solid whose melting point (90.5–91.0°), mixture melting point (90.0–91.0°), and ir were identical with the starting tosylate (**3**).

7,7-Dimethoxy-*exo*-2-ethoxybicyclo[2.2.1]heptane (21). To a solution of 2.0 g (0.0116 mol) of ketal alcohol (**1**) in 35 ml of dry dimethylformamide was added 0.86 g of 55% NaH in mineral oil. After foaming had subsided, 3.6 g of ethyl iodide was added followed by stirring overnight. To this solution, 35 ml of water was added and the resulting mixture was extracted three times with 25-ml portions of ether. The combined ethereal extracts were washed with a 25-ml portion of water and then dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed on a rotary evaporator. The crude product was distilled *in vacuo* to yield 1.1 g (47%) of the desired product, **21**, bp 74–75° (4 mm), n^{24}D 1.4547. *Anal.* Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.22; H, 10.10.

***exo*-2-Ethoxybicyclo[2.2.1]heptan-7-one (19).** A solution of 3.0 g (0.0150 mol) of ketal ether, **21**, and 15 ml of 5% sulfuric acid was stirred at room temperature for 12 hr. The solution was extracted three times with 10-ml portions of ether and the combined ether extracts were dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed by distillation through a 12-in. Vigreux column. The resulting crude product was distilled *in vacuo* to yield 1.64 g (71%) of **19**, bp 87–88° (3 mm), n^{27}D 1.4639. *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.91; H, 9.22.

***exo*-3,7,7-Triethoxybicyclo[2.2.1]heptane (18).** A solution of 0.871 g (0.00436 mol) of **21** and 0.4 g of anhydrous *p*-toluenesulfonic acid in 50 ml of absolute ethanol was stirred at reflux for 14 hr. The solution was poured into 50 ml of 5% sodium bicarbonate. The aqueous solution was then extracted three times with 25-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed by distillation through a 12-in. Vigreux column. Distillation of the product *in vacuo* yielded 0.714 g (71%) of **18**, bp 89–90° (3 mm), n^{27}D 1.4460. *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.18; H, 10.93.

2,2-Diethoxytricyclo[2.2.1.0^{3,5}]heptane (16). A solution of 3.0 g (0.0278 mol) of nortricyclanone (**12**) and 0.2 g of IR-120 ion exchange resin (strongly acidic) in 20 ml of triethyl orthoacetate and 50 ml of absolute ethanol was stirred at reflux for 12 hr. The solution was filtered and the solvent removed by distillation. The crude product was then distilled through a 12-in. Vigreux column to yield 4.1 g (81%) of **16**, bp 127–130° (86 mm), $n^{26.6}$D 1.4515. *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.17; H, 10.09.

***exo*-5-Ethoxybicyclo[2.2.1]heptan-2-one (17).** A solution of 5.2 g of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene was refluxed for 20 min and the water was removed azeotropically. The remaining benzene was stripped off on a rotary evaporator and 3.3 g of nortricyclanone (**12**) was added along with 50 ml of absolute ethanol. The solution was refluxed for 12 hr, after which the mixture was poured onto 100 ml of 10% aqueous sodium bicarbonate. The mixture was extracted three times with 50-ml portions of ether and the combined ether extracts were dried over anhydrous magnesium sulfate. After filtration of the ether solution, the solvent was removed by distillation through a 12-in. Vigreux column and the crude product was distilled *in vacuo* to yield 3.4 g of **17**, bp 97–99° (10 mm), $n^{22.8}$D 1.4671. *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.09; H, 9.15.

Acknowledgment. We are indebted to the Petroleum Research Fund, administered by the American Chemical Society, for Grant No. 1670-A1 which supported this investigation.

Steric Effects in Bicyclic Systems. IV. Base-Catalyzed Enolization of Bicyclo[2.2.2]octan-2-one, Bicyclo[2.2.1]heptan-2-one, and Bicyclo[2.1.1]hexan-2-one[1]

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Contribution from the Department of Chemistry, University of Toronto, Scarborough College, West Hill, Ontario, and University of South Carolina, Columbia, South Carolina. *Received April 7, 1973*

Abstract: Deuterium exchange of bicyclic ketones in 2:1 (v/v) dioxane–D_2O catalyzed by NaOD was measured by a mass spectrometric technique developed for this purpose. Second-order rate constants (M^{-1} sec^{-1}) at 25.0° and activation parameters ΔH^* (kcal mol^{-1}) and ΔS^* (eu) were determined as follows: bicyclo[2.2.2]octan-2-one (**1**) 3.03×10^{-2}, 13.1, and −21; bicyclo[2.2.1]heptan-2-one (**2**) 5.58×10^{-2}, 14.0, and −17 (exo); 8.26×10^{-5}, 17.1, and −20 (endo); and bicyclo[2.1.1]hexan-2-one (**3**) 6.04×10^{-6}, 17.8 and −23. The rate of base-catalyzed bromination of cyclohexanone was found to exceed that of **1** by a factor of 3.1 in water at 10.0°. The secondary isotope effect k_D/k_H for deuteration of **1** was 0.94 ± 0.04 at 25.0°. These results are interpreted as showing that the rates reflect the relative facility of proton abstraction from the different sites, and that the principal factors governing the rates of attack are the angle strain generated in the resulting enolates, which favors reactivity in the series **1** > **2** > **3**, and the greater steric blocking of access of the base to the reaction site by a two-carbon bridge as opposed to a one-carbon bridge, which favors reactivity in the series *exo*-**2** > *endo*-**2**, and **3** > **1**.

Bicyclic ring systems have been widely used as substrates for the examination of organic reactions, particularly the steric requirements of those reactions.[3] These compounds are attractive for this purpose because of their relatively fixed geometries, and because their molecular dimensions have been

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[1] Address correspondence concerning this work to the University of Toronto. For part III, see ref 2a. Portions of this work were reported in preliminary communications, ref 2b,c. Supported in part by the U. S. Public Health Service, the Petroleum Research Fund, administered by the American Chemical Society, and the National Research Council of Canada.

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rather successfully elucidated, as, for example, the bicyclo[2.2.1]heptyl,[4a] bicyclo[2.1.1]hexyl,[4b,d,e] and bicyclo[2.2.2]octyl[4c,f] systems.

Because of the general utility of reactions involving enolization of ketones, and because of other indications in the literature that enolization of bicyclic ketones could be particularly informative,[5] it appeared desirable to initiate a closer examination of this process. Complementary studies on the stereochemistry of anionic bicyclic species include the investigation of the rates of exo and endo proton abstraction from 5-nitrobicyclo[2.2.1]hept-2-ene and 2-nitrobicyclo[2.2.1]heptane,[6] isomerization of carbomethoxynorbornenes and norbornanes by base,[7] rates of exo and endo H/D exchange from bicyclic sulfoxides,[8] selectivity of deuteron capture by the 2-norbornyl,[9a] 2-norbornenyl,[9b] and 7-norbornenyl[9c] anions, and base-catalyzed exocyclic–endocyclic isomerization of bicyclic olefins.[10]

Recent investigations of base-catalyzed enolization have apparently resolved controversies regarding directive effects[11,12] and isotope effects[13,14] in these reactions.

Studies of the stereochemistry of base-catalyzed exchange of bicyclic ketones should also be of value for comparison with the extensive literature on substitution in bicyclic cations and radical reactions involving bicyclic systems.[15]

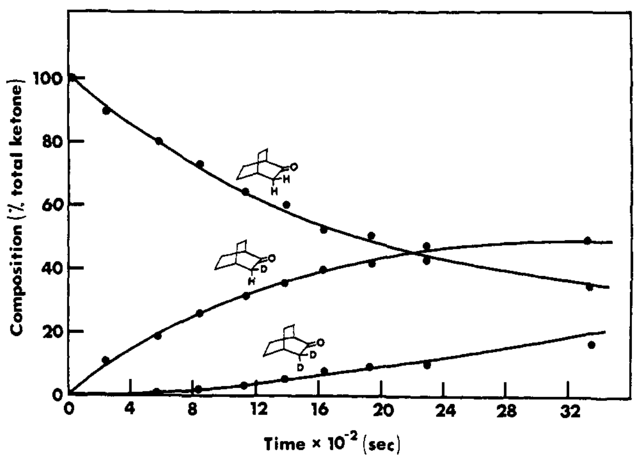

Figure 1. NaOD-catalyzed protium–deuterium exchange of bicyclo[2.2.2]octan-2-one (1) at 10°.

Techniques that have been utilized for measuring kinetics of base-catalyzed enolization include proton nmr,[8,11c,12] deuteron nmr,[16] infrared[17] and ultraviolet spectroscopy,[6b] halogenation[11b,13,14] tritium counting,[13] loss of optical activity,[18] and mass spectrometry.[5d,13] Under some circumstances these techniques suffer variously from defects such as lack of resolution, interference from other species, laborious experimental requirements, and particularly in the case of the elegant deuteron nmr technique, shortage of experimental facilities. The mass spectrometry technique for measuring isotope incorporation has been relatively little utilized, but with the availability of medium resolution instruments it appeared feasible to exploit this technique more fully.

Results

Deuterium uptake of bicyclo[2.2.2]octan-2-one (**1**), bicyclo[2.2.1]heptan-2-one (**2**), and bicyclo[2.1.1]hexan-2-one (**3**) in 2:1 (v/v) dioxane–D_2O containing NaOD was measured by isolating samples of ketone from the reaction medium at intervals, and monitoring the isotopic distribution of the molecular ion by mass spectrometry. Representative curves for the fraction of d_0, d_1, and d_2 species with time for **1** and **2** are shown in Figures 1–3. No d_3 species were observed under these conditions. First-order rate constants were calculated for the disappearance of the d_0 peak for **1**–**3** and also the d_1 peak of **2**. These were divided by a factor of 2 in the cases of **1** and **3** to correct for the number of equivalent hydrogens. The measured base concentrations showed slight changes during the reactions so the second-order rate constants were obtained by dividing the observed first-order rate constants by the average measured base concentrations.

The fast and slow exchanges for **2** were assigned to exo and endo exchanges, respectively. The second-order rate constants and derived activation parameters are reported in Table I. The activation parameters, particularly the sizable negative entropy factors, fall in the ranges commonly observed for base-catalyzed hydrogen removals.[6b,10a,19] Relative rates at 25° are depicted in Figure 4.

Independent investigators[20] of the deuteration of **1**

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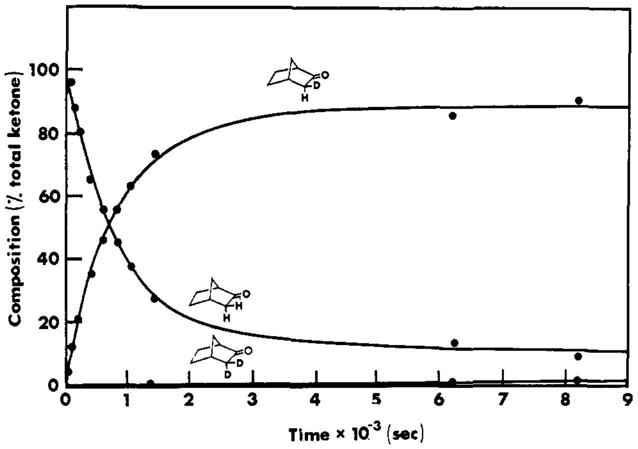


Figure 2. NaOD-catalyzed protium-deuterium exchange of bicyclo[2.2.1]heptan-2-one (**2**) at 25°.

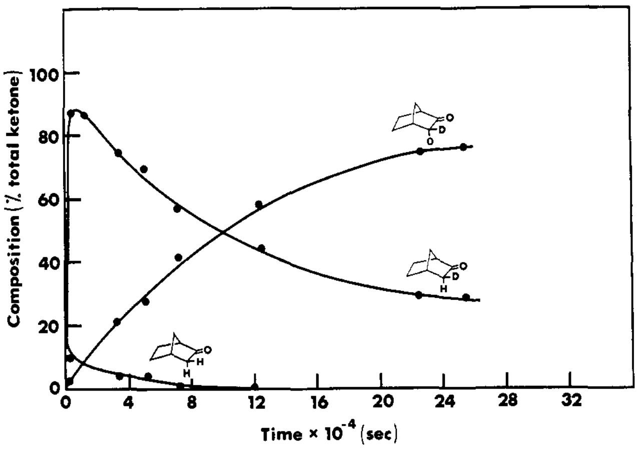


Figure 3. NaOD-catalyzed protium-deuterium exchange of bicyclo[2.2.1]heptan-2-one (**2**) at 25° (extended time period).

Table I. Second-Order Rate Constants of NaOD-Catalyzed Deuterium Exchange of Ketones in 2:1 Dioxane–D_2O[a]

Ketone	Temp, °C	k_2, M^{-1} sec^{-1}	ΔH^*, kcal/mol)[e]	ΔS^*, eu[f]
Bicyclo[2.2.2]octan-2-one[b] (**1**)	10.0[c]	9.10×10^{-3}	13.1	−21
	25.0[c]	3.03×10^{-2}		
	40.0[c]	9.45×10^{-2}		
Bicyclo[2.2.1]heptan-2-one (**2a**-*exo*)	3.1[c]	7.98×10^{-3}	14.0	−17
	9.8	1.53×10^{-2}		
	11.1	1.74×10^{-2}		
	25.0[c]	5.58×10^{-2}		
Bicyclo[2.2.1]heptan-2-one (**2b**-*endo*)	25.0[c]	8.26×10^{-5}	17.1	−20
	42.2	3.65×10^{-4}		
	42.7	3.81×10^{-4}		
	54.7	1.09×10^{-3}		
	54.9[c]	1.32×10^{-3}		
Bicyclo[2.1.1]hexan-2-one[b] (**3**)	25.0[d]	6.04×10^{-6}	17.8	−23
	25.2	6.40×10^{-6}		
	39.6[c]	2.48×10^{-5}		
	54.7[c]	1.03×10^{-4}		

[a] The rates have been remeasured, and differ somewhat from those reported previously (ref 2b). [b] Reported rates are observed rates divided by a factor of 2 to correct for the number of equivalent hydrogens. [c] Duplicate runs were made at this temperature, maximum deviation ±10%. [d] Extrapolated. [e] Maximum standard deviation 0.04. [f] Maximum standard deviation 0.1.

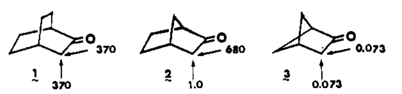
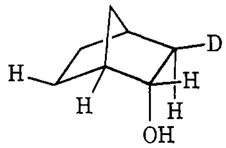


Figure 4. Relative rates of NaOD-catalyzed deuterium exchange of ketones at 25.0° in 2:1 dioxane–D_2O.

in 50% dioxane–D_2O at 25° reported a second-order rate constant (after insertion of the statistical factor of 2 utilized for **1** and **3** in this work) of 2.65×10^{-2} M^{-1} sec^{-1} for the first exchange of this compound. Since we have found[21] that increasing percentages of water in the aqueous dioxane in the range of 40–70% cause modest rate depressions in these reactions, this value is in satisfactory agreement with our value of 3.03×10^{-2} M^{-1} sec^{-1} in 2:1 dioxane–D_2O. These independent investigators[20] also analyzed the simultaneous concentrations of d_0, d_1, and d_2 species and arrived at a factor of 0.99 ± 0.02 for the secondary deuterium isotope effect retardation of uptake of the second deuterium. Application of their procedure to our data gave values for k_D/k_H of 0.90 ± 0.04, 0.94 ± 0.04, and 0.94 ± 0.06 for **1** at 10.0, 25.0, and 40.0°, respectively. Other independent investigators using slightly different solvent systems have measured rates of deuterium exchange by mass spectrometry[5d] and deuteron nmr[16] that are in qualitative agreement with ours for absolute rates, and, in the case of camphor, in quantitative agreement for exo/endo rate ratios.

The stereochemistry of the first deuterium substituted in **2** was confirmed to be predominantly exo by carrying out the deuteration for 10 half-lives for exchange of one deuterium and isolating the ketone, which was found to consist of 3% d_0, 96% d_1, and 1% d_2 species. Reduction of the ketone by $LiAlH_4$ gave the known[22] mixture of 9.9% *exo*-bicyclo[2.2.1]heptan-2-ol and 90.1% of the endo isomer. The endo 2-H of the exo alcohol absorbs at δ 3.61 and the exo 2-H of the endo alcohol at 4.10.[23] In undeuterated endo alcohol the exo 2-H appears as a multiplet between δ 3.85 and 4.25 due to the couplings to the 1, 3, and exo 6 protons. In the deuterated material the large exo 2, exo 3 coupling disappears and the absorption of the exo 2-H collapses to a broad absorption between δ 3.92 and 4.15. Irradiation of the bridgehead hydrogens caused further simplification of the resonance to a broad doublet, $J_{2x,3n} \approx 3$ Hz. The spectrum of the exo 2-H in the monodeuterio endo alcohol resembled that published for *exo*-3-deuterio-*endo*-2-methoxybicyclo[2.2.1]heptane[24] (this reference gives values of 3.6, 9.7, 3.6, and 1 Hz for $J_{1,2}$, $J_{2,3x}$, $J_{2,3n}$, and $J_{2,6}$, respectively, in *endo*-2-methoxybicyclo[2.2.1]heptane). A reasonable estimate would be that 5–10% of the *endo*-3-deuterio alcohol would have been detected in this spectrum and none was observed.



Rate constants (Table II) for base-catalyzed bro-

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Table II. Second-Order Rate Constants for Bromination of Ketones at 10°

Ketone	Base	Solvent	k_2, M^{-1} sec^{-1}
1	NaOH	H_2O	3.4×10^{-3}
Cyclohexanone[a]	NaOH	H_2O	1.1×10^{-2}
2	NaOD	2:1 dioxane–D_2O	1.3×10^{-2}
2-*exo-d*	NaOD	2:1 dioxane–D_2O	2.7×10^{-3}

[a] Measured rate constant adjusted by a statistical factor of 2, for two pairs of equivalent hydrogens.

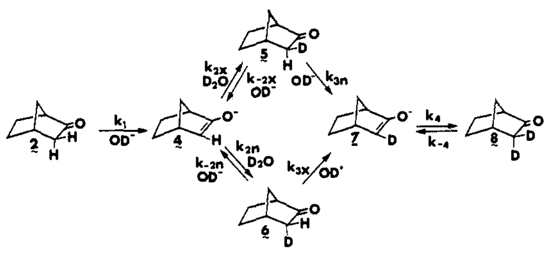


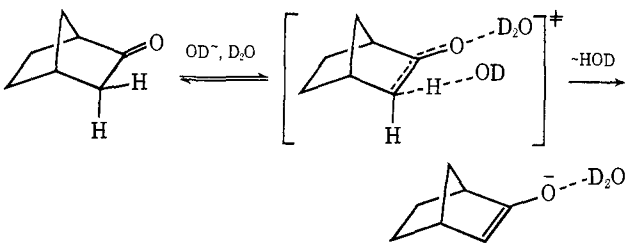
Figure 5. General mechanism for base-catalyzed protium–deuterium exchange of bicyclo[2.2.1]heptan-2-one (**2**) in deuterated media.

mination of **1**, **2**, and cyclohexanone at 10° were also obtained by monitoring the excess bromine concentration by iodometric titration.[25] These rates are calculated for uptake of the first bromine, which is followed by rapid consumption of a second bromine in the case of **1** and cyclohexanone. The latter rate was also corrected by a statistical factor of 2 to account for the number of equivalent pairs of hydrogens. Previous studies of the bromination of norcamphor[26] showed that the steric bias against reaction of the endo H exceeded the accelerating effect of incorporation of the first bromine, so that monobromination was about four times faster than dibromination. However, there was evidence[26] that further bromination of **2** occurs in aqueous base, with ring cleavage and consumption of a third bromine, so the bromination kinetics for **2** must be interpreted with great caution.

Relatively good agreement is nevertheless observed between the bromination rate of **2** at 10.0° (1.3×10^{-2} M^{-1} sec^{-1}) and the interpolated exo-deuteration rate (1.60×10^{-2} M^{-1} sec^{-1}). Comparison of the rates of bromination of **2** and **2**-*exo-d* gives a primary isotope effect k_H/k_D for abstraction by deuteroxide of 5.0. Reported[13] values for the isotope effect for diisopropyl ketone with abstraction by hydroxide vary from 6.45 at 0° to 5.48 at 40°.

Discussion

A general mechanism to represent the protium–deuterium exchange process of **2** is given in Figure 5. The intermediates are written as enolates, although they and the transition states preceding them undoubtedly have some enol character. The question of the degree of enol and enolate character in the transition states for such reactions has been discussed by various authors,[11d,27] but in these highly aqueous solvents hydrogen-bonded enolate and enol intermediates are probably indistinguishable. The protium-abstraction steps will be effectively irreversible, as the ketone concentrations did not exceed 0.25 *M*, so that deuterium would still make up more than 99% of the exchangeable hydrogen in the medium after complete exchange. Internal return of the protium abstracted before it equilibrates with the medium is conceivable, but the available evidence suggests that this phenomenon is not important for ketones.[28]



There are a number of steric and electronic factors which may be considered as contributing to the observed rate effects. Steric factors include angle strain (I-strain),[17,29a] nonbonded repulsion (F-strain),[3d,29b] and eclipsing or torsional strain.[29c] Electronic factors include hybridization effects[29a] and orbital overlap.[29b,d]

The bicyclooctyl ring system is expected to be relatively free of angle strain, so that bicyclo[2.2.2]octan-2-one (**1**) should be a good model for a bicyclic ketone free from this influence. For example the reported C_1–C_2–C_3 bond angle in bicyclo[2.2.2]octane-1,4-dicarboxylic acid was[4c] 110°, and the corresponding angle in bicyclo[2.2.2]oct-2-ene was reported[4f] as 114°. The fact that cyclohexanone differs from **1** by a factor of only 3.1 in base-catalyzed bromination suggests that **1** is indeed a good model, with no abnormal features.

The bond angles of bicyclo[2.1.1]hexan-2-one must be very strained, as evidenced by the reported C_1–C_2–C_3 bond angles of 102° for bicyclo[2.1.1]hexane[4b] and 108° for bicyclo[2.1.1]hex-2-ene.[4d] The rate depression of 5000 for **3** relative to **1** evidently reflects the increased strain that would result upon formation of an additional sp^2 center upon enolization of **3**. Steric barriers to attack by base would presumably be larger in **1** than in **3**, and would tend to reduce the rate difference. The orbitals of the enolizing C–H bonds of **3** would also be more nearly parallel to the p orbitals of the carbonyl group, so that any stereoelectronic factor[29b,d] favoring this orientation would also minimize the rate difference between **1** and **3**, as would the greater s character of the external orbitals of **3**. Clearly, in this pair of compounds angle strain overwhelmingly dominates the reactivity.

It is interesting to note in comparison to **1** that bicyclo[2.2.2]oct-2-en-5-one (**9**) takes up a first deuterium at a rate 0.7 times that of **1**, and a second deuterium at a rate only slightly slower than the first, so that the preferred position of substitution is not readily differentiated.[21] There is independent evidence that the steric bulk of an etheno (–CH=CH–) bridge may

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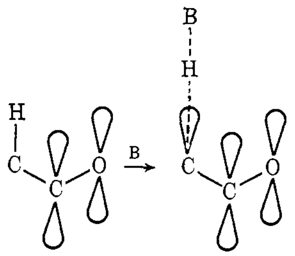
(25) P. D. Bartlett, *J. Amer. Chem. Soc.*, **56**, 967 (1934).

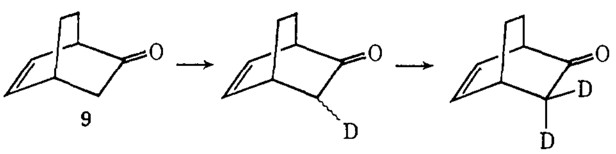
(26) W. G. Woods and J. D. Roberts, *J. Org. Chem.*, **22**, 1124 (1957).

(27) (a) C. G. Swain, *J. Amer. Chem. Soc.*, **72**, 4578 (1950); (b) W. D. Emmons and M. F. Hawthorne, *ibid.*, **78**, 5593 (1956).

(28) F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 575 (1973).

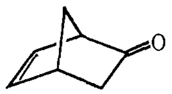
(29) (a) A. Streitweiser, Jr., R. A. Caldwell, and W. R. Young, *J. Amer. Chem. Soc.*, **91**, 529 (1969); (b) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956); (c) P. v. R. Schleyer, *ibid.*, **89**, 701 (1967); (d) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6749 (1968).





9

be as great as that of an ethano ($-CH_2CH_2-$) bridge,[30] so the behavior of **9** confirms that the bicyclooctyl ring system is relatively free of strain effects and behaves normally. By contrast, bicyclo[2.2.1]hept-2-en-5-one (**10**) shows greatly depressed rates relative



10

to **1**, but a high exo/endo specificity,[2c] indicating than the etheno bridge is bulkier than the methano bridge, and that strain effects become critical in the bicycloheptyl system.

The high rate of *exo*-**2** relative to *endo*-**2** may be attributed in large part to the greater nonbonded repulsion of the attacking base by the endo-5,6 hydrogens on the endo side of **2** relative to the syn-7 hydrogens on the exo face. The greater steric accessibility of the exo face of the norbornyl ring system has been documented many times, for example, in the 250 to 1 preference for reduction of norcamphor by lithium tri-*sec*-butylborohydride,[3a] and the preference for exo addition of halogen to the norbornyl radical by factors of 2–42, depending on the donor.[15]

Another steric factor which has been proposed to account for the high exo/endo specificity for reactions of the norbornyl system is the eclipsing effect of the substituent at the 1 position, but results by ourselves[2a] and others[3c,5d] demonstrate that replacement of hydrogen by methyl at the 1 position does not significantly enhance the exo/endo selectivity, and suggest that this effect may be relatively minor.[30a]

The fact that *exo*-**2** exchange is faster than exchange in **1** despite the greater bond angle strain in **2** (typical values[4a] for the C_1–C_2–C_3 angle in norbornanes are 103–104°) confirms that the methano bridge exerts a considerably smaller steric repulsion than the ethano bridge. Examination of models also indicates that any stereoelectronic bias in **2** would favor endo exchange, as this carbon–hydrogen bond is geometrically better disposed for overlapping the p orbitals of the carbonyl group.

It has been tacitly assumed in the preceding discussion that the observed rates of deuterium uptake correspond to discrete hydrogen-abstraction steps. This is clearly satisfactory in the case of **1** and **3**, but it is appropriate to examine this premise in more detail for **2**. The rate expressions for deuteration of **2** according to the scheme in Figure 5 can be derived as eq 1–4, after making steady-state assumptions for the enolate intermediates **4** and **7**.

$$-\mathrm{d}[\mathbf{2}]/\mathrm{d}t = k_1[\mathbf{2}][\mathrm{OD}^-] \qquad (1)$$

$$-\mathrm{d}[\mathbf{5}]\mathrm{d}t = [\mathrm{OD}^-](k_{2x}(k_1[\mathbf{2}] + k_{-2x}[\mathbf{5}] + k_{-2n}[\mathbf{6}])/(k_{2x} + k_{2n}) - (k_{-2x} + k_{3n})[\mathbf{5}]) \qquad (2)$$

$$-\mathrm{d}[\mathbf{6}]/\mathrm{d}t = [\mathrm{OD}^-](k_{2n}(k_1[\mathbf{2}] + k_{-2x}[\mathbf{5}] + k_{-2n}[\mathbf{6}])/(k_{2x} + k_{2n}) - (k_{3x} + k_{-2n})[\mathbf{6}]) \qquad (3)$$

$$-\mathrm{d}[\mathbf{8}]/\mathrm{d}t = [\mathrm{OD}^-](k_{3n}[\mathbf{5}] + k_{3x}[\mathbf{6}]) \qquad (4)$$

These individual rate constants cannot be extracted from the available data, but in view of the fact that the primary isotope effect k_H/k_D is significant (4–7) whereas the secondary isotope effect is essentially unity, the following analysis can be made. Since reactions on the exo face of **2** are preferred, the initial monodeuteration product is mainly **5**, as confirmed by the proton nmr studies. Since the rate constant k_1 is composed of two components, k_{1x} and k_{1n}, the observed rate of monodeuteration represents a maximum value for k_{1x}, but the difference between k_{1x} and k_1 must be slight (less than the experimental error in the rate constants), for if k_{1n} were appreciable, k_{3n} would be also, and **5** would not build up. Most of **5** would not proceed directly to **7**, because reversion of **5** to **4** would be faster, and some portion of **4** would proceed to **6**. However, **6** would be converted to **7** and then to dideuterated **8** as rapidly as it is formed. Reversion of **6** to **4** is disfavored by both the stigma of endo attack and the unfavorable isotope effect. Thus the conversion of **4** to **6** would be effectively irreversible, and the reversion of **5** to **4** can only lead to an observed rate of dideuteration that is actually faster than that due to endo proton removal from **5**, so that the observed rate of dideuteration represents a maximum value for k_{3n}. Thus the ratio of k_{1x}/k_{3n} approximately equals or exceeds the measured monodeuteration/dideuteration rate ratio. The smooth kinetics and the well-behaved plots of concentration of d_0, d_1, and d_2 species *vs* time suggest that the actual specificities for exo/endo proton removal in fact closely approximate the measured monodeuteration/dideuteration ratios.

Experimental Section[31]

Bicyclo[2.2.2]octan-2-one (**1**) was prepared by hydroboration of bicyclo[2.2.2]oct-2-ene (Chemical Samples Co.) followed by oxidation of the alkylborane with chromic acid[32] and purification by sublimation. Bicyclo[2.2.1]heptan-2-one (**2**) was obtained from Aldrich Chemical Co., and sublimed before use. Bicyclo[2.1.1]hexan-2-one (**3**) was prepared by the known procedure[33] and was purified by vpc (10 ft × 3/8 in. Carbowax 20M, 165°, 120 ml/min) before use. Deuterium oxide was obtained from Columbia Organic Chemicals, Inc. (99.77%), and Diaprep, Inc. (99.8%).

Kinetic Procedure, Deuteration Runs. The procedure for a

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[30] E. N. Peters and H. C. Brown, *J. Amer. Chem. Soc.*, **95**, 2398 (1973).

[30a] NOTE ADDED IN PROOF. Calculations based on the principle of least motion suggest that this factor would favor exo over endo hydrogen abstraction: O. S. Tee, J. Altman, and K. Yates, submitted for publication.

[31] Further details are available in the M.S. Thesis of G. A. Abad, University of South Carolina, 1971.

[32] G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

[33] J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968).

typical run for endo deuteration of **2** is described. A sample of 0.917 g (8.34 mmol) of **2** was dissolved in 24 ml of purified[34] dioxane in a 50-ml glass centrifuge tube. In a similar tube was placed 0.20 ml of a 40% NaOD solution in D_2O (Diaprep, Inc.) and 11.8 ml of D_2O.

Both tubes were sealed with rubber serum caps fitted with inlet and outlet tubes and dry nitrogen was bubbled through the solutions for 30 min. The tubes were then placed in the constant-temperature bath for 30 min. To initiate the reaction, the NaOD solution was syringed into the ketone solution. After an interval of 25 min to allow for complete monodeuteration, 2-ml samples were removed by hypodermic syringe at intervals over a period of 30 hr (5 half-lives) and placed in 125-ml separatory funnels containing 20 ml of water, 25 ml of pentane, and 2 ml of 0.25 *N* nitric acid. The layers were separated and the aqueous layer was extracted three times more with pentane. The combined pentane layers were washed with distilled water and the bulk of the pentane was distilled away. The residual oil (*ca.* 0.5 ml) was injected on the vpc (10 ft × $^3/_8$ in. 30% SE-52 on Chromosorb W, 145°, 100 ml/min, retention time 15 min) and collected as a white solid. This was washed into a vial with ethyl ether and evaporated to a volume of a few drops for mass spectral analysis.

At two points during the run (shortly after the first and last kinetic points) *ca.* 3.5 ml of the reaction mixture was withdrawn by means of a hypodermic syringe, and a volumetric pipet was used to measure out precisely 3.0 ml of this volume, which was then titrated with standard hydrochloric acid to a phenolphthalein end point. Concentrations found were 0.101 and 0.0958 *M*, respectively.

Control experiments showed that different quenching procedures (increasing the amount of nitric acid, or omitting it altogether) did not affect the deuterium content of the ketones.

Mass Spectral Technique. Mass spectra were run on a Perkin-Elmer Hitachi RMU instrument operating at 70 eV. Several scans of each cluster of molecular ion peaks were made at different detector sensitivities. Peak heights were taken as proportional to ion concentrations (peak areas at expanded scale settings were found to be proportional to peak heights). The relative height of each peak in the molecular ion cluster was calculated as a fraction of the total cluster, and expressed as H^0 (molecular ion peak) and H^{-1} (peak at one *m/e* unit less than the molecular ion). Pseudo-first-order rate constants were found by the least-squares fit of a straight line to the data in the form: $\ln (H_t^0 - \Delta_t)/(H_\infty^0 - \Delta_\infty)$ *vs.* t where the term Δ_t equals $H_0^{-1} - H_t^{-1}$ and is subtracted from H^0 to account for that portion of the peak at the molecular ion position coming not from molecular ionization but from fragmentation of the monodeuterated species. The H_0^{-1} peak for **1**, **2**, and **3** is 1.9, 11.9, and 1.6% of the H_0^0 peak, respectively. Second-order rate constants were found by dividing the pseudo-first-order rate constants by the arithmetic mean of the initial and final base concentrations (which differed from one another by no more than 5%). Duplicate runs usually agreed within ±3%, although variations as high as 10% occurred. Duplicate isotope analyses of the same sample agreed within ±1%.

Kinetic Procedure, Bromination Runs. The experimental procedure described by Bartlett[25] was followed. For a typical run, 100 ml of distilled water and 20 ml of a 0.0446 *M* aqueous solution of ketone were placed in a 250-ml glass-stoppered, round-bottom flask and thermostated to 10.0° for a period of 1 hr. A 0.0385 *M* aqueous solution of bromine (40 ml) (made up with 1.0 ml of bromine and distilled water up to a total volume of 500 ml with the bromine concentration determined iodometrically) was placed in a centrifuge tube, and the tube was sealed with a rubber septum cap and cooled to 10.0°. To initiate the reaction the bromine solution was transferred to the flask containing the ketone solution. At appropriate time intervals, 20-ml aliquots of the reaction mixture were withdrawn by means of a 20-ml syringe and placed in a 125-ml erlenmeyer flask containing 5 ml of 0.3 *M* acetic acid and an excess of sodium iodide added just before the sample. The liberated iodine was titrated with a 0.104 *N* sodium thiosulfate solution measured in a microburet. No starch indicator solution was needed since the end points were sharply determined by the disappearance of the iodine to give a water-clear soluton. No drift of the end points was observed. An analogous procedure was followed for runs in dioxane–D_2O.

To calculate the pseudo-first-order rate constants it was assumed that one molecule of bromine was consumed on enolization by **2**, and two molecules each by **1** and cyclohexanone. A further statistical adjustment was made in the latter case by dividing the measured rate constant by a factor of 2 to account for the two equivalent pairs of enolizable hydrogens. Second-order rate constants were obtained by dividing the first-order rate constants by the average base concentration during the run (base is stoichiometrically consumed in the reaction but since a 100-fold excess over ketone was present this was neglected).

Acknowledgment. Thanks are due to Professors N. H. Werstiuk, L. K. Montgomery, and K. Yates for helpful discussions, and to Professor F. T. Bond for our initial sample of **3**.

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(34) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 245.