

Base-catalyzed Detritiation of Some Bicyclo[2.2.1]heptanones

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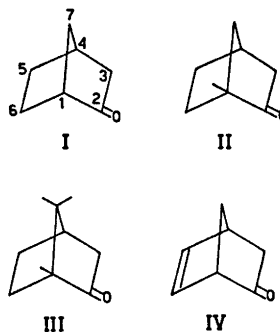
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Detritiation-protonation rates have been measured for *exo* and *endo* hydrogens at the 3-position of norcamphor, 1-methylnorcamphor, camphor, and dehydronorcamphor in aqueous sodium hydroxide solutions and the activation parameters have been calculated. The *exo/endo* rate ratios, 30 (81), 34, 2.6 (4), and 8.5 (19) at 75°C (extrapolated to 25°C within parentheses), are of the same order of magnitude as those measured earlier for dedeuteration-protonation reactions of norcamphor and camphor. The discussion of the rate ratios has been based on a mechanism presented earlier.

Base-catalyzed hydrogen exchange at the 3-position of bicyclo[2.2.1]heptanones has been the subject of intensive studies during the last decade.^{1–10} The *exo/endo* rate ratios of deprotonation-deuteration reactions have been observed to be almost of the same order of magnitude as the *exo/endo* solvolysis (*via* carbocations) rate ratios of bicyclic esters.^{11–12} The rate ratios in the hydrogen exchange have been explained to be caused by angle strains, torsional strains, nonbonded repulsions as well as hybridization effects and orbital overlapping.^{5–10} A mechanism for the reaction has been presented by Abad, Jindal, and Tidwell.⁹ The *exo/endo* rate ratios of the opposite reaction, dedeuteration-protonation, have recently been measured to be approximately one tenth of that measured for the deprotonation-deuteration reactions.¹⁰ The mechanism mentioned above also explains these data.

The technique employed for measuring the exchange rates of the α -hydrogens of bicyclic ketones has mostly been mass spectrometry,^{5–10} which is, however, quite laborious. An easier technique, tritium counting, has been utilized for measuring the exchange rates of hydrogens at the equivalent α -sites of some symmetrical

aliphatic ketones¹³ and more recently at the nonequivalent α -sites of an unsymmetrical ketone.¹⁴ The latter technique was now employed for measuring detritiation-protonation rates of norcamphor (I), 1-methylnorcamphor (II), camphor (III), and dehydronorcamphor (IV) in aqueous base solutions.



EXPERIMENTAL

Tritium labeling. One gram of the ketone was dissolved in 10 cm³ of a tritiation solution containing dimethyl sulfoxide, ordinary water, tritiated water (0.8 Ci/cm³), and tetramethylammonium hydroxide in the volume ratios 91:9:0.01:0.4. The tritiation times of the ketones were 3 h for I and II, 5 h for III, and 31 h for IV at room temperature. The times were estimated on the basis of the data reported by Tidwell,⁵ by employing an acceleration effect of dimethyl sulfoxide measured in this laboratory.¹⁵ Labeling per mol of camphenilone and fenchone was after 48 h 4 and 2 % of that measured for the substrates I–IV under the same conditions; thus labeling occurred dominantly at the 3-position of I–IV. The mol ratio of the ketone to tritium was *ca.* 10⁸ in the tritiation solution; thus the exchange of only one protium to tritium per molecule was probable.

After tritiation the solution was neutralized by addition of dilute sulfuric acid and shortly after that extracted three times with 10 cm³ of pentane. The pentane layers were washed two times with water and dried over anhydrous sodium sulfate. Pentane was distilled off and the residues were used without further purification. The purities of the ketones were analyzed by GLC (FFAP column) to be >99.5 % for I, III and IV, and 95.6 % for II (4.4 % of bicyclic alcohols).

Kinetic measurements. The reaction medium (130 cm³ of 0.01–0.1 M aqueous sodium hydroxide) was thermostated in a narrow-necked flask equipped with a ground-glass stopper. The reaction was started by adding the ketone (0.002–0.003 M) to the flask, shaking vigorously, and replacing the flask into the thermostated bath. The samples, 5 cm³ in volume and *ca.* 20 in number, were transmitted after appropriate intervals into glass cylinders, which contained 10 cm³ of cyclohexane and equivalent amounts (as compared with hydroxide ion) of nitric acid. The ketone was extracted into the organic phase by shaking for 2 min, after which the layers were allowed to separate over the night. Aliquots of 5 cm³ were pipetted from the organic layer and transferred into counting vials containing 10 cm³ of the scintillation liquid (0.1 g of *p*-bis(*o*-methylstyryl)benzene and 4 g of diphenyloxazole in

1.0 dm³ of toluene). The samples were analyzed on a Wallac 81000 scintillation counter. The final samples were taken after the reaction had continued for ten halflives from the first samples.

In the case of norcamphor (I) and 1-methylnorcamphor (II) the detritiation rates of the *exo* and *endo* hydrogens were measured consecutively since their rates were different enough and the first-order rate coefficients were calculated from the usual equation. In the case of camphor (III) and dehydronorcamphor (IV) the exchange rates of the *exo* and *endo* hydrogens were measured concurrently and the first-order rate coefficients were calculated from the equation¹⁴

$$\frac{N_0 - N_t}{N_0 - N_\infty} = x_{exo}[1 - \exp(-k_{exo}t)] + x_{endo}[1 - \exp(-k_{endo}t)] \quad (1)$$

In the equation N_0 , N_t and N_∞ refer to the activities of the first sample, the sample taken after time t had elapsed from the first sample and the final sample, respectively, x_{exo} and x_{endo} are the fractions of labeling at the *exo*-3 and *endo*-3 positions in the first sample ($x_{exo} + x_{endo} = 1$), and k_{exo} and k_{endo} are the first-order rate coefficients for the detritiation from the *exo*-3 and *endo*-3 positions. For all sub-

Table 1. Observed detritiation-protonation rates of *exo*-3 and *endo*-3 hydrogens of some bicyclo[2.2.1]heptanones in aqueous 0.01–0.1 M sodium hydroxide solutions at different temperatures. Method A: the *exo* and *endo* rates were measured consecutively, method B: the rates were measured concurrently (eqn. 1).

Substrate	Method ^a	Temp./°C	$k_{b,exo}/10^{-4} \text{ M}^{-1} \text{ s}^{-1}$	$k_{b,endo}/10^{-4} \text{ M}^{-1} \text{ s}^{-1}$
I	A	45	52.8 ± 0.7	—
	A	55	125 1	—
	B	55	119 1	2.54 ± 0.01
	A	65	253 4	6.34 0.06
	A	75	510 7	15.6 0.1
	A	85	—	36.2 0.2
II	A	75	362 ± 3	9.51 ± 0.14
III	B	55	3.45 ± 0.01	1.04 ± 0.01
	B	65	6.94 0.01	2.84 0.01
	B	75	15.0 0.1	6.26 0.01
	B	85	36.9 0.1	13.6 0.1
IV	B	55	5.14 ± 0.01	0.464 ± 0.008
	B	65	12.3 0.02	1.27 0.01
	B	75	28.1 0.02	3.08 0.03
	B	85	52.3 0.01	7.38 0.02

^a [NaOH] = 0.01 M for the *exo* exchange and 0.1 for the *endo* exchange in method A; [NaOH] = 0.1 M in method B.

In method B x_{exo} was between 0.45 and 0.52 in eqn. (1).

Table 2. Observed detritiation-protonation rates of hydrogen at the *exo*-3 position of norcamphor (I) in different sodium hydroxide solutions at 45 °C.

[NaOH]/M	$k_{exo}/10^{-4} \text{ s}^{-1}$	$k_{b,exo}/10^{-3} \text{ M}^{-1} \text{ s}^{-1} \text{ }^a$
0.01	0.524 ± 0.007	5.28 ± 0.07
0.03	1.56	0.02
0.07	3.44	0.05
0.10	4.70	0.03

$$^a k_{b,exo} = k_{exo}/[\text{NaOH}].$$

strates k_{exo} was assumed to be greater than k_{endo} (cf. Refs 1–10). The parameters x_{exo} , x_{endo} , k_{exo} , and k_{endo} and their standard errors were calculated from the experimental data on a computer by the method of least squares. The second-order rate coefficients were calculated by dividing the first-order ones with the sodium hydroxide concentration.

RESULTS AND DISCUSSION

The detritiation-protonation rates of hydrogens at the *exo*-3 and *endo*-3 positions of norcamphor (I), 1-methylnorcamphor (II), camphor (III), and dehydronorcamphor (IV) were measured in aqueous 0.01–0.1 M sodium hydroxide solutions at different temperatures with the exception of II which was studied only at one temperature. The *exo* and *endo* exchange rates of I and II were measured consecutively (method A) and those of III and IV

were measured concurrently (method B).¹⁴ The results are collected in Table 1.

In order to check that the methods employed give equivalent results, the detritiation rates of hydrogens at the 3-position of norcamphor were measured in both ways. The rate coefficients in the 0.1 M solution at 55 °C measured by methods A and B for the *exo* exchange, 0.0112 (estimated from a measurement in the 0.01 M solution by the aid of the rate coefficients in Table 2) and 0.119, and for the *endo* exchange; 0.000245 (extrapolated from the rates measured by method A at 65, 75 and 85 °C) and 0.000254, respectively, (all with the dimension $\text{M}^{-1} \text{ s}^{-1}$) are fairly the same.

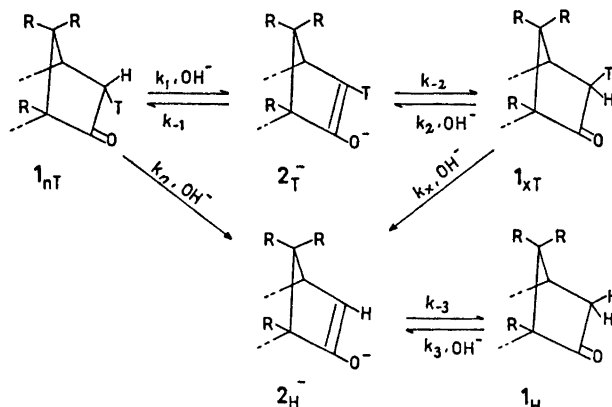
The effect of the base concentration upon the exchange rate was studied by measuring the detritiation rate of the *exo* hydrogen of norcamphor in different base concentrations in the range 0.01 to 0.1 M. The second-order rate coefficients in Table 2 show that a negative salt effect is observable, but not marked. The same kind of effect can also be seen in the dedeuteration-protonation rates of the *exo*-3 and *endo*-3 hydrogens of norcamphor.¹⁰

The activation parameters of the exchange reactions are given in Table 3. In the calculations all the rates were corrected to correspond with the base concentration 0.1 M. The activation parameters are of the same order of magnitude as those observed for the deprotonation-deuteration reactions of the bicyclic ketones.⁹ The rate coefficients calculated from the activation parameters (Table 3) allow

Table 3. Activation parameters of the detritiation-protonation of *exo*-3 and *endo*-3 hydrogens of some bicyclo[2.2.]heptanones and the rate coefficients at 75 °C calculated from them. [NaOH] = 0.1 M.

Tritium/ substrate	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J mol}^{-1} \text{ K}^{-1}$	$k_b/10^{-4} \text{ M}^{-1} \text{ s}^{-1}$
<i>exo</i> /I	66.3 ± 1.4	-81 ± 4	461 ± 13
<i>endo</i> /I	83.8	0.6	15.6
<i>exo</i> /II	—	—	ca. 324 ^a
<i>endo</i> /II	—	—	ca. 9.51 ^a
<i>exo</i> /III	74.0	4.5	16.3
<i>endo</i> /III	80.3	2.4	6.24
<i>exo</i> /IV	73.3	2.7	26.4
<i>endo</i> /IV	86.9	0.8	3.11

^a The values have been taken from Table 1 and the correction from the 0.01 to 0.1 M base concentration has been made for the *exo* rate coefficient according to Table 2.



Scheme 1.

the comparison of the rates. The *exo/endo* rate ratios at 75 °C (extrapolated to 25 °C within parentheses): 30 ± 1 (81 ± 8) for I, ca. 34 for II, 2.6 ± 0.2 (4 ± 1) for III, and 8.5 ± 0.4 (19 ± 4) for IV, are clearly smaller than those measured for the deprotonation-deuteriation reactions (660–715 for I, 18–21 for III, and 120 for IV in dioxane-water mixtures at 25 °C)^{8,9,10} but of the same order of magnitude as those measured for the dedeuteriation-protonation reactions (72 for I and 2 for III in dioxane-water mixtures at 25 °C).¹⁰ The data support the idea that the hydrogen exchange reactions of the bicyclic ketones are not simple processes.¹⁰

Scheme 1, which is in agreement with the mechanism presented by Abad, Jindal, and Tidwell⁹ and later by Banerjee and Werstiuk,¹⁰ leads to eqn. (2) when estimating the rate of detritiation from the *exo*- position

$$k_{exo}(T \rightarrow H) = k_x + k_2 - \frac{k_2 k_{-2} (k_n + k_1)}{(k_n + k_1)(k_{-1} + k_{-2}) - k_1 k_{-1}}$$

$$= k_x + k_2 \left(1 - \frac{k_{-2}}{k_{-1} + k_{-2} - \frac{k_1 k_{-1}}{k_n + k_1}} \right) \quad (2)$$

of the ketone (1_{xT}) if the steady-state approximation is made for the concentrations of intermediate enolate ions (2_T^- and 2_H^-) and for the *endo*-3 tritiated ketone (1_{nT} ; the last approximation may be somewhat invalid for camphor). The scheme leads to eqn. (3) when estimating the rate of detritiation from the *endo*-3 position of the ketone (1_{nT})

$$k_{endo}(T \rightarrow H) = k_n + k_1 - \frac{k_1 k_{-1} (k_x + k_2)}{(k_x + k_2)(k_{-1} + k_{-2}) - k_2 k_{-2}} \quad (3)$$

if the steady-state approximation is made for the concentrations of enolate ions (2_T^- and 2_H^-) and for the *exo*-3 tritiated ketone (1_{xT}) (cf. Ref. 10).

In the cases of norcamphor, 1-methylnorcamphor and dehydronorcamphor the approximation $k_1 \gg k_n$ can be made, since the primary isotope effect of tritium^{13,16} further retards the slow departure of *endo*-tritium and the secondary isotope effect of tritium is probably small on the fast departure of *exo* protonium.^{9,16} The retarding effect of the *syn*-methyl group on k_1 is marked, but k_1 is evidently so much greater than k_n that the same approximation is valid for camphor. Thus, eqn. (2) is simplified to the form (cf. Ref. 10)

$$k_{exo}(T \rightarrow H) \approx k_x \quad (4)$$

particularly, since $k_x > (>) k_2$ in the cases of I, II and IV and $k_x \sim k_2$ in the case of III.

The following approximation can also be made in the cases of I, II and IV: $(k_x + k_2)(k_{-1} + k_{-2}) \gg k_2 k_{-2}$, since $k_{-1} \gg k_{-2}$ and $k_x > (>) k_2$. Thus $k_{endo}(T \rightarrow H)$ gets the simpler form (cf. Ref. 10)

$$k_{endo}(T \rightarrow H) \approx k_n + k_1 \left(1 - \frac{k_{-1}}{k_{-1} + k_{-2}} \right) \quad (5)$$

In these cases $k_1 \gg k_n$ and therefore the term $k_{-1}/(k_{-1} + k_{-2})$ (≈ 1) is important. In the case

of camphor (III), the approximation may not be valid, since the departure of *exo*-tritium (k_x) is retarded by both the primary isotope effect of tritium and the steric effect of the *syn*-7 methyl group and the rate ratio k_{-1}/k_{-2} is also decreased by the steric effect on k_{-1} .

The *endo/exo* rate ratio

$$\frac{k_{endo}(T \rightarrow H)}{k_{exo}(T \rightarrow H)} \approx \frac{k_n}{k_x} + \frac{k_1}{k_x} \left(1 - \frac{1}{1 + \frac{k_{-2}}{k_{-1}}} \right) \quad (6)$$

can be used for evaluation of values for k_x/k_n and k_{-1}/k_{-2} if we assume that $k_x/k_n \approx (k_1/k_2 \approx) k_{-1}/k_{-2}$ and estimate a value for k_1/k_x , which is the primary isotope effect (k_H/k_T) on the departure of hydrogen from the ketone as corrected for the secondary isotope effect of the hydrogen atom at the same carbon. The isotope effects on the rate coefficients in the other terms of eqn. (6) cancel out if the isotope effects (both primary and secondary) of the similar hydrogens at the *exo* and *endo* positions are equal.

If we assume the rough value of 13 for k_1/k_x ($13 = 6^{1.44}$; the secondary effects are assumed to be unity, since 6 is a very rough mean for the primary deuterium isotope effect, k_H/k_D),^{13,16} we get the following values for k_x/k_n at 25 °C (at 75 °C within parentheses; $k_1/k_x = 8.7$ as extrapolated¹³ to 75 °C): 1100 (290) for I, (330 for II), 50 (25) for III and 270 (80) for IV, which seem quite reasonable (*cf.* Ref. 17). However, if eqn. (6) is applied for the evaluation of the ratio k_x/k_n in dedeuteration-protonation and deprotonation-deuteration reactions^{5,10} by employing the k_{exo}/k_{endo} values presented above and the appropriate estimates for k_1/k_x (6 and 1/6, respectively), the values (500–800 for I, 15–25 for III and 140 for IV at 25 °C) are obtained, which are of the same order of magnitude, but regularly smaller than those calculated for the detritiation-protonation reactions. The values of k_x/k_n estimated in this way are, however, sensitive to the primary isotope effects, which may vary markedly with varying substrates and also with varying solvents.^{13,16} The systematic differences may be caused by these facts, as well as by the approximations made, and do not conflict with the mechanism presented.

According to eqns. (4) and (5) the *exo* detritiation rates [$k_{exo}(T \rightarrow H)$] are approxi-

mately the same as the departure rates of *exo* tritium (k_x), but the *endo* detritiation rates $k_{endo}(T \rightarrow H)$ are greater than the departure rates of *endo* tritium (k_n). Thus the comparison of the departure rates (k_n) is more reasonable than that of the detritiation rates in the case of the *endo* exchange. The relative rates of departure of *exo* tritium are (1.0 for I) *ca.* 0.70 for II, 0.035 for III, and 0.057 for IV and the approximate relative rates of departure of *endo* tritium [$= (k_n k_{exo}(T \rightarrow H)/k_x)_i / (k_n k_{exo}(T \rightarrow H)/k_x)_I$, $i = I, II, III$ or IV] are (1.0 for I), 0.6 for II, 0.4 for III, and 0.2 for IV at 75 °C (the values calculated directly from $(k_{endo}(T \rightarrow H))_i / (k_{endo}(T \rightarrow H))_I$ are, however, approximately equal).

The retarding effect of the 1-methyl group is slight as can be seen from the relative rates of II (*exo*- and *endo*-T) and is probably inductive by nature, since carbon 2 preserves its sp^2 hybridization at all the stages of the exchange reaction. The steric retarding effect of the *syn*-7 methyl group of III on the *exo*-T departure is *ca.* 0.09 (0.035/0.4), which seems reasonable (*cf.* Ref. 17; in the noncyclic two-stage free-radical addition of thiophenol to norbornene and 7,7-dimethylnorbornene $k_{latter}/k_{former} = 0.03$ at 0 °C). The retarding effect of the homoallylic double bond of IV is significant, although acceleration was expected due to the inductive effect and a possible homollylic stabilization effect of the ethylenic linkage. The same observation in the deprotonation-deuteration reaction of dehydronorcamphor has not got a satisfactory explanation from the differences in steric characters of the ethano ($-\text{CH}_2-\text{CH}_2-$) and etheno ($-\text{CH}=\text{CH}-$) bridges.^{5,10} The effect of the hybridization change at carbon 3 ($sp^3 \rightarrow sp^2$) upon torsional strain and homoconjugation in the transition state of IV is unknown.⁵ However, some kind of initial-state homoconjugation may occur in dehydronorcamphor, but not in norcamphor, and this may decrease the relative rate of IV.¹⁸

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