Highly Strained Ring Systems. Hydrolysis of *endo*-Tetracyclo-[5.2.0.0^{2,4}.0^{3,5}]non-8-en-6-yl *p*-Nitrobenzoate. Importance of Anchimeric Assistance by Bicyclobutane Ring. II[1]

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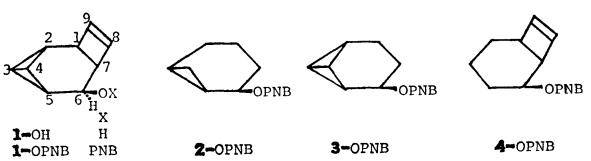
Solvolytic reactivity of *endo*-tetracyclo[5.2.0.0^{2,4}.0^{3,5}]non-8-en-6-yl *p*-nitrobenzoate(**1**-OPNB), *endo*-bicyclo-[4.1.0]hept-2-yl *p*-nitrobenzoate(**2**-OPNB), and *endo*-bicyclo[4.2.0]oct-7-en-2-yl *p*-nitrobenzoate(**4**-OPNB) was investigated in 50% aqueous acetone. **1**-OPNB was less reactive than **2**-OPNB that has no cyclobutene ring and more reactive than **4**-OPNB that has no bicyclobutane ring. Product study in solvolysis of **1**-OPNB was undertaken leading to the rearranged tricyclic alcohol as a major product. The importance of conformational factor for anchimeric assistance by bicyclobutane ring is discussed.

In spite of many studies of solvolytic reactions of cyclopropyl systems,[2] only a few investigations with bicyclo[1.1.0]butane derivatives, which involve the highest strain energy in bicyclic ring systems, have been reported.[3]

Masamune *et al.*[3a] reported that in ethanolysis of 5,6-diphenyltricyclo[2.1.1.0^{5,6}]hexan-2-yl *p*-toluenesulfonate a portion of the driving force for the reaction could arise from relief of angle strain on ring opening of the bicyclobutane ring. In contrast, Breslow *et al.*[3b] reported that none of the overall strain relief was found at the transition state for solvolyses of bicyclo[1.1.0]but-2-ylcarbinyl derivatives in spite of the fact that all products were derived from ring expanded cations. These studies have been made with the bicyclobutane derivatives substituted with phenyl groups or alkyl groups on the bridge heads of the bicyclobutane ring. Thus, there may be some influence on the reactivity due to π-electron systems or alkyl groups, and the effect of the bicyclobutane itself to the reaction center has some ambiguous factors.

On the other hand, we previously demonstrated importance of anchimeric assistance by bicyclobutane ring in solvolysis of a tricyclic system.[1] Taking these results into consideration, we have synthesized *endo*-tetracyclo[5.2.0.0^{2,4}.0^{3,5}]non-8-en-6-yl *p*-nitrobenzoate (**1**-OPNB),[4] *endo*-bicyclo[4.1.0]hept-2-yl *p*-nitrobenzoate(**2**-OPNB),[5] and *endo*-bicyclo[4.2.0]oct-7-en-2-yl *p*-nitrobenzoate(**4**-OPNB),[6] which have a partial structure of **1**-OPNB, and investigated their solvolytic reactivity to assess the effect of bicyclobutane and cyclobutene[7] in a polycyclic ring system.



1-OH H
1-OPNB PNB **2**-OPNB **3**-OPNB **4**-OPNB

Results and Discussion

The synthesis of tetracyclo[5.2.0.0^{2,4}.0^{3,5}]non-8-en-6-one (**5**) has been previously described.[4] Sodium borohydride reduction of **5** afforded exclusively the *endo* alcohol (**1**-OH). The stereochemical assignment of the *endo* isomer (geometry of the hydroxyl group relative to the cyclobutenyl group of **1**-OH) was based upon lanthanoid-induced chemical shift studies of ^{1}H NMR (Table 1). From the values of increment in chemical shift, it was predicted that the distances of the hydrogens (H_7, H_8) from the oxygen are shorter than that of H_4($\overline{OH}_7$, $\overline{OH}_8$<$\overline{OH}_4$).[8] This prediction was supported by an examination of the oxygen-hydrogen distances from the molecular model of the *endo* alcohol (**1**-OH) using Frame work Molecular Models. The stereospecific reduction of **5** from the less hindered side of the carbonyl group by sodium borohydride also suggested the *endo* isomer.[9] Additional information about the *endo* structure was gained from the coupling constants ($J_{6,5}$ and $J_{6,7}$) of the C_6 proton signal on the NMR spectrum of **1**-OPNB. From the corresponding dihedral angles (θ) obtained from the molecular model (FMM) of **1**-OPNB, the vicinal coupling constants were calculated as $J_{6.5}^{endo}$=2.50 Hz (θ=55°) and $J_{6.7}^{endo}$=7.21 Hz (θ=20°), and $J_{6.5}^{exo}$=1.83 Hz (θ=60°) and $J_{6.7}^{exo}$=0 Hz (θ=100°) using the Karplus equation.[10] The NMR data of **1**-OPNB showed $J_{6,5}$=2.0 Hz and $J_{6,7}$=9.4 Hz supporting the *endo* structure. Contrary to our all effort, attempts to prepare the *exo* epimer of **1**-OPNB encountered with failure.

The hydrolysis of **1**-OPNB, **2**-OPNB, and **4**-OPNB were measured in 50% aqueous acetone by titrating released *p*-nitrobenzoic acid using Bromothymol Blue as an indicator. All runs showed nice first-order plots. The kinetic data were summarized in Table 2 with literature values for a related compound. From Table 2, **1**-OPNB is 38 times more reactive than **4**-OPNB suggesting that this bicyclobutane ring stabilizes the transition state of the solvolysis of **1**-OPNB by *ca.* 2.7 kcal/mol (100 °C). On the other hand, the rate of **1**-OPNB decreases to one sixth comparing with that of **3**-OPNB in spite of the fact that **4**-OPNB is more reactive than cyclohexyl *p*-nitrobenzoate.[11] The difference in the reactivity of **1**-OPNB and **3**-OPNB is rationalized by considering the following two factors. First, when compared to **3**-OPNB, **1**-OPNB has a more rigid six-membered ring caused by the cyclobutene ring, and, as a result, it has a less favorable geometry for the "bisected" ion type interaction (**10**) that is the most stable structure of its transition state.[12] Second, the reactivity of **1**-OPNB probably decreases due to an inductive effect by the double bond (*ca.* by a factor

Table 1. Lanthanoid-induced chemical shifts in 1-OH[a)]

Weight of $Eu(dpm)_3$ (mg)	Chemical shifts of hydrogen								
	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9
0	2.84	2.48	1.67	1.67	2.76	3.70	3.04	6.18	6.18
19.6	5.50	5.25	3.90	5.00	8.54	16.25	10.15	12.52	8.75
Increment in chemical shifts	2.66	2.77	2.23	3.33	5.78	12.55	7.11	6.34	2.57

a) 1-OH (9.2 mg) in CCl_4 (0.136 ml).

Table 2. Kinetic data for hydrolysis of *p*-nitrobenzoates in 50% aqueous acetone (v/v)

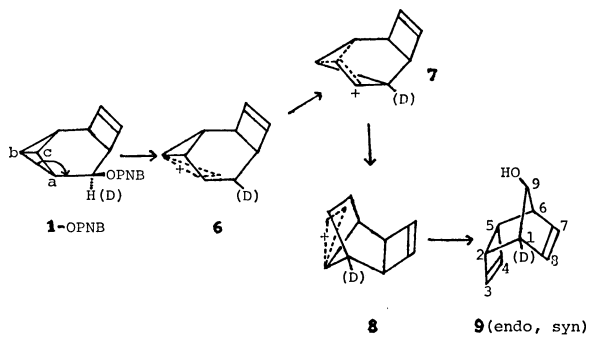
Substrate	Temp/°C[a)]	k_1/s^{-1}	$\Delta H^{\neq}$, kcal/mol	$\Delta S^{\neq}$, eu	k_{rel}
1-OPNB	100	$(5.18\pm0.12)\times10^{-5}$ [b)]	25.0	−11.5	38
	125	$(5.10\pm0.06)\times10^{-4}$ [b)]			
2-OPNB	80	6.59×10^{-4}			
	100	$(3.31\pm0.09)\times10^{-3}$ [b)]	20.4	−15.7	2400
3-OPNB	80	4.93×10^{-5} [c)]			
	100	2.96×10^{-4} [c)]	22.7	−14.2	218
4-OPNB	100	1.36×10^{-6} [d)]	31.4	−1.6	1
	125	$(2.08\pm0.02)\times10^{-5}$ [b)]			

a) ±0.2 °C. b) The errors are deviation from the average of two runs. c) Reference 1. d) Extrapolated value using the data at higher temperature ($k_1=2.30\times10^{-4}$ s^{-1} at 150 °C).

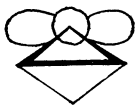
2—3).[7d,7e,13)] The rate acceleration of **4**-OPNB compared to the cyclohexyl *p*-nitrobenzoate by a factor of 7×10^4 might be mainly related to a relief of back side strain[14)] and rate retarding effect by the double bond (by a factor 2—3) would be small enough compared with the back side strain. In the case of **1**-OPNB, however, the ground-state strain resulting from nonbonded interaction between the cyclobutene ring and the leaving group would bend the leaving group to the conformationally undesirable direction for the interaction between the bicyclobutane ring and p orbital at C_6 in the transition state. In consequence, the anchimeric assistance by the bicyclobutane ring in **1**-OPNB was so important that the cyclobutene ring would influence the ionization rate of **1**-OPNB negatively. Similar relation exists in the rigid molecules such as *endo*-bicyclo[3.1.0]hex-2-yl *p*-nitrobenzoate and *endo*-tricyclo[4.2.0.$0^{2,4}$]octan-5-yl *p*-nitrobenzoate.[2f)] In them the ionization rate of the latter involving the cyclobutane ring appears comparable with the former under allowance for solvent differences.

The cyclopropylcarbinyl derivative (**2**-OPNB) which is a partial structure of **1**-OPNB underwent solvolysis at a rate *ca.* 60 times as fast as **1**-OPNB (100 °C), and its reactivity was even greater than that of **3**-OPNB by a factor of 10. In the other words, **1**-OPNB and **3**-OPNB which involve the bicyclobutane ring that has greater strain energy than the cyclopropane ring were less reactive than **2**-OPNB involving the cyclopropane ring. This result indicates that the most important factor ruling the solvolytic reactivity of **1**-OPNB is the conformational factor for stabilization of its transition state by the anchimeric assistance of the cyclopropyl ring in the bicyclobutane rather than the relief of its ring strain.[1,3b)]

Hydrolysis of **1**-OPNB produced predominantly *endo, syn*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-dien-9-ol (**9**) (91%, GLC analysis) and two unidentified minor products (<5%). Although **1**-OH was found to be unstable under the solvolysis conditions, it did not produce **9** (from GLC and TLC) suggesting that **9** is a solvolysis product of the C–O bond cleavage rather than that of alkaline hydrolysis of the ester. The structural assignment of **9** was based upon its NMR spectrum and physical property. The *endo* fusion of the cyclobutene ring to the norbornene moiety in **9** was supported by its NMR data of vinyl protons (δ 5.76, s, 4H) shifting toward up-field from that of *exo*-fused alcohol (δ 6.66 or 6.24)[7a)] due to the long range shielding effects by the other double bond.[15)] The disposition of the hydroxyl group *syn* to the cyclobutene ring was determined by its physical property (mp 87.5—88.5 °C) since the *anti* epimeric alcohol has a different melting point (41.5—42.5 °C).[16)] This assignment was also in agreement with the following mechanism: the backside participation of a–b bond of **1**-OPNB affords the "bicyclobutonium" ion **6**,[1,12)] which rearranges to **7**, and further the ion **7** gives predominantly **9** through stable bishomocyclopropenyl ion **8**.[17)] In this process, the fused cyclobutene ring is thought to act only as a stereochemical marker. The deuterated **1**-OPNB (C_6-*d*) was hydrolyzed to the C-1 (C-6) labeled alcohol **9** (C_1-*d*).



In summary, the difference in the solvolytic reactivity of **1**-OPNB, **2**-OPNB, and **3**-OPNB may depend on their effective conformations, which are related to the deviation from the most stable "bisected" structure (**10**) toward the less stable "bicyclobutonium" structure (**11**) in the transition state, for anchimeric assistance. The hydrolysis product study of **1**-OPNB also suggests the importance of anchimeric assistance by the bicyclobutane ring.



10

"bisected" ion

11

"bicyclobutonium" ion

Experimental

Melting points were taken on a Yamato MP-21 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-400 spectrophotometer and nuclear magnetic resonance spectra were recorded using a Hitachi R-24 instrument with chemical shift (δ) given in parts per million downfield from Me_4Si. Gas-liquid chromatography was performed on a Shimadzu GC-4B instrument. Microanalyses were determined in the microanalytical laboratory of the Institute of Physical and Chemical Research, Wako-shi, Saitama.

endo-*Tetracyclo*[*5.2.0.0*^{2,4}.*0*^{3,5}]*non-8-en-6-yl* p-*Nitrobenzoate (1-OPNB).* To a solution of *endo*-tetracyclo[5.2.0.0^{2,4}.0^{3,5}]-non-8-en-6-one[4] (639 mg, 4.84 mmol) in 15 ml of methanol was added sodium borohydride (114 mg, 3.02 mmol) at 0 °C. The resulting solution was allowed to stir at room temperature for 15 h. After addition of 15 ml of saturated sodium chloride solution, the resulting solution was extracted with ether three times. The ethereal solution was washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated under vaccum to give 554 mg (85%) of the crude alcohol (**1**-OH) as a colorless liquid. Owing to unstability of **1**-OH, the NMR spectrum of **1**-OH was examined without purification. **1**-OH: IR (neat) 3370 (OH), 2990, 2920, 1275, 1140, and 1040 cm^{-1}; NMR (CCl_4) δ 6.19 and 6.07 (2d, 2H, vinyl, J=3.0, 7.0 Hz), 3.95—3.35 (m, 1H), 3.30—2.25 (m, 5H), and 1.63 (t, 2H, J=2.8 Hz).

To a solution of **1**-OH (554 mg, 4.13 mmol) in 15 ml of dry pyridine was added *p*-nitrobenzoyl chloride (1060 mg, 5.71 mmol) in small portions at 0 °C. The resulting solution was allowed to stand in a refrigerator for 3 d, and then poured onto 60 g of ice with 2 ml of concentrated hydrochloric acid. The product was extracted with chloroform (60 ml×3), washed with 5% HCl solution (twice), water, 5% $NaHCO_3$ solution (twice), water (twice), dried ($MgSO_4$), and concentrated give 831 mg (71%) of **1**-OPNB: mp 90.0—91.0 °C; IR (KBr) 1710 (C=O), 1515, 1340, 1285, 1260, 1100, and 715 cm^{-1}; NMR ($CDCl_3$) δ 8.28 (s, 4H, aromatic), 6.18 and 6.05 (2d, 2H, vinyl, J=3.0, 7.4 Hz), 5.22 and 5.07 (2d,1H, J=2.0, 9.4 Hz), 3.31 and 3.16 (2d, 1H, J=4.0, 9.4 Hz), 3.04—2.54 (m, 3H), 1.94—1.74 (m, 2H). Found: C, 67.58; H, 4.74%. Calcd for $C_{16}H_{13}O_4N$: C, 67.84; H, 4.63%.

endo-*Bicyclo*[*4.2.0*]*oct-7-en-2-yl* p-*Nitrobenzoate(4-OPNB).* To a solution of *endo*-bicyclo[4.2.0]oct-7-en-2-one[6] (1.23 g, 10 mmol) in 15 ml of methanol was added sodium borohydride (266 mg, 7 mmol) at 0 °C. The resulting solution was stirred at room temperature for 15 h. After the addition of the saturated sodium chloride solution, ether extraction gave 1.17 g (94%) of the crude alcohol as a colorless liquid. This alcohol was purified by chromatography on a silica gel column to yield the *endo*-alcohol (61%): IR (neat) 3350 (OH), 3040, 2920, 2870, 1445, 1325, 1040, 785, and 725 cm^{-1}; NMR (CCl_4) δ 6.22 (s, 2H, vinyl), 3.97 (m, 1H), 2.87—3.25 (m, 2H), 2.56 (s, OH), 1.62 (bs, 6H). The *endo* alcohol (410 mg, 3.3 mmol) was converted to its corresponding *p*-nitrobenzoate (**4**-OPNB) as described above for **1**-OPNB to yield 512 mg (57%): mp 52.0—54.0 °C; IR (KBr) 1725 (C=O), 1525, 1355, 1280, 1120, 1110, and 730 cm^{-1}; NMR (CCl_4) δ 8.29 (s, 4H, aromatic), 6.43—6.17 (m, 2H, vinyl), 5.45 (br d, 1H, J=4.6 Hz), 3.56—3.07 (m, 2H), 2.17—1.57 (m, 6H). Found: C, 65.63; H, 5.52%. Calcd for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53%.

Kinetic Measurements. The *p*-nitrobenzoates were hydrolyzed in aqueous acetone, and the rates were measured as previously described.[7b] The kinetic data are shown in Table 2.

Solvolysis Product Study. *p*-Nitrobenzoate (**1**-OPNB) (300 mg, 1.06 mmol) in 150 ml of 50% aqueous acetone containing 267 mg of sodium hydrogencarbonate was divided and sealed into nine test tubes under nitrogen and the tubes were heated for 30 h at 100 °C. After cooling, the contents were evaporated for removal of acetone and added saturated sodium chloride solution. The resulting slurry was extracted with three portions of chloroform (40 ml). The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated. The product was purified by chromatography on a silica gel column eluting with 30% ether in hexane to give 58 mg (41%) of **9** as white crystals (mp 87.5—88.5 °C). The low isolated yield were attributed to sublimation during drying and an unidentified hydrocarbon which had a very short retention time in GLC. **9**: IR (KBr) 3280 (OH, br), 2975, 2950, 1286, 1225, 1065, 1055, 782, and 740 cm^{-1}; NMR (CCl_4) δ 5.76 (s, 4H, vinyl), 3.98 (br s, 1H), 3.21 (d, 2H, J=4.0 Hz), 2.55—2.30 (m, 2H), 1.99 (br s, 1H, OH).

The NMR spectrum of **9** from hydrolysis of the deuterium labeled **1**-OPNB (C_6-*d*) showed that the proton intensity at δ 2.55—2.30 (2H) was reduced to 1H indicating the deuterium staying on C_1 (or C_6).

Stability of 1-OH under the Solvolysis Conditions. Alcohol (**1**-OH) (44 mg) in 16 ml of 50% aqueous acetone containing 82.7 mg of sodium hydrogencarbonate was sealed in a test tube under nitrogen and the tube was heated at 100 °C for 30 h. After work up, the crude product was examined by GLC and TLC analyses to indicate no existance of **9** and **1**-OH.

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11) Using a factor of 1/500 for converting a rate of the cyclohexyl tosylate in acetic acid at 25 °C ($k=4.88\times10^{-8}$ s^{-1})[18] to that of 3,5-dinitrobenzoate in 60% aqueous acetone at 100 °C (J. E. Baldwin and W. D. Foglesong, *J. Am. Chem. Soc.*, **89**, 6372 (1967); **90**, 4303, 4311 (1968)), a rate of the 3,5-dinitrobenzoate was converted to that of the *p*-nitrobenzoate by a factor of 0.09 under the allowance of the next assumption, $(k_{OPNB}/k_{ODNB})_{60\%} = (k_{OPNB}/k_{ODNB})_{80\%} = 0.09$,[2f] and k_{OPNB}(60% aqueous acetone) was converted to a rate in 50% aqueous acetone by a factor of 2.2 for the solvent change.[1] Thus, a value for the rate of cyclohexyl *p*-nitrobenzoate in 50% aqueous acetone at 100 °C was roughly estimated to be 1.93×10^{-11} s^{-1}.

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