Rates of Reaction of Sodium Borohydride with Bicyclic Ketones. Steric Approach Control and Steric Departure Control in the Reactions of Rigid Bicyclic Systems[1,2]

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Abstract: In order to explore the effect of structure in bicyclic systems on chemical reactivity, rates of reaction of sodium borohydride with a number of representative bicyclic ketones were determined at several temperatures, yielding values for the relative rates at 0° and for the enthalpies and entropies of activation. Taking cyclopentanone as the standard (relative rate 1.00), it is observed that the rate for 2-norbornanone is very similar (0.755). On the other hand, 7-norbornanone is exceedingly reactive (2100), the most reactive ketone yet examined by this reaction. Nortricyclenone (with a relative rate of 21.5) is more reactive than 2-norbornanone, and bicyclo[2.2.2]octanone (0.268) is less reactive, presumably reflecting the differences in the steric environment of the carbonyl groups in the three structures. The introduction of a double bond in 2-norbornenone (1.71) and bicyclo[2.2.2]octenone (0.433) results in a modest increase in the rate, presumably due to the inductive effect. However, in 7-norbornenone (200) the double bond causes a decrease from the parent compound, attributed to a decrease in I-strain which overcomes the favorable inductive influence of the double bond. The effect of methyl substituents was explored in 2-norbornanone (0.755), 1-methyl-2-norbornane (0.0797), 7,7-dimethyl-2-norbornanone (0.00365), and camphor (0.000375). The data indicate that the steric influences of the substituents are additive. The isomer distributions realized in the reduction of the bicyclic ketones were determined and used to estimate partial rate factors for exo–endo and syn–anti reductions. The data are discussed and compared with the solvolysis of the corresponding arenesulfonate esters. It is pointed out that in the reduction of simple acyclic and monocyclic ketones the reaction course appears to be influenced primarily by thermodynamic factors ("product development control"), but in the reduction of bicyclic ketones, steric influences become dominant ("steric approach control"). It is suggested that the same phenomenon may be present in solvolytic processes, with the rate of reaction in acyclic and monocyclic systems being determined predominantly by thermodynamic factors, such as the strain in the initial state and the stability of the carbonium ion which is formed. On the other hand, it is proposed that in rigid bicyclic systems steric hindrance to the departure of the leaving group introduces a new factor which might be termed "steric departure control." This interpretation would provide a single hypothesis to account for the marked differences in behavior of bicyclic ketones and of bicyclic tosylates from their acyclic and monocyclic analogs.

The development of a quantitative treatment of chemical reactivity in acyclic and monocyclic derivatives, similar to that achieved for meta and para aromatic derivatives,[5,6] has been frustrated by the conformational ambiguities of these flexible systems.[7] Rigid bicyclic systems would appear to offer considerable hope of circumventing such difficulties. Unfortunately, with the exception of solvolytic behavior,[8–10] there have been few systematic, extensive studies of the reactivities of such derivatives.[11]

The reaction of sodium borohydride with ketones exhibits simple second-order kinetics, first order in each component,[12] and it is quite sensitive to the struc-ture of the ketone. Consequently, it appears to provide a useful probe for examining the relationship of structure and reactivity. It has been applied to acyclic ketones,[13] cyclic ketones,[14,15] steroids,[16] substituted acetophenones[17] and benzophenones,[18] α-phenyl substituted acetones,[19] and cyclopropyl ketones.[20] In view of the current discussion as to the factors influencing the reactions of bicyclic derivatives,[8–10,21] it appeared desirable to apply this reaction to a study of the reactivities of a number of representative bicyclic derivatives.

Results

The reaction of sodium borohydride with the bicyclic ketones was carried out in isopropyl alcohol, following the reaction by titration of aliquots for residual borohydride. However, the reactions of 7-norbornanone and 7-norbornenone proved to be so fast that the rate

(1) Chemical Effects of Steric Strains. XVII.

(2) Based upon a thesis submitted by John Muzzio in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Research assistant, 1960–1962, on Grants G-3007 and G-2013 supported by the National Science Foundation.

(4) Monsanto Chemical Co. Fellow, 1962–1963.

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(21) H. C. Brown, Special Publication No. 16, The Chemical Society, London, 1962, pp 140–158, 174–178.

Table I. Rate Constants and Derived Data for the Reaction of Sodium Borohydride with Cyclic and Bicyclic Ketones in Isopropyl Alcohol

Ketone	Rate constants $k_2 \times 10^4$ (1. mole^{-1} sec^{-1}) 0.0°	25.0°	Rel rate at 0°	E_{act}, kcal/mole	Log A	ΔH, kcal/mole	ΔS, eu
Acetone[a]	15.1	63.0	2.13	9.3	4.6	8.8	−39.1
Cyclobutanone[b]	266		37.9	8.6	5.4	8.1	−36.4
Cyclopentanone[b]	7.01	31.8	1.00	9.8	4.7	9.3	−38.8
Cyclohexanone[b]	161	565	22.9	5.8	2.9	5.1	−48.1
2-Methylcyclo-hexanone	34.0	120	4.85	8.2	4.1	7.6	−41.8
2,2-Dimethyl-cyclohexanone	8.84	37.5	1.26	9.3	4.4	8.8	−40.7
2-Norbornanone	5.29	24.0	0.755	9.8	4.6	9.3	−39.5
Bicyclo[2.2.2]-octanone	1.88	8.07	0.268	9.4	3.8	8.9	−42.8
7-Norbornanone	15,000[c]		2100				
Nortricyclenone	151	642	21.5	9.4	5.7	8.9	−34.3
2-Norbornenone	12.0	53.5	1.71	9.7	4.8	9.1	−38.3
Bicyclo[2.2.2]-octenone	3.04	16.4	0.433	10.9	5.2	10.4	−36.5
7-Norbornenone	1,400	3000[d]	200	4.3	2.6	3.8	−48.2
1-Methyl-2-nor-bornanone	0.558	3.60	0.0797	11.6	5.1	11.1	−37.1
7,7-Dimethyl-2-norbornanone	0.0256	0.201	0.00365	13.3	5.1	12.8	−36.2
Camphor	0.00263[e]	0.0258	0.000375	14.8	5.3	14.2	−36.6

[a] From ref 12. [b] From ref 14. [c] Determined by approximate techniques. See the Experimental Section. [d] Calculated using $k_2 = 310 \times 10^{-4}$ at −43.7°. [e] Calculated using $k_2 = 0.161 \times 10^{-4}$ at 48.6°.

constants had to be determined by modified, approximate procedures. The rate constants were generally determined at two temperatures, usually 0 and 25°, to permit calculation of the enthalpy and entropy of activation.

The experimental results are summarized in Table I. It should be noted that the entropies of activation, with a few exceptions, appear to be relatively constant, in the neighborhood of −40 eu. Those cases which exhibit entropies of activation markedly different, such as cyclohexanone, nortricyclenone, 7-norbornenone, and camphor, are compounds which offer difficulties, either because of an unusually fast rate or because of an exceptionally slow rate. Consequently, we doubt that these exceptions are real. It is of especial interest that there does not appear to be any significant change in this quantity for the acyclic example, the monocyclic (with the exception of cyclohexanone just discussed), or the bicyclic.

For molecules such as acetone, cyclohexanone, and bicyclo[2.2.2]octanone, reduction leads to a single product. Consequently, it is necessary only to divide the observed rate constant by 2 to get the partial rate constant corresponding to the rate of reaction on each side of the molecule. (It could, of course, be argued that even in cyclohexanone the approach to the carbonyl group will be preferentially from one direction.[22] However, this is a small factor which it appears safe to ignore for the present.)

However, bicyclic ketones undergo reduction by hydride reagents predominantly in one of the two possible directions.[23] It appeared desirable to establish the partial rate constants for these reductions in order to examine the effect of the neighboring environment upon the rate.

At first glance it would appear simple enough to establish the isomeric distribution in the product and

then to divide up the observed rate constant in the product ratio. Unfortunately, there are objections to this procedure.

The observed rate constant measures the rate of transfer of the first hydride of sodium borohydride to the ketone. The product of this first stage and of the

$$R_2CO + BH_4^- \xrightarrow{k_2} H_3BOCHR_2^-$$
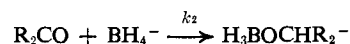
following stages appears to be more reactive than the parent molecule,[24] so that the three remaining hydrides are rapidly utilized in fast reactions that do not affect the observed kinetics. The net result is that 75% of the product is produced by intermediates that are not involved in the rate expression.

Unfortunately, we could not see any way out of this difficulty.[25] Consequently, we were forced to adopt the expedient of simply dividing up the observed rate constant into two parts corresponding to the relative amounts of the two isomers formed.

In spite of the fact that there are obvious objections to this procedure, there are reasons to believe that its use does not lead to any great error. First, most of the reductions proceed predominantly (85%) in one direction. The maximum error possible would involve formation of 40% of that isomer in the rate-determining stage, followed by 100% in each of the three succeeding stages. This appears highly improbable. Second, it has been observed that the reduction of dihydroisophorone by sodium trimethoxyborohydride in isopropyl alcohol yields an isomer distribution (65% trans) that is not very different from that realized with sodium borohydride in the same solvent (56% trans).[26]

(22) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(23) S. Beckmann and R. Mezger, *Ber.*, **89**, 2738 (1956).

(24) H. C. Brown, E. J. Mead, and C. J. Shoaf, *J. Am. Chem. Soc.*, **78**, 3613 (1956).
(25) Professor R. E. Davis of Purdue University has discovered that when the reduction of ketones is carried out by sodium borohydride in highly dilute methanol solution, the methanol destroys the initial intermediate, the monoalkoxyborohydride. Consequently, it now becomes possible to establish the stereochemistry of the first reduction stage in methanol: R. E. Davis and J. A. Gottrath, *ibid.*, **84**, 895 (1962).

Table II. Isomer Distribution and Partial Rate Constants for the Reaction of Sodium Borohydride with Cyclic and Bicyclic Ketones in Isopropyl Alcohol at 0°

Ketone	Isomers, % exo or anti	Isomers, % endo or syn	Rate constants, $k_2 \times 10^4$ l. mole⁻¹ sec⁻¹ Total	exo or anti attack[a]	endo or syn attack[a]
Acetone			15.1	7.55	7.55
Cyclopentanone			7.01	3.51	3.51
Cyclohexanone			161	80.5	80.5
2-Methylcyclohexanone	69[b]	31[c]	34.0	10.5[d]	23.5[e]
2,2-Dimethylcyclohexanone			8.84	4.42	4.42
2-Norbornanone	14	86	5.29	4.55	0.74
Bicyclo[2.2.2]octanone			1.88	0.94	0.94
7-Norbornanone			15000	7500	7500
Nortricyclenone			151	75.5	75.5
2-Norbornenone	5	95	12.0	11.4	0.6
Bicyclo[2.2.2]octenone	18	82	3.04	2.49	0.55
7-Norbornenone	85	15	1400	210	1190
1-Methyl-2-norbornanone	15	85	0.558	0.474	0.084
7,7-Dimethyl-2-norbornanone	80[f]	20	0.0256	0.0051	0.0205
Camphor	86	14	0.00263	0.00037	0.00226

[a] In symmetrical compounds a statistical factor of two was used to get the partial rate constants. [b] *trans.* [c] *cis.* [d] *trans* attack. [e] *cis* attack. [f] A value of 78.4% *exo* at 50° has been reported: R. Howe, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 379 (1965).

Even more significant, it has been observed that the reduction of 2-methylcyclohexanone by sodium trimethoxyborohydride gives almost the same isomeric distribution (70% *trans*, 30% *cis*) as the reduction with sodium borohydride (69% *trans*, 31% *cis*).[27]

Accordingly, the ketones were reduced by sodium borohydride in isopropyl alcohol at 0° and the isomer ratio established by gas chromatographic examination. The data were then used to convert the observed rate constants into partial rate constants. These results are summarized in Table II.

In order to avoid confusion it is important to call attention to the fact that the partial rate constants are for *exo* or *anti* attack of the borohydride where the alcohol obtained is the *endo* or *syn* isomer.

Discussion

Cyclic Derivatives. As was pointed out previously, the rates of reaction of the simple acyclic and cyclic model systems exhibit the order, cyclohexanone (22.9) > acetone (2.13) > cyclopentanone (1.00).[14] This typical I-strain order[28] is attributed to the influence of bond-opposition forces on the energetics of the initial and final states, reflected in the transition state.

Thus cyclopentanone has its carbonyl oxygen nicely staggered with respect to the two α-methylene groups. Reduction produces an alcohol in which there now exist enhanced bond oppositions. Consequently, the system resists the change. On the other hand, cyclohexanone has two of its α hydrogens almost in the same plane as the carbonyl group. Reduction produces an alcohol in which all the bonds are nicely staggered. Consequently, the change is energetically favorable and cyclohexanone exhibits an enhanced reactivity.

In 2-methylcyclohexanone (4.85), the presence of the methyl group in the α position brings about a decrease in the rate by a factor of 4.7 over that exhibited by cyclohexanone itself. The presence of two methyl

groups, as in 2,2-dimethylcyclohexanone (1.26), causes the reactivity to decrease by a factor of nearly 20. These decreases presumably reflect the combined inductive and steric influences of the methyl substituents.

In view of the considerable effect of the methyl substituents in the α position, it is rather surprising that reduction of 2-methylcyclohexanone yields the *trans* isomer predominantly. As was pointed out, in effect this requires the reagent to react with the carbonyl group preferentially from the side of the methyl substituent, presumably the more hindered side.[27] It was pointed out that, in a molecule such as 2-methylcyclohexanone, the small alkyl substitutent will presumably occupy the equatorial position to minimize the steric interactions. In this position, the steric effect of the substituent will be small and the course of the reaction will be determined primarily by the relative stabilities of the two isomeric alcohols formed in the reduction. This was termed "product development control."
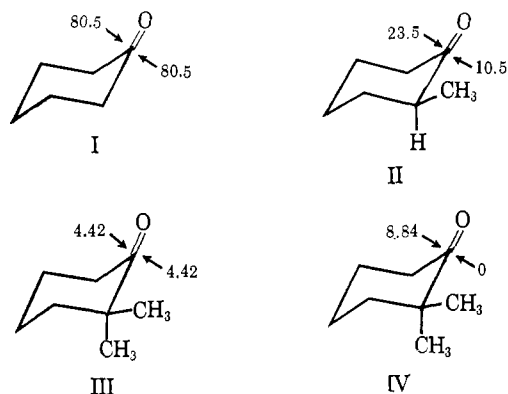
The availability of the partial rate constants allows us to examine more precisely the effect of the methyl substituents on the rates (Table II). It will be noted that the partial rate constant, 80.5 × 10⁻⁴ l. mole⁻¹ sec⁻¹,[29] for cyclohexanone (I), is decreased to 23.5 for reaction from the "more hindered" side and to 10.5 for reaction from the "less hindered" side (II). Finally, 2,2-di-

(26) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

(27) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(28) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(29) For convenience and brevity, the factor and units will be omitted from subsequent representations of the partial rate constants. In all cases, it should be understood that the values include the factor 10⁻⁴ l. mole⁻¹ sec⁻¹. The reader is cautioned that these numbers should not be translated into rates of approach of the reagent from the axial or equatorial directions. According to the transition state theory, now at the basis of our interpretation of reaction rates, the relative rates of reduction to give the two products will be determined primarily by the difference in energies of the two transition states involved—in these cases the initial states are identical. We do not have any information at present to reach a definite conclusion as to the precise mechanism involved in the transfer of the hydride moiety from the borohydride ion to the carbonyl group. Indeed, it is entirely possible that the reaction may involve a four-centered transition state. In the absence of such information, there would appear to be no point at this time in attempting a more detailed analysis of the transition state or of the extent to which the terms axial and equatorial retain any significance in that state. It is unfortunate that we continue to talk of the rates of axial approach or attack *vs.* the rates of equatorial approach or attack as a sort of vestigal hangover of the collision theory of reaction rates.[22]

methylcyclohexanone (III) exhibits a decrease to 4.42. In this case, it might be argued that reaction from the direction of the axial methyl group is prohibitive (IV), so that practically the entire rate constant, 8.84, should be used in comparing the partial rate constants. However, even with this modification the partial rate constant for reaction from the less hindered direction is only one-third that in the monomethyl derivative.

The use of a more bulky group, as in 2-*t*-butylcyclohexanone, or the use of more sterically demanding reagents, such as lithium trimethoxyaluminohydride[30] or diisopinocamphenylborane,[31] increases the importance of the steric factor and results in a preference for reduction from the side away from the substituent.

Bicyclic Systems. The norbornyl structure contains the elements of both cyclopentane and cyclohexane rings. The latter is in the boat conformation. Nevertheless, it has become customary in discussing the reactivities of norbornyl derivatives to use the corresponding cyclohexyl compounds as reference.[8,32,33]

However, the carbonyl group stretching vibration for cyclopentanone ($1748^{32,34}$ or 1740 cm^{-1} [33,34]) is much closer than that of cyclohexanone (1716 cm^{-1}) to norbornanone (1751 cm^{-1}).[32] For this reason and because of the greater similarity in the bond opposition forces in the norbornyl and cyclopentyl systems, it was suggested that cyclopentane derivatives provide a more realistic model for the reactions of 2-norbornyl derivatives.[35]

It is therefore of especial interest to note that the rate of reduction of 2-norbornanone (0.755) is very close to the rate of reduction of cyclopentanone (1.00). (Indeed, if we compare the partial rate constants for *exo* attack, the agreement is even closer. We shall discuss this point later.)

Bicyclo[2.2.2]octanone, which contains the boat cyclohexanone moiety, reacts more sluggishly (0.268), presumably a reflection of the fact that the ethylene bridge provides greater hindrance to the reaction of the borohydride ion than the methylene bridge in 2-norbornanone.

On the other hand, 7-norbornanone proved to be enormously reactive, with a rate relative to cyclopentanone of 2100. It is by far the most reactive

ketone we have yet encountered, corresponding in its reactivity to the remarkable inertness of 7-norbornyl tosylate.[36] Finally, nortricyclenone exhibited an intermediate relative reactivity, 21.5.

The reduction of 2-norbornanone by sodium borohydride under these conditions produces 14% *exo* alcohol (*endo* attack) and 86 % *endo* alcohol (*exo* attack). Thus, in contradiction to the results with simple cyclic ketones, the reduction results in the preferential formation of the less stable of the two possible alcohols. This behavior appears to be general in bicyclic systems[23,30] and corresponds to the class of reductions termed "steric approach control" in contrast to "product development control" operative in simple cyclic derivatives.[27]

The partial rate constant for *exo* attack in 2-norbornanone (V) becomes 4.55, in close agreement with the value for cyclopentanone, 3.51. On the other hand, the value for *endo* attack is far smaller, 0.74, and corresponds closely to the corresponding partial rate factor, 0.94, for bicyclo[2.2.2]octanone (VI).
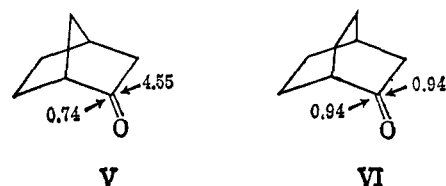
The great reactivity of 7-norbornanone (partial rate constant, 7500) must arise from the same factors that are responsible for the enormous inertness of 7-norbornyl tosylate. The latter case has been subjected to a detailed analysis[37] and the discussion need not be repeated here. Perhaps the only point which should be made is the observation that the carbonyl stretching vibration is shifted from 1751 cm^{-1} for 2-norbornanone to 1773 cm^{-1}, indicative of a greatly decreased angle.[38] Consequently, chemical changes involving a change from sp^2 to sp^3 hydridization will be strongly favored, and the reverse will be resisted.[28]

Nortricyclenone is an interesting case. If the rate is compared with 2-norbornanone (IX and V) there is evident a considerable increase accompanying the formation of the transannular bond, which might be attributed to the less hindered approach to the carbonyl group in the tricyclic structure. On the other hand, comparison of the structure with 7-norbornanone (VIII and VII) would indicate a marked decrease in rate accompanying the formation of the cyclopropane ring. This decrease might be attributed to the more favorable

(30) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).

(31) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 3166 (1961).

(32) C. S. Foote, *ibid.*, **86**, 1853 (1964).

(33) P. von R. Schleyer, *ibid.*, **86**, 1854, 1856 (1964).

(34) Cyclopentanone exhibits a split carbonyl absorption. The uncertainty in the carbonyl frequency arises from the difficulty in integrating and averaging the two bands.

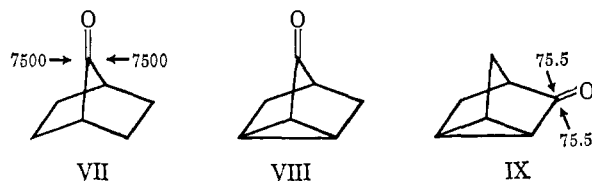(35) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1247 (1964).

(36) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

(37) P. von R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 182 (1961).

(38) Recent X-ray crystallographic studies indicate that the bridgehead angle is in the neighborhood of 96 to 97°: A. C. Macdonald and J. Trotter, *Acta Cryst.*, **18**, 243 (1965); *ibid.*, **19**, 456 (1965). Yet 7-norbornanone is far more reactive than cyclobutanone with an internal angle of 90°. Consequently, some factor in addition to simple I strain must be involved in the high reactivity of 7-norbornanone and the remarkable inertness of 7-norbornyl tosylate.

angle at the carbonyl group (ν_{co} 1762 cm^{-1}), or to electron supply by the cyclopropyl ring to the carbonyl group, or both. Evidently, we are faced with the problem of deciding which system, if either, provides a satisfactory model for nortricyclenone.

Effect of Unsaturation. A double bond results in a modest increase in rate for 2-norbornenone (1.71) and bicyclo[2.2.2]octenone (0.433) over the values for the saturated derivatives (0.755 and 0.268). On the other hand, in 7-norbornenone (200), the double bond causes a major decrease from the parent compound (2100). However, since these derivatives all undergo reduction to form two isomeric alcohols, the behavior of these compounds is best discussed in terms of the partial rate constants.

2-Norbornenone undergoes reduction by sodium borohydride under the kinetic conditions to produce 5% *exo-* (*endo* attack) and 95% *endo*-2-norborneol. This leads to the partial rate constants, 11.4 for *exo* and 0.6 for *endo* attack (X).

X   XI
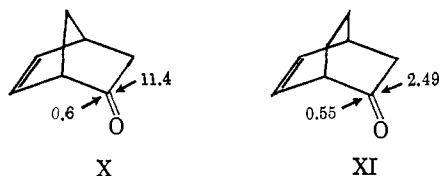
Compared with norbornanone (V), there is a 2.5-fold increase for *exo* attack. Presumably this is a reflection of the −I inductive effect of the double bond. On the other hand, the rate of attack in the *endo* direction is about the same as or slightly less than in 2-norbornanone. The preference for *exo* attack in the saturated compound was attributed to the lesser steric requirements of the 7-methylene group over the 5,6-ethylene bridge. We appear to be forced to the conclusion that the π electrons of the double bond exert a steric (and electrostatic) influence on the attacking borohydride anion that is even larger than that of the saturated bridge.

This conclusion is supported by the 18-82 distribution observed in bicyclo[2.2.2]octenone (XI). Here, the rate of *exo* attack is enhanced over that observed in the saturated derivative (VI), 2.49 *vs.* 0.94. The observed rate enhancement, a factor of 2.6, is almost identical with the factor of 2.5 noted in 2-norbornenone. Here also the inductive effect of the double bond provides a reasonable explanation. The partial rate constant for *endo* attack, 0.55, is again smaller than the *exo* value, or the value for the saturated derivative (0.94). Consequently, here also the steric requirements of the π electrons appear to be more controlling than the steric requirements of the saturated bridge. Finally, attention should be called to the similarity in the partial rate constants for *endo* attack in both the saturated (0.71 *vs.* 0.94) and the unsaturated systems (0.6 *vs.* 0.55).

We next turn our attention to 7-norbornenone (XII). Here the inductive effect of the double bond might have been expected to result in an enhanced rate, as

XII
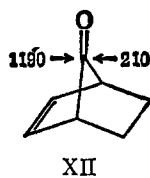
compared to 7-norbornanone. However, the observed rate for the unsaturated derivative is less by a factor of 10.

Originally, we considered the possibility that interaction of the 7-keto group with the π electrons of the double bond (XIII), similar to that postulated for the corresponding nonclassical ion, might account for the reduced rate.


XIII
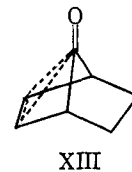
However, such interaction would be expected to result in a preferred reaction of the reagent from the *anti* direction to give the *syn* alcohol, whereas the opposite is observed (85% *anti*-7-norbornanol).

The high rate for the parent compound was attributed to the great strain and reduced angle at the 7-keto group. It was suggested by Bartlett and Giddings that a double bond in the norbornane structure should not only shorten the length of the C_2–C_3 bond, but should bring about an attendant flattening of the molecule as a whole, increasing the C_1–C_4 distance.[39] The result should be an opening of the C_1–C_7–C_4 angle, bringing about a less strained condition, thereby accounting for the observed decreased reactivity of the ketone toward borohydride.

Unfortunately, doubt is cast on this explanation by the recent X-ray data of Macdonald and Trotter.[38] In the case of *anti*-8-tricyclo[3.2.1.0^{2,4}]octyl and *anti*-7-norbornenyl brosylates their results do not indicate any significant flattening of the molecule accompanying the introduction of the double bond. However, judgment should perhaps be reversed until crystallographic data are available for the parent compound, 7-norbornyl brosylate, to permit a direct comparison of the effect of the double bond on the geometry.

Methyl Derivatives. Finally, we turn our attention to the methyl derivatives. The reduction of 1-methyl-2-norbornanone involves 85% *exo* attack, practically identical with that in 2-norbornanone itself. On the other hand, the reduction of both 7,7-dimethyl-2-norbornanone and camphor involves predominantly *endo* attack, 80 and 86%, respectively. These lead to the partial rate constants shown (V, XIV, XV, and XVI).

V   XIV

XV   XVI
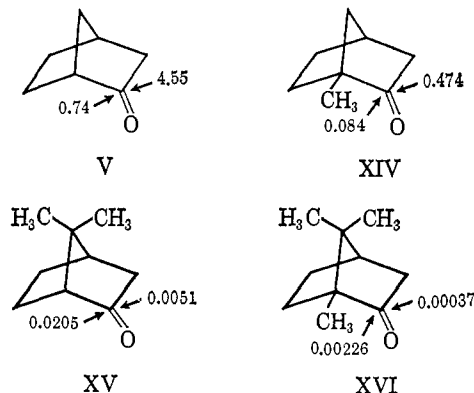
(39) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960).

The presence of the 1-methyl substituent results in a decrease in the rate of reduction of 1-methyl-2-nor-bornanone (XIV), in both the *exo* and *endo* directions, by a factor of approximately 10, over that of the parent compound (V). Again, comparison of XV and XIV, where the sole difference is the 1-methyl, reveals the same influence on the rate. The inductive effect of methyl is relatively small. Consequently a change of this magnitude suggests an important steric contribution. An examination of models reveals that the 1-methyl substituent is almost in the same plane as the carbonyl group, so that the similarity in a steric effect on both *exo* and *endo* attack is not unreasonable.

In 2-methylcyclohexanone, the methyl substituent resulted in an over-all decrease by a factor of 4.7. The smaller factor in the monocyclic system is presumably a consequence of its more flexible structure which can serve to minimize steric interactions.

The 7,7-dimethyl substituents cause a reduction by a factor of nearly 1000-fold in the rate of reaction. This clearly is a major steric effect.
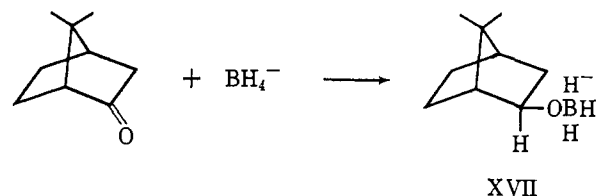
This enormous effect of 7,7-dimethyl substituents, as contrasted with the relatively small effect of the *gem*-dimethyl structure in cyclanones, emphasizes the point made later—that the steric requirements of the boro-hydride reaction are exceedingly large in these rigid bicyclic systems.[40]

An unexpected feature of these derivatives is the observation that the rate of *endo* attack is also markedly influenced by the 7,7-dimethyl substituents. In both XV and XVI there is observed a decrease in the rate of reaction in the *endo* direction by a factor of 35 over the corresponding derivatives not containing the 7,7-dimethyl groups (V, XIV). The inductive effect of the methyl substituents should cause a decrease. However, the substituents are relatively remote from the reaction center and only a small influence on the rate from this factor would be anticipated. It is probable that we are observing here a buttressing action of the 7,7-dimethyl groups which causes the two planes of the cyclohexane boat structure to move closer together,[41] making approach of the borohydride more difficult. An even larger factor in the diminished rate may be the additional strain engendered by the movement of the oxygen atom into the environment of the *gem*-dimethyl groups during

the transfer of the hydride moiety to the carbonyl group from the *endo* direction (XVII).

XVII

The Carbonyl–Carbonium Ion Correlation. We originally pointed out that carbonium ions are fugitive intermediates and it becomes exceedingly difficult to test the many unusual structures proposed for these particles. We suggested the possibility that carbonyl derivatives might serve as models for carbonium ions and that a study of the rates of reaction of sodium borohydride with a family of ketones might reveal whether or not the proposed nonclassical structure was really required by the experimental facts.[14]

For example, α-phenylethyl chloride solvolyzes considerably faster than isopropyl chloride, whereas acetophenone reacts with sodium borohydride at a considerably slower rate than acetone.[12] Presumably we are observing manifestations of the same phenomenon, stabilization of the transition state for the solvolysis reaction and stabilization of the initial state in the ketone reaction, both as a result of resonance contributions from the aromatic system.

Similarly, cyclopropylcarbinyl chloride exhibits a greatly enhanced rate of solvolysis.[42] The enhanced rate has been attributed to the special stabilization afforded by the formation of a nonclassical bicyclo-butonium ion. However, cyclopropyl methyl ketone and dicyclopropyl ketone exhibit greatly decreased rates of reaction with sodium borohydride.[20] It is of course possible that we are dealing with totally different phenomena in the two systems. However, the similarity in the results makes it reasonable to raise the question whether both phenomena may not have an identical basis—facile electron supply from the cyclopropyl system to the electron-deficient center, whether that center be an incipient cation in the transition state for the solvolysis or the carbon atom of the carbonyl group.[21] The need for a special structural explanation, the bicyclobutonium ion, to account for the enhanced reactivity of cyclopropylcarbinyl derivatives then becomes less convincing.

For example, a hydrogen-bridged structure was briefly considered for the cyclodecyl cation on the basis of the enhanced rate of solvolysis of cyclodecyl tosylate, the most reactive of the cyclic derivatives, and the transannular rearrangements which occur in this system.[43] However, the general pattern of reactivity of the cyclic tosylates parallels that for many cyclic derivatives[44] where there appear to be no possibility for the formation of nonclassical intermediates. Similarly, the general pattern of reactivity of the cyclanones with sodium borohydride[13] reveals the same pattern, with a maximum in rate at cyclohexanone (corresponding to the minimum in rate at cyclohexyl tosylate) and a minimum in rate at cyclodecanone (corresponding to the maximum in rate at cyclodecyl tosylate).

(40) It has been argued that the observation that the apobornyl cation, with its 7,7-dimethyl substituents, substitutes exclusively *exo* requires the cation to have a nonclassical bridged structure:[10] R. Howe, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, 87, 379 (1965). This argument makes two implicit assumptions which should be pointed out, namely, that the steric requirements for the reaction of a cation with solvent are similar to the steric requirements of the ketone reacting with the complex hydride, and that no other mechanism is possible to account for the observed *exo* substitution other than nonclassical bonding between C1, C2, and C6 of the norbornane structure. We shall discuss this in detail in a later publication. Attention is called to the recent fascinating results of A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, No. 18, 1309 (1965). They report that the base-catalyzed deuteration of both isofenchone and camphor leads to a monodeuterated derivative which contains the deuterium in the α position to the ketone group with clean *exo* stereochemistry. Apparently here also the 7,7-dimethyl groups fail to invert the direction of deuteration of the carbanion in the manner that they invert the direction of reduction of the carbonyl group by complex hydrides. This result emphasizes the need for caution in extrapolating the reduction results to the behavior of the cation.

(41) There is a suggestion of support for this conclusion in the crystallographic data on (−)-2-bromo-2-nitrocamphane: D. A. Brueckner, T. A. Hamor, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 799 (1962). In this molecule the C3–C4–C7 angle is reported to be 104°, as compared to 100 and 101° for *anti*-7-norbornenyl and *anti*-8-tricyclo-[3.2.1.0²·⁴]octyl brosylates, respectively.[38]

(42) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, 73, 2509 (1951).

(43) R. Heck and V. Prelog, *Helv. Chim. Acta*, 38, 1541 (1955).

(44) V. Prelog, *J. Chem. Soc.*, 420 (1950).

Even this qualitative parallelism suggests the possibility that the maximum in rate of cyclodecyl tosylate and the minimum in rate of cyclodecanone may have a common basis. It was therefore suggested that it is not necessary to postulate that the cyclodecyl tosylate ionizes to an unusually stable hydrogen-bridged cation to account for the reactivity of the tosylate. Instead, it was proposed that the cyclodecyl system is highly strained with many bond oppositions. A reaction involving the loss of a bond, such as solvolysis, will be strongly favored; one which involves the formation of an additional bond, such as the reduction of the ketone, will be resisted.[45]

Linear free-energy relationships of broad applicability, of the kind which have proved so successful in correlating the side-chain reactions of aromatic derivatives[5] and directive effects in aromatic substitution,[6] have not yet been established in aliphatic or alicyclic derivatives. However, the close similarity in the reactivity patterns indicated by the cyclic derivatives encouraged the examination of possible limited linear free-energy relationships among these compounds. Indeed, an excellent linear free-energy relationship was demonstrated for the rates of reaction of sodium borohydride with the cyclanones from 5 to 17 ring atoms and the equilibrium constants for the dissociation of the corresponding cyanohydrins.[14]

A partial correlation was indicated by the data for the cyclic tosylates. To quote:[14,46] "Comparison of the rate data for the acetolysis of the cyclic tosylates with the rate data for the borohydride reaction also reveals a rough linear relationship for the 5- to 10- ring derivatives... Larger rings deviate from this relationship and so do related aliphatic compounds. The two reactions under comparison must have significantly different steric requirements, so that the deviations are not unexpected... It is the existence of a limited linear relationship for the six consecutive ring systems, 5- through 10-, which must be considered unexpected. The fit, rough as it is, appears to be too good to be considered purely fortuitous. It may be that the fit arises from the fact that the rings from 5- through 10-members are relatively rigid, with comparatively fixed conformations, resembling the aromatic structures in that characteristic, whereas the larger rings possess greater mobility of conformation and more closely resemble aliphatic derivatives."

A rough linear relationship was also observed between

(45) For a more detailed analysis of the factors influencing the solvolysis of cyclodecyl tosylate, see V. Prelog, W. Küng, and T. Tomljenović, *Helv. Chim. Acta*, **45**, 1352 (1962).
(46) The present discussion of the applicability of the borohydride reaction has been expanded considerably from the original version to satisfy the requirements of one of the referees. The original version dealt primarily with the examination of the applicability of the proposed carbonyl–carbonium ion correlation to bicyclic systems, an area not previously explored. However, the referee recommended a general discussion of the correlation and urged that all of the available data be shown on a single plot. He apparently believed that we have previously proposed that there would exist a general quantitative correlation between the rates of borohydride reduction and the rates of tosylate solvolysis. Since our first publication on the subject[14] had made it clear that no general correlation could be expected, we fail to see the point of such a plot. The absence of a general quantitative correlation does not invalidate the demonstration of limited quantitative correlations or the existence of qualitative correlations and their utilization in analyses of structural effects. Since the referee, who must be considered an expert in the field, evidently misunderstood our position, as expressed in previous publications, others may be in a similar difficulty. Consequently, it has appeared desirable to restate our position to avoid further misunderstanding.

the rates of reduction of the α-phenyl-substituted acetones and the rates of solvolysis of the corresponding tosylates.[47] Again, quoting, "It is unfortunate that we do not have a really satisfactory treatment for the reactivities of aliphatic derivatives comparable to that which has worked so well for *meta* and *para* aromatic derivatives. In the absence of a sound theoretical basis for such correlations involving aliphatic compounds, great importance cannot be ascribed to the fact that a linear free-energy relationship is indicated for the limited series of compounds under examination. Nevertheless, simple examination of the data reveals a good qualitative correlation of the reactivities in the two systems, and [the figure] reveals that a reasonable quantitative relationship exists."

"It is, of course, possible that the observed correlation is purely accidental, the result of the fortuitous cancellation of unrelated factors. Nevertheless, it appears reasonable to explore the possibility that the correlation is a reflection of the operation of similar factors in influencing the reactivities of the two families of compounds."

It should not be necessary to emphasize that such approaches must be used and interpreted with caution. No successful attempts to develop quantitative free-energy correlations in aliphatic or alicyclic systems, similar to those which have been demonstrated for *meta* and *para* derivatives,[5,6] have yet stood the test of time.[48] It is apparent that the steric interactions between the reagent and the reaction center in a mobile system are simply too large to be ignored and too difficult to calculate. Nevertheless, this is no reason not to explore the possibility that such a free-energy correlation may exist within a severely limited group of related structures with similar steric environments.[49]

Failure of the Quantitative Correlation for Bicyclics. Accordingly, we undertook to examine the existence of such a correlation between the rates of reaction of this group of bicyclics (omitting the methyl derivatives) and the carbonyl frequency, and the rates of solvolysis of the tosylates *vs.* the rates of reduction of the ketones. For convenience, the data used in these plots are summarized in Table III.

Originally we had hoped that simple cyclic derivatives and those bicyclic compounds which do not involve participation, such as *endo*-norbornyl, *endo*-norbornenyl, 7-norbornyl, etc., would exhibit a reasonable first-order correlation. Then those compounds whose tosylates clearly undergo solvolysis with participation, such as *anti*-7-norbornenyl and *exo*-bicyclo[2.2.2]octenyl, would deviate from the correlation. We might then be in postiion to provide an answer to the question of whether the solvolyses of cases under review, such as *exo*-norbornyl and bicyclo-[2.2.2]octanyl tosylates, proceed at normal rates or at anchimerically accelerated rates.

As is indicated above, we were seeking a first-order correlation, *i.e.*, one which would exhibit a linear correlation without the introduction of correction factors or adjustable parameters. In such a first-order

(47) H. C. Brown, R. Bernheimer, and K. J. Morgan, *J. Am. Chem. Soc.*, **87**, 1280 (1965).
(48) Attention is called to the interesting attempt to correlate rates of acetolysis with the carbonyl frequency and other factors.[32,33]
(49) See H. C. Brown, *J. Chem. Educ.*, **36**, 424 (1959), for an example of such a linear relationship in the Menshutkin reaction.
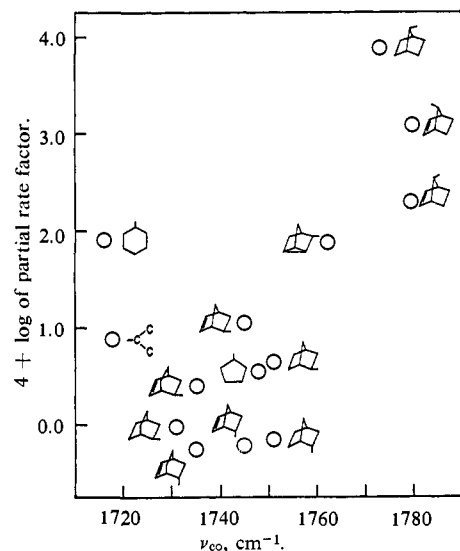
Figure 1. Plot of logarithms of the partial rate constants for reaction of borohydride with ketones *vs.* carbonyl frequencies.

correlation there would appear to be a reasonable probability that its existence reflects similar major structural influences in the two reactions being compared. Consequently, it can be helpful in achieving an understanding of these influences.

Table III. Carbonyl Stretching Frequencies and Related Rate Data

		Acetolysis,[a] log k_{rel}		Reduction,[b] 4 + log k_p	
Ketone	ν_{co}, cm^{-1}	exo or anti	endo or syn	exo or anti attack	endo or syn attack
Acetone	1718	0.15		0.88	
Cyclopentanone	1748	1.51		0.55	
Cyclohexanone	1716	0.00		1.91	
2-Norbornanone	1751	2.71	0.18	0.66	−0.13
Bicyclo[2.2.2]-octanone	1731	1.85		−0.03	
7-Norbornanone	1773	−7.00		3.88	
Nortricyclenone	1762	1.82		1.88	
2-Norbornenone	1745	2.42	−1.48	1.06	−0.22
Bicyclo[2.2.2]-octenone	1735	4.12	2.49	0.40	−0.26
7-Norbornenone	1780	4.11	−3.28	2.32	3.08

[a] From ref 32 and 33. [b] k_p is the partial rate factor from Table II.

A higher order correlation can be exeedingly valuable in providing an empirical correlation of data and in permitting extrapolations. However, it is our opinion that such correlations are highly dependent on the precise model utilized and the precise interactions adopted to achieve the correlation. Consequently, it is our opinion that higher order correlations, while highly satisfactory for many practical purposes, provide a less satisfactory basis for resolving theoretical questions.[50]

(50) It was suggested by one of the referees that our treatment might be misunderstood and interpreted by the reader as reflecting on the Foote–Schleyer correlation.[32,33] Consequently, the above discussion was introduced to make it clear that our primary objective was to seek a first-order correlation which we might hope to apply to the problem to resolve the question under current review of the importance of participation in the solvolysis of *exo*-norbornyl tosylate and similar bicyclic derivatives. Since we do not believe that higher order correlations pro-
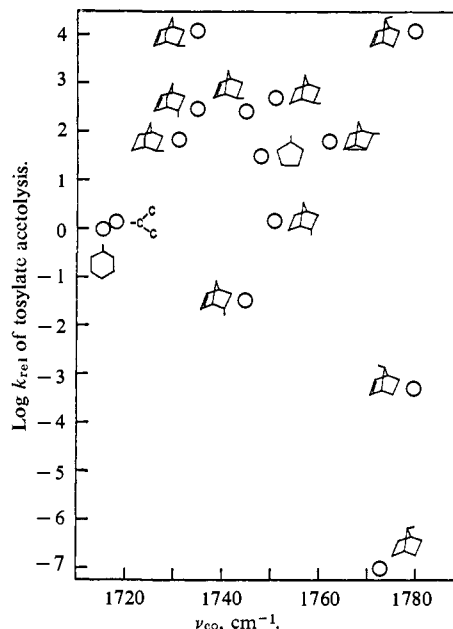

Figure 2. Plot of the logarithms of the relative rates of acetolysis of tosylates *vs.* the carbonyl frequencies of the corresponding ketones.

In Figure 1 is shown a plot of the logarithms of the partial rate constants for the reduction of the bicyclic ketones and several representative model compounds *vs.* the carbonyl frequency. While there is an indication of enhanced reactivities with higher frequencies, it is immediately evident that a simple linear relationship does not exist for these compounds.

We were puzzled by the lack of any correlation, when Foote[32] and Schleyer[33] have apparently been so successful with their related correlation. Accordingly, we examined a plot of the logarithms of the relative rates of acetolysis of the corresponding tosylates *vs.* the carbonyl frequency. The result is shown in Figure 2. The correlation is evidently no better.[51]

Finally, we examined the existence of a possible correlation between the logarithms of the relative rates of tosylate acetolysis and the logarithms of the partial rate constants for the borohydride reaction. The result is shown in Figure 3. Again there is no correlation.

vide reliable foundations for resolving theoretical questions, we made no effort to achieve such a correlation in the present study by introducing corrective terms for torsional effects, steric interactions, etc. The reader is referred to ref 49, where we describe our success in achieving a first-order correlation in reactions involving very large steric factors.

(51) It should be pointed out that Foote's approach is essentially empirical. He plots the data for 43 compounds and selects 18 (two of the compounds in his 20 were originally assigned incorrect structures: P. von R. Schleyer, W. E. Watts, and C. Cupas, *J. Am. Chem. Soc.*, **86**, 2722 (1964)) which give a reasonably good fit with a proposed line. The majority of compounds which do not fit the line are considered to deviate because of ground-state eclipsing or anchimeric assistance. Only three of the compounds in Figure 2 (isopropyl, cyclohexyl, and 7-norbornyl) were selected by Foote for his first-order correlation.

Schleyer introduces correction terms for torsional and nonbonded interactions, and inductive effects. With these correction terms approximately half of the 52 compounds examined fit his proposed correlation. The others are faster and the enhanced rates are attributed to anchimeric assistance. Six of the compounds in Figure 2, with the corrections, fit his proposed correlation.

Without deprecating the difficulties of the task that Foote and Schleyer have undertaken, we should point out that they have a degree of freedom available to them in the tosylate system that is absent in the borohydride system. Any time that the observed rate is faster than that estimated by their treatments, the discrepancies can be attributed to anchimeric assistance. It is evident that the true utility of their treatments will be tested only when we are in position to predict both the presence and the amount of participation independently and can then use the information with the correlation to predict the actual rate.

Even if we restrict ourselves to those structures which are believed to undergo solvolysis without anchimeric assistance (such as 7-norbornyl, endo-norbornenyl, and endo-norbornyl) there is no correlation apparent.

On the other hand, if we exclude exo-bicyclo[2.2.2]-octenyl and anti-7-norbornenyl (and possibly nortricyclyl), at the upper range, as involving large anchimeric assistance in the tosylate solvolysis, and exclude endo-norbornyl and endo-norbornenyl, as possibly being unduly slow in their tosylate solvolysis because of steric hindrance to ionization, we find that we can draw a line through 7-norbornyl and cyclopentyl which would provide a reasonably satisfactory locus for the remaining points.

It is evident, however, that a satisfactory first-order quantitative correlation cannot be achieved merely by excluding those bicyclic derivatives which are believed to undergo solvolysis with participation.

It was pointed out to us by Schleyer that a consideration of the results with the methyl-substituted derivatives makes it clear that no simple relationship can be anticipated in bicyclic derivatives between the rates of reaction of borohydride with the ketones and the rates of solvolysis of the corresponding tosylates, even in cases where there is no question of anchimeric assistance. Thus the rates of reaction of borohydride in the *endo* direction with norbornanone and its methyl derivatives reveals a sharp dependence on the structure (Table II): 2-norbornanone, 1.00; 1-methyl-, 0.11; 7,7-dimethyl-, 0.028; 1,7,7-trimethyl-, 0.0031. Thus, this series of compounds reveals a decrease in rate by a factor of over 300-fold. On the other hand, the corresponding tosylates exhibit almost identical rates of acetolysis: 1.00, 1.13, 0.75, and 0.82.[52]

It is evident from this comparison that the borohydride reaction must be much more sensitive to the steric environment of the carbonyl group in the rigid bicyclic system than is the tosylate solvolysis. The fact that in the 7,7-dimethyl derivatives, the OBH_3^- moiety, with its solvation shell, must be moving into a sterically crowded environment (XVII), must be a major factor in the large differences in the two systems. In the *endo* tosylate, there is only an *exo* hydrogen atom to interact with the bulky 7,7 substituents.

Failure of the Qualitative Correlation for Bicyclics. Even though the data clearly reveal the absence of a quantitative correlation, there remained the possibility of a qualitative relationship between the rate of reaction of borohydride with the ketone and the rate of solvolysis of the corresponding tosylate or other ester. Such a qualitative relationship has now been demonstrated for numerous aliphatic and alicyclic derivatives. Among these may be mentioned the following:[53] (1) α-phenylacetone > acetone; (2) α,α,α-triphenylacetone < acetone; (3) acetophenone < acetone; (4) p-methoxy-
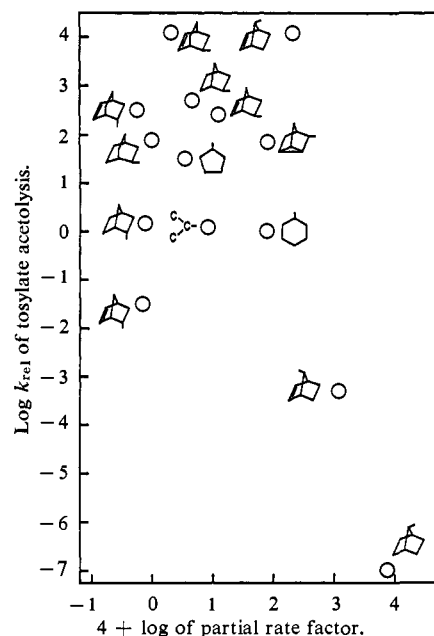

Figure 3. Plot of the logarithms of the relative rates of acetolysis of tosylates vs. the logarithms of the partial rate constants for the borohydride reaction.

acetophenone < acetophenone; (5) p-nitroacetophenone > acetophenone; (6) cyclopentanone < acetone; (7) cyclohexanone > acetone; (8) cyclodecanone < acetone; and (9) cyclopropyl methyl ketone < isopropyl methyl ketone.

As previously discussed, a number of qualitative correlations of this kind are observed in the bicyclics. Leaving out of consideration those cases involving large unquestioned participation, we note that 7-norbornanone reacts enormously faster than cyclopentanone or acetone. This corresponds to the much slower rate of solvolysis of 7-norbornyl brosylate. Similarly, the 7,7-dimethyl substituents in apocamphor decrease the rate of reaction of borohydride with the keto group from the *exo* direction as compared to norcamphor (steric hindrance), corresponding to the observed enhanced rate of solvolysis of the corresponding brosylate[52c] (steric assistance).

However, when we attempt to apply the correlation to the *endo* derivatives, even though participation is not a factor here, even the qualitative correlation breaks down.

Thus, the rate of solvolysis of endo-norbornyl tosylate (XIX) is considerably smaller than that of cyclopentyl tosylate (XVIII). On the basis of the qualitative relationship under examination, this would predict that 2-norbornanone (XXI) should react with sodium borohydride in the *endo* direction at a rate considerably faster than that exhibited by cyclopentanone (XX). However, the observed rate is not faster, but considerably slower.

Similar discrepancies are observed for all other bicyclic derivatives involving reduction from the *endo* direction and solvolysis from that direction. Either the rate of departure of the tosylate group from the *endo* direction is too slow to conform to the relationship, or the rate of attack of the borohydride group from the *endo* direction is too slow, *or both processes are slow.* In the following section we shall present our reasons for

(52) Data were obtained from following sources: (a) P. von R. Schleyer, M. A. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, 87, 375 (1965); (b) D. C. Kleinfelter, Ph.D. Thesis, Princeton University, 1960; (c) A. Colter, E. C. Friedrich, N. J. Holness,'and S. Winstein, *J. Am. Chem. Soc.*, 87, 378 (1965); (d) S. Winstein, et al., *ibid.*, 74, 1127 (1952).

(53) For brevity, only the two ketones under comparison are shown. It should be understood that the results are compared with the rates for the corresponding tosylates. For example, α-phenylacetone reacts faster with sodium borohydride, by a factor of 1.6, than does acetone. This corresponds qualitatively to the slower rate of acetolysis of 1-phenyl-2-propyl brosylate (0.3) as compared to 2-propyl brosylate (1.00).
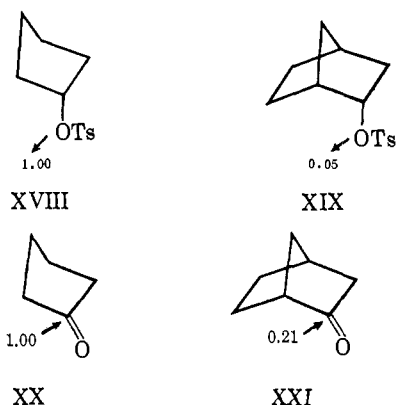
suggesting that the latter may be the preferred interpretation—both the approach and departure of a reagent or group in the *endo* direction may be sterically interfered with by the rigid 5,6-ethylene bridge.

Irrespective of the final interpretation of this phenomenon, it is quite clear that the results represent a major breakdown in the qualitative aspects of the proposed carbonyl–carbonium ion relationship.

Previously, we had realized excellent qualitative correlations and some limited quantitative correlations between the rates of reaction of borohydride with ketones and the corresponding solvolysis reactions. However, these earlier correlations had all been achieved with aliphatic and alicyclic systems. What could be the explanation for the major difference in the degree of correlation realized in the bicyclics as compared to the other two systems, restricting consideration only to cases where participation cannot be a significant factor? Was it possible that steric influences are far more important in rigid bicyclic systems than in the more flexible acyclic and monocyclic derivatives?

In the course of considering possible explanations for the major difference in the behavior of the monocyclic derivatives in the proposed correlation from that of the bicyclic derivatives, we arrived at a promising new interpretation of the factors influencing the behavior of these respective systems. This interpretation is discussed in the following section.

Steric Departure Control. It is common practice to base our analyses of structure and reactivity on thermodynamic arguments. Thus, in the simple reaction

$$A + B\text{-}C \longrightarrow A\text{-}B + C$$
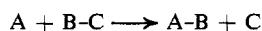
a structural change in A that causes the A–B bond to be stronger leads to the prediction of an enhanced rate of reaction.[5] It is a thermodynamic argument that leads us to predict that a *p*-methoxy substituent in acetophenone will stabilize the ketone group through resonance and lead to a decreased rate of reaction with borohydride. On the other hand, the same considerations lead us to predict that a *p*-methoxy substituent will have the opposite effect in a solvolytic reaction, bringing about an enhancement in the rate of solvolysis of 1-phenylethyl chloride.

Similarly, it is a thermodynamic argument that leads us to predict that the relatively stable cyclopentanone will exhibit a relatively slow rate of reaction with borohydride, a reaction in which there is formed a relatively strained derivative with enhanced bond oppositions. Contrariwise, cyclohexanone, with two unfavorable bond oppositions, reacts with unusual velocity to produce a relatively stable cyclohexane derivative with all bonds nicely staggered. In reactions of the reverse type (sp^3 → sp^2), such as solvolysis, we find that cyclohexyl derivatives react less readily than cyclopentyl derivatives.

Thus it is representative of the more common, more general behavior of carbon compounds for 2-methylcyclohexanone to undergo reduction by complex hydrides to form the more stable isomer, *trans*-2-methylcyclohexanol, preferentially. It is really a less common relatively exceptional phenomenon that in bicyclic systems the use of complex hydrides yields the stable alcohols preferentially (steric approach control).[54]

In solvolyses the same thermodynamic considerations have been at the basis of our interpretations. A sterically encumbered initial state leads us to predict an enhanced rate, since it is believed that strain resulting from the crowding will be largely relieved during ionization. Alternatively, the formation of a more stable ion leads us to predict that this will provide driving force for the reaction and result in an enhanced rate.

In extending these ideas to bicyclic derivatives, such as *exo*- and *endo*-norbornyl tosylates, we encounter a problem. A large difference in rate is observed between the *exo* and *endo* isomers.[55] The solvolysis of the two compounds leads to the same cation, Consequently, we cannot attribute the difference in rates to a difference in the stabilities of the products. The *endo* compound is slightly more strained (estimated at 1.0 kcal/mole)[33] than the *exo*. This is far too small to account for the observed difference in rates. Even more important, the effect is in the wrong direction—it is the strained *endo* compound that exhibits the slower rate! It was therefore proposed that the norbornyl cation is stabilized by nonclassical resonance and that this carries over to stabilize the transition state for the *exo* derivative, but not for the *endo*.[55] This again represents a thermochemical argument, with a stereochemical factor brought in to explain why the postulated resonance stabilization of the intermediate affects only one of the two transition states.

In view of the wealth of accumulated experimental data, there is no doubt as to the utility and validity of these thermodynamic considerations for the reactions of borohydride with ketones in flexible acyclic and monocyclic systems, or their applicability to solvolytic phenomena in these systems. However, just as it has been considered necessary to shift from this thermodynamic basis to a steric basis in the reaction of complex hydrides with bicyclic ketones (steric approach control), it is our opinion that it is necessary to shift to a steric basis to account for solvolytic phenomena in rigid bicyclic systems (steric departure control).

It might be asked why should there be a change in the controlling influences for both reactions as we

(54) The same dichotomy is evident in E2 eliminations. In the cases of simple alkyl halides, such as *sec*-butyl bromide, elimination proceeds to give preferentially the thermodynamically more stable of the two possible olefins (Saytzeff rule). On the other hand, the use of bases of large steric requirements or E2 elimination of compounds with large leaving groups, such as *sec*-butyltrimethylammonium salts, yields predominantly the less stable of the two possible olefins (Hofmann rule). Here also it is believed that large steric effects in the transition state overcome the more usual tendency for the reaction to proceed to form the more stable of the two possible products: H. C. Brown and R. Moritani, *J. Am. Chem. Soc.*, 78, 2203 (1956). For an alternate interpretation, see C. K. Ingold, *Proc. Chem. Soc.*, 265 (1962).

(55) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, 74, 1147, 1154 (1952).

Table IV. Physical Properties of Ketones

Ketone	Bp, °C (mm)	Mp, °C	n^{20}D	Lit. values Bp, °C (mm)	Lit. values Mp, °C	Lit. values n^{20}D
Norcamphor		93–94			91–93[a]	
Norbornen-2-one		18–20	1.4849		22–23[d]	1.4839
Bicyclo[2.2.2]-octanone		177–178			177–178[c]	
Bicyclo[2.2.2]-octenone		88–89			88.6–89.1[f]	
1-Methylnor-camphor	61–63 (15)		1.4672	61.5–63 (15)[e]		
7,7-Dimethyl-norcamphor	70–80 (2)			85 (6)		
Camphor		177–178			178[b]	
7-Norbornanone		76–77			79.5–80.5[g]	
7-Norbornenone			1.4786	62–63 (30)		1.4772
Nortricyclenone	73–74 (17)		1.4891	78–79 (24)	25	1.4878[a]

[a] H. K. Hall, *J. Am. Chem. Soc.*, **82**, 1209 (1960). [b] Heilbron Dictionary of Chemical Compounds. [c] O. Diels and K. Alder, *Ann.*, **478**, 137 (1930). [d] P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956). [e] G. Komppa, *Ann.*, **263**, 148 (1891). [f] N. A. LeBel and J. E. Huber, *J. Am. Chem. Soc.*, **85**, 3193 (1963). [g] G. Gassman and P. G. Pape, *Tetrahedron Letters*, No. **1**, 9 (1963).

change from acyclic or monocyclic systems, on the one hand, to bicyclic systems on the other? We attribute the change to the difference in the flexibility of the structures. Acyclic and monocyclic structures can usually adapt themselves to minimize the steric effect of a departing group in solvolysis or the approaching group in the borohydride reaction. Rigid bicyclic systems are incapable of such accommodation. If approach of borohydride to the carbonyl group from the *endo* direction of 2-norbornanone is badly hindered by the 5,6-ethylene bridge, the departure of the leaving group in *endo*-norbornyl tosylate may also be hindered.[56]

It should be emphasized that according to this interpretation there will not be a sudden and complete change in control by the thermodynamic factor in flexible systems to control by the steric factor in bicyclic systems. The thermodynamic factor will be important in all systems. Superimposed on the thermodynamic factor will be a steric factor which will generally be more important in rigid bicyclic than in the relatively flexible acyclic and monocyclic derivatives.

Even in bicyclic systems the steric factor need not always be dominant. For example, *exo* attack of borohydride on 2-norbornanone does not appear to be subject to any severe steric limitations—the rate is very similar to that observed for cyclopentanone itself. No significant interference to the departure of the anion in the *exo* derivative is indicated by an examination of the model. Similarly, the borohydride reduces 7-norbornenone predominantly from the *syn* side, even though the results with 2-norbornenone and bicyclo-[2.2.2]octenone indicate that the steric requirements of the double bond in this reaction are greater than those of the ethylene bridge in the saturated analogs.

The suggestion that there should be steric hindrance to ionization in bicyclic systems is one which is relatively accessible to experimental test. Such tests are underway[57] and will be reported shortly.

Finally, recognition of the change from predominantly thermodynamic control in acyclic and monocyclic systems to predominantly steric control in bicyclic

systems clarifies the failure to realize any simple correlation involving the reduction of bicyclic ketones (Figure 3). For example, in simple acyclic or alicyclic ketones, the observation that the reaction with borohydride is unusually slow, as in cyclodecanone, leads directly to the prediction that the solvolysis of the corresponding tosylate will be unusually fast. However, the data presented in this paper reveal that the rates of attack of borohydride in the *endo* direction of 2-norbornanone and 2-norbornenone are very slow, much slower than the rate of any simple model compound, such as cyclopentanone. Application of the usual thermodynamic considerations would lead one directly to the erroneous prediction that the departure of *endo* tosylate from these systems should be correspondingly fast, much faster than that of the model compound. Yet the rates of the *endo* tosylates are very much slower. Indeed, by any experimental yardstick, the *endo* tosylates are unusually stable derivatives, undergoing solvolysis with the most deliberate speed.

Thus it is our proposal that the behavior of bicyclic ketones in their reactions with the complex hydrides is not a unique phenomenon, but is a general one in bicyclic systems. If the validity of this proposal is confirmed by further experimental work, it will become necessary to reexamine and reinterpret much of the fascinating data for bicyclic systems.

Experimental Section

Materials. The purification of isopropyl alcohol and sodium borohydride for the kinetic runs was carried through according to the procedures described earlier.[12] Some of the ketones were commerical products, purified by recrystallization and sublimation to constant melting point. The other ketones and reference alcohols were prepared by standard procedures available in the literature. Bicyclo[2.2.2]octenone and the corresponding alcohols were provided by Professor Norman A. LeBel of Wayne State University. The 7-norbornyl alcohols were prepared by Story's procedure.[58] The oxidation of these alcohols to the ketones was accomplished with the chromic trioxide–pyridine–*t*-butyl alcohol complex in ligroin.[59]

Physical properties of the products utilized for kinetic studies are summarized in Table IV.

(56) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964).

(57) With Dr. Irvin Rothberg, David VanderJagt, and W. James Hammar.

(58) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

(59) K. Scherer, Ph.D. Thesis, Harvard University, 1961.

Kinetic Measurements. The experimental procedure was identical with that described previously.[12] The temperatures of 0, 25, and 48.6° were controlled to within ±0.02°. The temperature of the bath for the −43.7° determination (7-norbornenone) was maintained by immersing the bath (a Dewar vessel) into another bath which was cooled to −43.7° and maintained there by addition of Dry Ice, using a sulfur dioxide gas thermometer to follow the temperature.

In most cases the concentrations of the reactants were maintained at 0.16 M ketone and 0.02 M sodium borohydride. Usually, several kinetic runs were conducted for each temperature and the mean values are reported in Table II. Generally there was no difficulty in obtaining reproducible values to within 2 to 3%. For example, four successive determinations for 2-norbornanone yielded the values at 25.0° of ($k_2 \times 10^4$, 1. mole^{-1} sec^{-1}) 24.5, 24.0, 23.8, and 23.3, with an average value of 24.0.

Most runs were made at 0 and 25°. In the case of 7-norbornenone the rate at 0° was so fast that it represents close to the practical limit of measurement by the usual technique. Accordingly, to determine the temperature coefficient of the rate, it was necessary to select a lower temperature. The experimental difficulties result in a much larger experimental uncertainty in these values than those determined by the standard kinetic procedure.

The rate of reaction of 7-norbornenone was far too fast for the usual technique. Accordingly, its rate was determined by two approximate procedures. First, precooled solutions (0°) of the borohydride and the ketone in the two limbs of a U-shaped vessel were rapidly mixed by tilting and shaking vigorously. After a measured time interval, of the order of 30 to 60 sec, the reactions were quenched by the addition of aqueous acid. Analysis yielded the ketone/alcohol ratio for calculation of the rate constant. In a second procedure, borohydride was added to a mixture of benzaldehyde and 7-norbornanone. Gas chromatographic analysis of the product provided the data to estimate the relative magnitudes of the rate constants. Since the value for benzaldehyde is known,[12]

it was possible to calculate the value for 7-norbornanone. The two approaches yielded values which agreed with each other to within 20%.

Product Measurements. Vapor phase chromatography was used for all analyses and the retention times were compared with authentic samples. The only exceptions were *syn*-7-norbornenol and both *exo*- and *endo*-7,7-dimethylnorborneols, which were not available. Reduction of 7-norbornenone produced two products in a ratio of 85:15. The 85% product was identical with authentic *anti*-7-norbornenol. The minor peak was therefore assigned to the *syn* isomer. In the other case, 7,7-dimethyl-2-norbornanone was reduced by lithium aluminum hydride. Two products were formed in a ratio of 91:9. Camphor likewise yielded two products in a ratio of 90:10. In the latter case there was no difficulty in identifying the major product, 90%, as isoborneol, and the minor as borneol. The assumption was made that the 91:9 distribution in 7,7-dimethyl-2-norbornanone likewise corresponded to preferential *endo* attack.

For the analyses, we utilized a Perkin-Elmer Model 226 vapor phase chromatograph employing a 150 ft × 0.01 in. i.d. Ucon LBX-500 column, with block temperature at 260°, flame ionization detector at 160°, 20 psi, programed at 40° (5 min)–140° (15 min) at 10°/min. This instrument proved very effective in permitting us to analyze the reaction mixtures directly, without prior removal of the isopropyl alcohol.

The Synthesis and Solvolysis of 7-Ketonorbornyl Tosylates[1]

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Abstract: *exo*- and *endo*-2-hydroxybicyclo[2.2.1]heptan-7-one have been synthesized; their stereochemistry has been rigorously proven by a combination of chemical and spectroscopic methods. The tosylate of these epimeric alcohols have been prepared. Under the usual acetolysis conditions, the *endo* tosylate solvolyzed 6.0 times faster than the *exo* tosylate. Both tosylates yielded a mixture of *exo*- and *endo*-2-acetoxybicyclo[2.2.1]heptan-7-one. However, the product ratio was not the same for both the *exo* and the *endo* tosylate solvolyses. The implications of these results on bicyclic carbonium ion theory are discussed.

The importance of nonclassical carbonium ions in solvolysis reactions continues to be the subject of intensive investigations.[3,4] Of particular relevance are the studies of the solvolytic behavior of bicyclic tosylates, especially the well-known investigations of the acetolysis of bicyclo[2.2.1]heptyl tosylates.[5] We report here on the effect of the carbonyl function on the acetolysis of 2-*exo*-hydroxybicyclo[2.2.1]heptan-7-one tosyl-

ate (1) and 2-*endo*-hydroxybicyclo[2.2.1]heptan-7-one tosylate (2).

Synthesis and Stereochemistry

The starting material for the synthesis of 2-*exo*-hydroxybicyclo[2.2.1]heptan-7-one (3) was 7,7-dimethoxybicyclo[2.2.1]heptane (4).[6] Epoxidation of 4 with perbenzoic acid gave 7,7-dimethoxybicyclo[2.2.1]heptane *exo*-2,3-epoxide (5) in 87% yield. Although models suggest that the *exo* side of the double bond in 4 is more hindered than the *endo* side, the attacking reagent reacted from the *exo* position. The direction of this stereospecific epoxidation is probably due to hydrogen bonding of the attacking peracid with the oxygen of the 7-methoxyl group.[7] When 5 was reduced

(1) Part of this paper has appeared in preliminary form: P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, 87, 4648 (1965); *Tetrahedron Letters*, No. 46, 4073 (1965).

(2) National Science Foundation Cooperative Predoctoral Fellow, 1962–1963, 1964–1966.

(3) H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962.

(4) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(5) J. A. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 111.

(6) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, 29, 160 (1964).