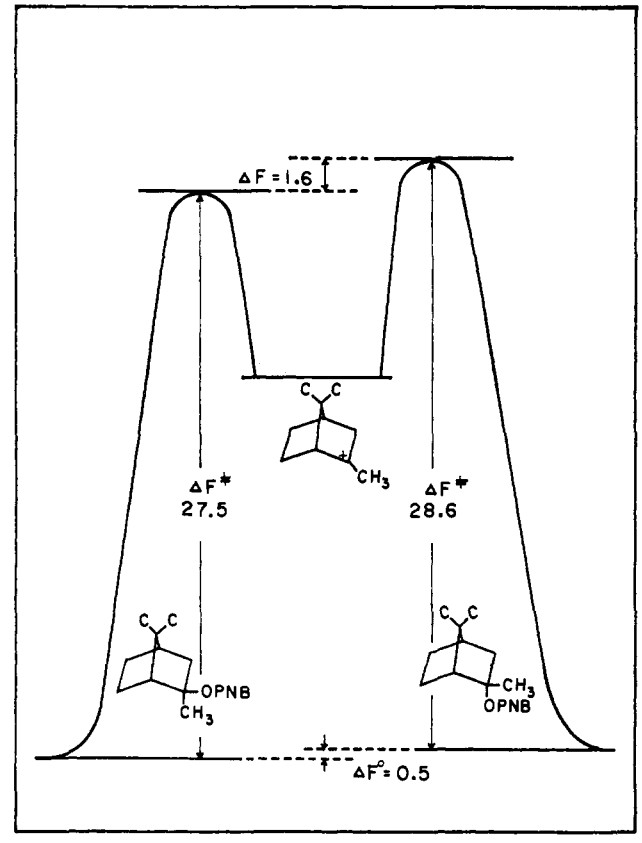


Figure 1. Goering–Schewene diagram for the solvolyses of 2,7,7-trimethyl-*exo*- and -*endo*-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone at 25° (all numbers in kcal/mol).

(10) W. Hückel and D. Volkmann, *Ann.*, **664**, 31 (1963), originally assigned the opposite configuration to the predominant alcohol produced in this reaction. However, the validity of the present assignment is established, without possible ambiguity, by the pmr spectra of the *exo* and *endo* alcohols. See also ref 11.

(11) H. Hirsjärvi, *et al.*, *Suomen Kemistilehti*, **B40**, 151 (1967).

(12) We have developed this procedure as a rapid, clean method for the reductive opening of bicyclic epoxides without rearrangement.

(13) In our earlier studies, such as ref 3, we followed previous workers in using aqueous dioxane for our solvolyses. However, we have encountered severe experimental difficulties, especially with the less reactive derivatives. Consequently we have shifted to aqueous acetone, recommended to us by Professor Schleyer of Princeton University, and have indeed found this solvolytic medium to constitute a major improvement.

(14) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 378 (1965).

(15) M.-H. Rei and H. C. Browh, *ibid.*, **88**, 5335 (1966).

(16) This suggests that by modification of the steric interactions it should be possible to develop a norbornyl system in which the *endo* isomer will be the more reactive and in which the *endo* alcohol will predominate in the solvolysis product.

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.

(17) Postdoctorate research associate on a grant (GP 6492 X) supported by the National Science Foundation.

Herbert C. Brown, Shiro Ikegami[17]
Richard B. Wetherill Laboratory
Purdue University, Lafayette, Indiana 47907
Received August 22, 1968

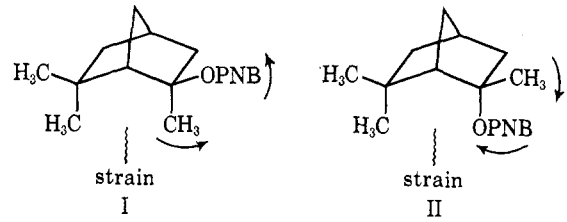
An Unusually High *exo*:*endo* Rate Ratio in the Solvolysis of the 2,6,6-Trimethyl-2-norbornyl *p*-Nitrobenzoates. Further Evidence for Steric Effects as a Major Factor in the *exo*:*endo* Rate Ratios of Norbornyl Derivatives

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.

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°.

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