(15*R*)-9β,11α,15-trihydroxyprostanoate (dihydro-PGF$_{1\beta}$ methyl ester, XVb),[15] mp 62–63°, was prepared from PGE$_1$ (I) by catalytic hydrogenation[9,28] and reduction with sodium borohydride.[29]

The synthetic racemic ketoester, XIVa, was reduced with sodium borotritide, hydrolyzed, and reesterified with diazomethane, yielding a mixture of 9-tritiated-9-hydroxy epimers. A sample (XVa) enriched in the 9β-hydroxy isomer by chromatography on silica gel was combined with optically active, crystalline XVb. Two crystallizations afforded material of constant melting point (62–63°) and specific activity (0.249 μcurie/mg) unchanged on two further crystallizations (0.238 and 0.236 μcurie/mg). Isotope dilution indicated that XIVa contained at least 22% of product of the same optical configuration at all asymmetric centers as XIVc.[30,31]

Acknowledgment. The authors wish to express their appreciation to their associates in these laboratories, especially Marvin Grostic for his contributions in mass spectroscopy, Byron Johnson for preparation of intermediates, and George Cartland and James Weeks for biological studies.

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(28) B. Samuelsson and G. Stallberg, *Acta Chem. Scand.*, **17**, 810 (1963).

(29) S. Bergström, L. Krabisch, B. Samuelsson, and J. Sjövall, *ibid.*, **16**, 969 (1962).

(30) Stereochemical randomness would produce only 6% of the natural isomer in the introduction of four asymmetric centers.

(31) NOTE ADDED IN PROOF. D. H. Nugteren and D. A. vanDorp, Unilever Laboratories, and B. Samuelsson and S. Bergstrom, Karolinska Institute, announced independently at the 2nd Nobel Symposium on The Prostaglandins, June 6, 1966, that reexamination of the original data indicates that the absolute configuration of the prostaglandins should now be represented by the mirror image of that used in this paper and in earlier publications.

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Ground- and Transition-State Free Energy Relationships in σ and π Routes to the Nonclassical 7-Norbornenyl Cation[1]

Sir:

One of the most interesting of the nonclassical carbonium ions is the intermediate II in solvolysis of *anti*-7-norbornenyl derivatives[2] such as I-OTs. In this communication we report on kinetic and thermodynamic product control and ground- and transition-state free energy relationships in σ and π routes[3] to cation II in methanolysis.

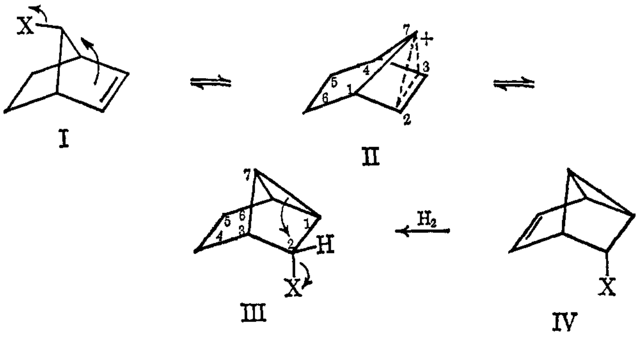
A tricyclic derivative suitable for the σ route to cation II, namely, III-OCH$_3$, was obtained very recently in an elegant investigation by Tanida, Tsuji, and Irie,[4a] who observed considerable tricyclic product IV-OCH$_3$ in methanolysis of 7-norbornadienyl chloride in the presence of substantial concentrations of sodium methoxide. Hydrogenation of IV-OCH$_3$ led to III-OCH$_3$, an 85% pure sample of which was isolated. Tanida and co-workers[4a] also reported tricyclic III-OCH$_3$ from methanolysis of I-OTs with alkali, but in only 1% yield.

Table I. Kinetic Product Control in Methanolysis of I-OTs[a] at 25.0°

[NaOCH$_3$], *M*	% I-OCH$_3$	% III-OCH$_3$
. . .[b]	100	. . .
3.5 × 10^{-8} [c]	99.7	0.3[d]
0.20	93.6	6.4
0.88	79.7	20.3
1.93	65.3	34.7
3.98	48.5	51.5

[a] *Ca.* 0.01 or 0.02 *M* I-OTs. [b] Solution allowed to become acidic. [c] 0.0452 *M* NaOAc–0.0394 *M* AcOH buffer; (MeO$^-$) varies from 7.5 × 10^{-8} *M* to 3.8 × 10^{-8} *M*. [d] This material disappears in acidic 80% acetone with the same half-life as for III-OCH$_3$.

We noted and remarked previously[2a] on the fact that the C$_7$:C$_2$ reactivity ratio in cation II is quite dependent on the nature of the nucleophile when it is varied widely. Thus, tricyclic alcohol III-OH was not observed[2a] from neutral hydrolysis of I-OTs, but considerable tricyclic hydrocarbon III-H is obtained from borohydride trapping,[2] and some tricyclic nitrile III-CN is formed in the reaction of I-Cl with NaCN in aqueous alcohol.[4b] We have now observed striking changes in product composition in methanolysis of I-OTs as methoxide concentration is varied. In methanol at 25.0°, I-OTs undergoes first-order methanolysis with a rate constant of 1.31 × 10^{-3} sec^{-1} to form I-OCH$_3$ quantitatively. No tricyclic III-OCH$_3$ is observed, but even if it were formed, it would not survive the acidic conditions since it is very easily isomerized to I-OCH$_3$ in the presence of acid. As summarized in Table I, methanolysis of I-OTs with increasing concentrations of NaOCH$_3$ gives increasing proportions of tricyclic III-OCH$_3$ in the product. Thus, with 4 *M* NaOCH$_3$, the observed ether contains 51.5% tricyclic III-OCH$_3$. The data make it evident that sodium methoxide does not serve merely to preserve the tricyclic III-OCH$_3$, but instead is largely responsible for its formation.



The kinetic control product from neutral methanolysis of I-OTs was determined from solvolysis in methanol containing an AcOH–NaOAc buffer. Control experiments showed the tricyclic III-OCH$_3$ to be fully stable under these conditions. The product ether from buffered methanolysis contained 0.3% of the tricyclic III-OCH$_3$, as determined by vpc. Examination of the nmr spectrum, using a Varian C-1024 time-averaging computer (CAT), confirmed the presence of III-OCH$_3$ with its characteristic C$_2$ α-proton quartet centered at τ 6.35. Thus, kinetic product control in methanolysis of I-OTs involves a C$_7$:C$_2$ reactivity ratio[5] of *ca.* 300.

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(1) Research supported by the National Science Foundation.

(2) *E.g.*, (a) S. Winstein, A. H. Lewin, and K. C. Pande, *J. Am. Chem. Soc.*, **85**, 2324 (1963); (b) H. C. Brown and M. Bell., *ibid.*, **85**, 2324 (1963).

(3) S. Winstein and P. Carter, *ibid.*, **83**, 4485 (1961).

(4) (a) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **88**, 864 (1966); (b) H. Tanida and Y. Hata, *J. Org. Chem.*, **30**, 977 (1965).

(5) The situation regarding kinetic and thermodynamic control in

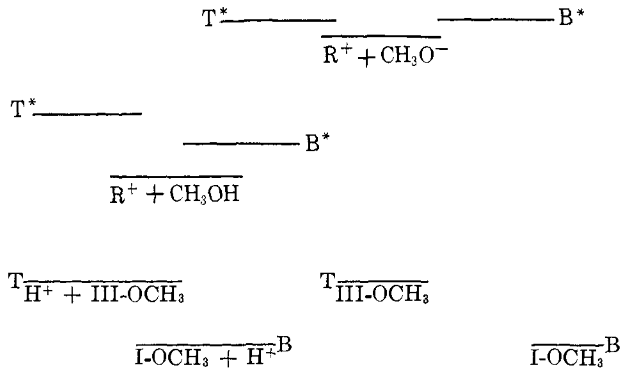

Figure 1. Ground- and transition-state free energy diagrams for ether equilibrations at 25°.

In reactivity, the tricyclic derivatives III surpass the bicyclic analogs I by a large factor. In 80% aqueous acetone containing dilute $HClO_4$, tricyclic III-OCH_3 is transformed quickly and quantitatively to bicyclic I-OH, while the bicyclic I-OCH_3 reacts much more slowly. From the available data summarized in Table II it is clear that the rate of acid-catalyzed heterolysis of tricyclic III-OCH_3 at 25° exceeds that of bicyclic I-OCH_3 by a factor of 7×10^6.

Table II. Kinetics of Hydrolysis in 80% Acetone

Temp, °C	$[HClO_4]$, 10^3M	10^5k, sec^{-1}	$10^3k/(HClO_4)$ l. mole^{-1} sec^{-1}
	Tricyclic III-OCH_3		
25.0	0.145	145	10,000
25.0	0.245	250	10,200
25.0	0.386	367	9.500
25.0	2.57	2300	9,100
	Bicyclic I-OCH_3		
25.0[a]	228	0.042	0.0018
25.0[b]	108.5	0.0105	0.0010
50.0[c]	108.5	0.046	0.0043
75.0[d]	108.5	0.19	0.018

[a] Reaction followed to 9%. [b] Extrapolated from 50 and 75°. [c] Reaction followed to 15%. [d] Reaction followed to 56%.

The above data provide a rather clear picture of kinetic and thermodynamic control in methanolysis involving the 7-norbornenyl cation. Considering acid-catalyzed ether equilibration as in eq 1, kinetic and thermodynamic product control is correlated with reactivity by means of eq 2,[6] where K measures thermodynamic control, (k_T/k_B) is a reactivity ratio R between tricyclic and bicyclic isomers, and (k_{-B}/k_{-T}) is a partition factor P representing kinetic control of products. The value of P, namely, 300, is known from kinetic control of products in buffered methanolysis of I-OTs. The value of R can be approximated as 7×10^6, the value from acid-catalyzed hydrolysis of the ethers. On this basis, K is estimated to be 2×10^9. In other words, the standard free energy of tricyclic III-OCH_3 exceeds that of bicyclic I-OCH_3 by *ca.* 12,700 cal/mole. This leads to the ground and transition free energy diagram in Figure 1. The free energy of the tricyclic transition state T* exceeds that of the bicyclic B* by 3400 cal/mole, *ca.* one-fourth of the ground-state difference.

$$H^+ + \text{III-OCH}_3 \underset{k_{-T}}{\overset{k_T}{\rightleftharpoons}} R^+ + CH_3OH \underset{k_{-B}}{\overset{k_B}{\rightleftharpoons}} \text{I-OCH}_3 + H^+ \quad (1)$$

$$K = \frac{(\text{I-X})}{(\text{III-X})} = \left[\frac{k_T}{k_B}\right]\left[\frac{k_{-B}}{k_{-T}}\right] = RP \quad (2)$$

$$\text{III-OCH}_3 \underset{k_{-T}}{\overset{k_T}{\rightleftharpoons}} R^+ + {}^-OCH_3 \underset{k_{-B}}{\overset{k_B}{\rightleftharpoons}} \text{I-OCH}_3 \quad (3)$$

From the striking changes in composition of kinetic control product of methanolysis of I-OTs as $[MeO^-]$ is increased, it is evident that methoxide is involved in some reaction involving a quite favorable C_2:C_7 reactivity ratio. Just how favorable this ratio may be is not yet clear, since, even at 4 M $[NaOCH_3]$ in MeOH, the methoxide reaction is not yet in complete control. As regards mechanism of the methoxide ion effect, an S$_N$2′ mechanism or methoxide ion capture of a $R^+$$^-$OTs ion pair are conceivable explanations. However, the most attractive explanation seems to us to involve an inherently substantial sensitivity of the partition factor P to the nature of the nucleophile in reactions of an ion such as II. When the nucleophile is CH_3O^- instead of CH_3OH, the partitioning of the cation II is now the microscopic reverse of the ionization of the neutral ethers, III-OCH_3 and I-OCH_3. This is represented in eq 3, and eq 2 can be applied to this situation, just as was done for the acid-catalyzed scheme in eq 1. In eq 2, P would now be less than unity and, correspondingly, the reactivity ratio (k_T/k_B) would now be greater than 2×10^9.

The free-energy diagram for the situation represented in eq 3 is shown in Figure 1 alongside the one for eq 1. For present purposes we can place the ground-state levels at the same positions for both acid-catalyzed and neutral equilibrations. For simplicity, we write the $(R^+ + {}^-OCH_3)$ level for dissociated ions, and this puts it $-RT \ln K_{MeOH}$, or 22.6 kcal/mole, higher than the level for $(R^+ + CH_3OH)$ in the acid-catalyzed scheme. (K_{MeOH} represents the autoprotolysis constant for MeOH, namely, 2.27×10^{-17}.)

The contrast between the free energy diagrams corresponding to eq 1 and 3 is quite in line with predictions from the Hammond postulate.[7] Thus, in the much more endothermic ionization of the neutral ethers, the transition states come much later than in acid-catalyzed ionization; putting this another way, in the reactions of R^+ with the more nucleophilic CH_3O^- transition states come earlier than for reaction with neutral CH_3OH. Thus, in neutral equilibration of ethers, transition states will resemble much more the carbonium ion and reflect much less the ground-state difference than in acid-catalyzed equilibration. With C_2 and C_3 favored over C_7 by a statistical factor of 2 and much greater positive charge,[8] preferred reaction at C_2 and C_3 by the strongest nucleophiles becomes perfectly logical.

The findings and discussion here presented have more general implications for our understanding and control of carbonium ion behavior. They certainly emphasize the desirability of exploring a range of nucleophiles,

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the methanolysis of 7-norbornadienyl chloride reported by Tanida and co-workers is not so clear, since these investigators did not study neutral methanolysis.

(6) *E.g.* (a) S. Winstein, F. Gadient, E. T. Stafford, and P. E. Klinedinst, Jr., *J. Am. Chem. Soc.*, **80**, 5895 (1958); (b) S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(7) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(8) M. Brookhart, A. Diaz, and S. Winstein, *ibid.*, **88**, 3135 (1966).

and, in partitcular, of adding substantial concentrations of solvent lyate ion in certain solvolyses.[9]

[9] A related example is in methanolysis of isobornyl chloride and camphene hydrochloride, where addition of $NaOCH_3$ does not increase over-all rate but shifts the result from mainly substitution to mainly elimination [P. Beltrame, C. A. Bunton, A. Dunlop, and D. Whittaker, *J. Chem. Soc.*, 658 (1964)].

[10] National Institutes of Health Predoctoral Fellow, 1965–1966.

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Structure of the Nonclassical 7-Norbornenyl Cation[1]

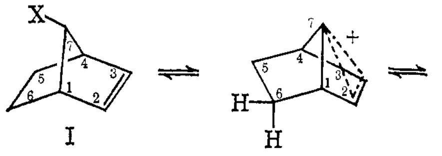
Sir:

In this communication we return to the question of the structure and behavior of the 7-norbornenyl cation. The high rate (10^{11} times 7-norbornyl) and over-all retention of structure and configuration in the solvolysis of *anti*-7-norbornenyl *p*-toluenesulfonate[2] (I-OTs) were previously[2a–c] accounted for on the basis of an intermediate nonclassical "bishomocyclopropenyl"[2e] cation II. This interpretation has been seriously questioned by Brown.[3] Most recently,[3b,c] he has formulated the intermediate as a rapidly equilibrating pair of "classical" tricyclic ions (IVab), and Deno has supported this formulation.[4] We can now report the direct observation of cation II from both σ and π routes[2d] and discuss further its structure and chemical behavior.

Much of the previous discussion of the 7-norbornenyl cation revolved around the nature of the observed products. Thus, in connection with structure IVab for the 7-norbornenyl cation, Brown[3b,c] suggested that the tricyclic alcohol V-OH might well be the chief kinetic control product of neutral hydrolysis of I-OTs, but that it was not isolated because of instability toward the reaction conditions. In the case of methanolysis reported in the previous communication,[2d] where tricyclic V-OCH_3 is now available for control experiments, it is clear that methanol attack at C_2 of the cationic intermediate is very much less important than at C_7. Kinetic control in neutral methanolysis of I-OTs yields 99.7% bicyclic I-OCH_3 and 0.3% tricyclic V-OCH_3.

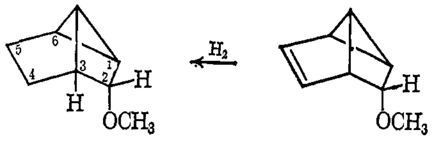
While the C_2:C_7 reactivity ratio is small for methanol, it is much more favorable with nucleophiles such as $^-BH_4$,[2c,3c] ^-CN,[5a] and $^-OCH_3$.[2d] While Brown[3c] found it difficult to rationalize substantial C_2 attack on the basis of the nonclassical structure II, we[2c] found it difficult to rationalize predominant C_7 attack on a classical cation IV. In fact, all the previous and present[2d] information on the gradations in C_7:C_2 product partitioning is well accommodated by the nonclassical formulation II.

Just as stereochemistry at C_7 was previously[2a–c] employed as an argument for the nonclassical structure II instead of the classical structure III, stereochemistry at C_2 (or C_3) can help us decide between structure II and a "classical" tricyclic ion IV. The usual stereoelectronic considerations predict *endo* nucleophilic attack at C_2 or C_3 of ion II; on the other hand, a mixture of *endo* and *exo* products, probably predominantly *exo*, would be expected from a "classical" tricyclic cation IV. The tricyclic ether product from methanolysis of I-OTs in the presence of 4 *M* NaOMe[2d] was separated from I-OCH_3 by vapor phase chromatography, a *ca.* 97% pure fraction of V-OCH_3 being obtained. The nmr spectrum of this material was essentially identical with the one described by Tanida[5b] for the product from hydrogenation of the tricyclic ether VI-OCH_3 from basic methanolysis of 7-norbornadienyl chloride. The C_2 α-proton signal appeared as a clean quartet with vicinal coupling constants (3.8 and 7.4 cps) appropriate for an *endo*-methoxyl group[5b] (*exo* C_2 proton). No evidence of another C_2 α-proton signal was visible even on 60 scans using a Varian C-1024 time-averaging computer (CAT).[6] While further investigation is required to set a lower limit to the *endo*:*exo* ratio in the tricyclic ether, it is already clear that the latter is at least very predominantly *endo* (>97%). Thus, C_2 or C_3 methoxide attack on II is quite highly stereospecific in the *endo* sense. This is true also of attack by ^-CN.[5] Such *endo* specificity is also observed in C_2 or C_3 attack by $^-BH_4$,[7a] $^-AlH_4$,[7a] and $^-OCH_3$[5b] on the 7-norbornadienyl cation VII, an analog of II without the C_5- and C_6-*endo*-protons. Obviously, stereochemistry supports the nonclassical structures implied by II and VII.



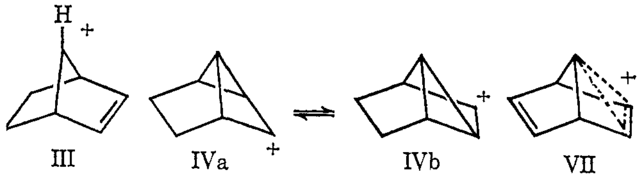
I

II



V-OCH_3

VI—OCH_3



III IVa IVb VII

Cation II may be generated in SO_2–SbF_5–FSO_3H medium[8] at low temperatures by addition of a cold (−50°) CH_2Cl_2–CCl_4 solution of I-OH to a cold SO_2–SbF_5–FSO_3H mixture, followed by vibration and stirring in the cold. The light orange lower layer which separates is the SO_2–SbF_5–FSO_3H solution of the cation containing some CH_2Cl_2 useful as an internal

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[1] Research was supported by the National Science Foundation.

[2] S. Winstein, *et al.*, *J. Am. Chem. Soc.*: (a) 77, 4183 (1955); (b) **78**, 592 (1956); (c) **85**, 2324 (1963); (d) **88**, 3133 (1966); (e) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

[3] (a) H. C. Brown, "Strained Carbonium Ions," Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 21–30, 1961; (b) H. C. Brown, "Non-Classical Intermediates," Organic Reaction Mechanisms Conference, Brookhaven, N. Y., Sept 5–8, 1962; (c) H. C. Brown and M. Bell, *J. Am. Chem. Soc.*, **85**, 2324 (1963).

[4] N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 159 (1964).

[5] (a) H. Tanida and Y. Hata, *J. Org. Chem.*, **30**, 977 (1965); (b) H. Tanida, T. Tsuji, and T. Irie, *J. Am. Chem. Soc.*, **88**, 864 (1966).

[6] The tricyclic ether fraction shows an additional methyl signal in the nmr spectrum, indicating *ca.* 3% of an impurity whose nature is still not clear.

[7] (a) P. R. Story, *et al.*, *J. Am. Chem. Soc.*: (a) **88**, 374 (1966); **83**, 3347 (1961); (b) **84**, 4876 (1962); **85**, 3630 (1963).

[8] G. Olah, *et al.*, *ibid.*, **87**, 2997 (1965).