0.63 g of an oil which could be used for the final step as is. For characterization, 0.2 g of the oil was chromatographed on an analtech 2000 μm, SiO_2 plate. Elution with 10% methanol in chloroform gave 0.19 g (98%) of **21** as an oil which was identical with an authentic sample prepared by Weinreb[10] as judged by TLC, ^1H NMR, IR, MS, and UV comparisons. UV_{max} (95% EtOH) 213 nm (ε 22 500), 242 (ε 6100), 270 (sh, ε 660); IR ($CHCl_3$) 3550 (m, OH), 3500–3200 (br, OH), 1625 (vs, unsat. C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 3.69 (s, 3), 5.53 (d, J = 3 Hz, 1), 5.96 (d, J = 1.8 Hz, 1), 6.04 (d, J = 1.8 Hz, 1), 6.25 (s, 1), 6.51 (d, J = 3 Hz, 1) ppm; m/e (rel intensity) 223 (M + 1, 0.94), 222 (M^+, 4.90), 83 ($C_4H_3O_2$, 100).

Racemic Aflatoxin M_1 (1). The phenol **18** (0.15 g, 0.00086 mol) was dissolved in dry methylene chloride (35 mL) and anhydrous, powdered sodium bicarbonate (10.5 g, 0.125 mol) and zinc carbonate[10] (7.0 g, 0.0558 mol) were added, followed by the bromide **19** (0.28 g, 0.0012 mol) in methylene chloride (35 mL). The slurry was stirred for 24 h at 25 °C under a nitrogen atmosphere and was then transferred to a Soxhlet thimble and continuously extracted for 24 h with 2% methanol in chloroform (500 mL). The extract was washed with saturated, aqueous sodium bicarbonate solution (2 × 150 mL) and brine (1 × 150 mL) and dried over anhydrous sodium sulfate. The solid in the thimble was treated with 1:4 concentrated hydrochloric acid–water (250 mL) and the suspension was extracted with chloroform (3 × 100 mL). The combined extracts were washed with sodium bicarbonate solution (2 × 100 mL) and brine (1 × 100 mL), dried, and combined with the chloroform solution of the Soxhlet extraction. Filtration and concentration in vacuo gave 0.17 g of residue which was triturated with methanol (5 × 1 mL) to give 0.06 g (27%) of **1** as a light yellow crystalline solid. The methanol washes were chromatographed on an analtech 2000 μm, SiO_2 plate. Elution with 10% methanol in chloroform gave an additional crop of 0.01 g (5%) of **1** bringing the total yield to 32%. Aflatoxin M_1 (**1**) was identical with an authentic sample as judged by chromatographic and spectral comparisons: UV_{max} (95% EtOH) 228 nm (ε 23 200), 260 (sh, ε 10 900), 266 (ε 11 800), 358 (ε 18 500); IR ($CHCl_3$) 1760 (br, C=O), 1630 (C=C), 1620 (aromatic C=C) cm^{-1}; ^1H NMR (pyridine-d_5) 2.53 (m, 2), 3.07 (m, 2), 3.82 (s, 3), 6.05 (d, J = 2.9 Hz, 1), 6.63 (s, 1), 6.91 (d, J = 2.9 Hz, 1), 6.95 (s, 1) ppm; m/e (rel intensity) 328 (M^+, 67.38), 299 ($C_{14}H_9O_6$, 75.89), 271 ($C_{13}H_9O_5$, 100).

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Complete Retention in Substitution and Stereospecificity in Transannular Reactions of *cis*- and *trans*-3-*tert*-Butylcyclooctyl Tosylates

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Abstract: The stereochemistry of solvolysis reactions including 1,5 hydride shifts is investigated with 3-*tert*-butylcyclooctyl compounds. The hitherto undetected epimeric alcohols can be differentiated by ^{13}C NMR but not by the nearly identical ^1H NMR and IR spectra. Their configuration, confirmed by an unpublished X-ray analysis, is compared to the stereoselectivity of corresponding ketone reductions. Solvolysis of the epimeric tosylates in aqueous acetone, acetic acid, and trifluoroethanol is accompanied by at least 99% retention; the precursor configuration is retained too in the transannular 1,5 hydride shift reaction products. These amount to approximately 50%, as found by ^{13}C and ^2H NMR spectroscopic analysis of ^2H distribution in solvolysis products of C^α-deuterated tosylates. Solvolysis rates of the epimeric tosylates differ by a factor of 15, which is attributed not to different degrees of transannular hydrogen participation but to strain energy variations. Other isomerization products such as 1- and 2-*tert*-butylcyclooctanols are not observed.

Although almost 3 decades have passed since Cope, Prelog, and their schools discovered the unique transannular reactions of medium-ring compounds,[1] very little is known about the stereochemistry of the corresponding substitutions. With 5-methyl-,[2a] 5-phenyl-,[2b] and 5-*tert*-butylcyclooctyl tosylates,[2c] Allinger, Cope, and their co-workers showed that only the cis epimer undergoes solvolysis with a transannular 1,5 hydride shift; the stereochemistry of the substitution was not investigated, and it was not clear whether the solvolysis rate was enhanced by participation of the migrating hydrogen. Arguments against a hydrogen participation have been put forward earlier;[1,2b] a more recent isotope effect study of Parker and Watt,[3] however, demonstrates definite, although perhaps small, participation in cyclooctyl sulfonate solvolysis. The high solvolysis rates of medium-ring compounds have been attributed by Brown[4] to I strain relief and not to transannular participation, and we recently[5] could show that trifluoroethanolysis rates of cycloalkyl tosylates indeed are quantitatively predicted by force field calculated strain energy differences between multiple-ring conformations containing an sp^3 or sp^2 hybridized carbon. Harris, Raber, et al. have found particularly low solvent assistance in cyclooctyl sulfonate solvolysis rates and have attributed this to the inherent strain of the ring;[6] steric shielding by different hydrogens against solvent attack or hydrogen participation might offer an alternative and preferable explanation.

Cyclooctyl sulfonates bearing an alkyl group in the 3-position are particularly intriguing systems as here 1,5 hydride shifts can lead to structurally identical products. Introduction of deuterium

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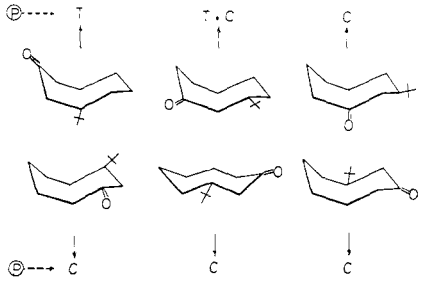
Table I. Stereochemistry of 3-*tert*-Butylcyclooctanone Reductions

	% *cis*-ROH (2)	% *trans*-ROH (3)
$LiAlH_4$	77	23
Raney Ni/H_2	37	63
$Li/NH_3/EtOH$	89	11
L-Selectride	9	91

Scheme I. Alcohol Configurations[a] from "P"-Controlled Reduction of Different 3-*tert*-Butylcyclooctanone Conformers



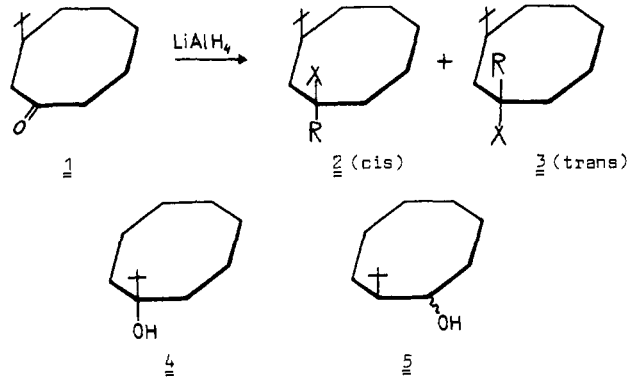
[a] C = *cis*-2 and T = *trans*-3.

at the α-carbon will then remove the degeneracy of the isomerization. The products can be identified by modern techniques such as ^2H and ^{13}C NMR spectroscopy. Observation of 1:1 ratios for rearranged and nonrearranged products from both epimers would be indicative of symmetrical hydrogen bridging or of fast 1,5 shifts.

3-*tert*-Butylcyclooctanols have been prepared before[7] but resisted any effort to detect more than one stereoisomer, the configuration of which, furthermore, remained unidentified. The unique situation of a seemingly missing epimer provided a challenge for the use of ^{13}C NMR spectroscopy, which later on proved to be the only spectroscopic method for the differentiation of these stereoisomers.

Results

Reduction of 3-*tert*-butylcyclooctanone (**1**)[7] with lithium aluminum hydride yields a mixture of alcohols which in the ^{13}C NMR spectrum shows eight larger and eight smaller signals in addition to the *tert*-butyl peaks, indicating formation of epimers in the ratio of 3:1. The alcohols **2** and **3** (X = OH) can be separated both

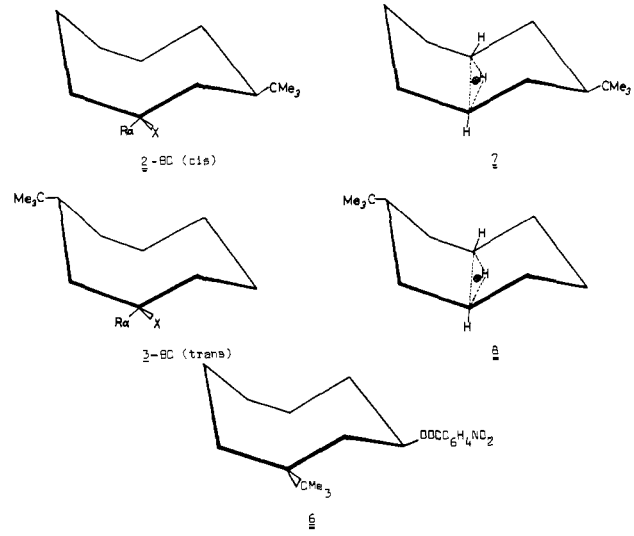


1 **2** (cis) **3** (trans) **4** **5**

by gas–liquid and column chromatography on silica and indeed gave ^1H NMR and IR spectra (supplementary material) which are virtually identical even in the IR fingerprint area.

Even though cyclooctanones are flexible ketones offering little differential steric hindrance for nucleophilic attack at the carbonyl group, one can make the reduction rather selective in either desired direction (Table I). Attack of a bulky boron hydride[8] occurs

Chart I



mostly from the less hindered pseudoequatorial side by steric approach control "S", whereas reduction with lithium in ammonia/ethanol proceeds largely via product stability controlled transition states "P".[9] Scheme I contains the most stable 3-*tert*-butylcyclooctanone conformations, the relative stabilities estimated from literature data,[10] and the preferential epimer to be expected from a "P"-controlled reduction. It is tempting to assign the configuration from the experimentally observed predominance of one stereosiomer—and X-ray analysis later on indeed proved that "P"-controlled reduction furnishes the cis alcohol—but one cannot exclude faster attack on one of the listed conformers which would produce the alternative epimer.

^{13}C NMR shifts, which differ substantially for all ring carbon atoms (Table III), are similar to those in corresponding cyclohexanes.[11] They provide a safe method for identification of **2** and **3** (X = OH) from the reactions but no reliable way for configuration assignment. The latter was accomplished by X-ray analysis[12] of the *p*-nitrobenzoate **2** (X = $OOCC_6H_4NO_2$), which showed the boat–chair conformation **6** as being present in the crystal (Chart I).

Solvolysis product studies from the tosylates were performed in buffered aqueous solutions and in the particularly weakly nucleophilic trifluoroethanol. Reactions in formic acid and in trifluoroacetic acid led largely to thermodynamic control, recognized by time-dependent product compositions, and were not further investigated. GLC analysis furnished accurate ratios of elimination and substitution products as well as of the stereoisomers formed (Table II); only the epimeric trifluoroethyl ethers could not be separated and were analyzed by NMR spectroscopy. ^{13}C NMR spectra confirmed the identity of the alcohols; the presence of 1,2 or 1,3 hydride shift substitution products was excluded by GLC comparison with authentically prepared 1- and 2-*tert*-butylcyclooctanols **4** and **5**.

The 1,5-shifted substitution products are recognizable in the ^{13}C NMR spectra of **2** and **3**, yielding for C^α (R^α = D) a triplet shifted upfield from the C^α of **2** and **3** (R^α = H) and, in the ^2H NMR spectra, yielding signals typical for functional and aliphatic deuterons (Table III), which could be accurately integrated. ^2H NMR spectra of the olefins yielded aliphatic signals, due to the transannular isomerization, indistinguishable from those in the spectra of the corresponding substitution products; but the amount

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Table II. Solvolysis Products[a,i]

solvent	ROTs	substitution sum[b]	substitution % retention	substitution % 1,5-shift[c]	elimination sum[b]	elimination % 1,2-shift[c]	elimination % 1,*n*-shift[c]
H_2O/Me_2CO[d]	cis	45	>99.5	50	55	10	40
	trans	30	>99	50	70	3	35
$H_2O/Me_2CO + NaHCO_3$[e]	cis	35	>99	40	65	3	30
	trans	21	>99	40	79	2	35
CH_3COOH[f]	cis	61	>99	50	39	5	40
CF_3CH_2OH[g]	cis	65[h]	>95[h]	50	35	3	50
	trans	55	>95[h]	50	45	3	50

[a] In percent. [b] From GLC data, ±2%. [c] From ^2H NMR signal integration and comparison to GLC data. Shift: rearranged material relative to substitution or elimination product ≡ 100%; accuracy ±5%, except for hydrolysis products (±3%, from preparative GLC fractions). [d] 0.5 ± 0.1 M ROTs in 10% (v/v) H_2O solution with 0.8 ± 0.2 M pyridine at 60 °C for 6 h. [e] 0.3 ± 0.05 M ROTs in 10% (v/v) H_2O solution with 0.6 ± 0.1 M $NaHCO_3$ at 60 °C for 6 h. [f] 0.5 ± 0.1 M ROTs in absolute CH_3COOH (99%+) with 1 ± 0.1 M pyridine at 60 °C for 6 h. [g] 0.25 ± 0.05 M ROTs in 97% CF_3CH_2OH with 0.3 ± 0.05 M pyridine at 20 °C for 15 h. [h] ±5%; differentiation between epimers by ^1H and ^2H NMR only (identical GLC retention times). [i] Rates in 80% ethanol/water (80 ± 20 volume parts) at 25 °C: 2 (X = OTs, cis), 5.25×10^{-4} s^{-1}, $\Delta G^* = 21.93$ kcal/mol; 3 (X = OTs, trans), 0.36×10^{-4} s^{-1}, $\Delta G^* = 23.51$ kcal/mol; cyclooctyl tosylate; 1.27×10^{-4} s^{-1}, $\Delta G^* = 22.77$ kcal/mol.

Table III. NMR Data of the Stereoisomers 2 and 3 and Olefins[a,b]

compd		1	2*	3	4***	5**	6**	7***	8*	9*	10
^{13}C NMR ROH[c]	cis	73.67	34.95	43.80	30.10	22.56	24.55	28.10	34.29	37.22	27.21
	trans	70.19	35.16	41.85	27.95	27.30	23.27	29.64	37.24	34.25	27.56
ROTs[d]	cis	*e*	32.24	44.00	29.70	22.42	24.63	27.69	34.12	34.38	27.00
	trans	*e*	34.55	41.52	29.41	26.81	25.90	31.82	34.30	34.55	27.27

compd		olefinic[h]	functional	allylic[h]	aliphatic
^2H NMR ROH[f,g]	cis	5.5	3.4	2.2	1.5
	trans	5.6	3.7	2.3, 2.0	1.4
^1H NMR ROH	cis	5.5	3.5		0.8–2.0
	trans	5.4	3.8		0.9–2.0

[a] Shifts (δ) relative to Me_4Si; solutions 10–20% in $CFCl_3$ at ambient temperature; internal reference Me_4Si for ^1H and ^{13}C, and $CDCl_3$ for ^2H (δ_{Me_4Si} 7.24). [b] Interchangeable assignments marked by asterisks. [c] For 2 and 3 (R_α = D, X = OH) isotope shifts at Cl ± 0.50 ppm and at C2/C8 ± 0.15 ppm. [d] $C_6H_4CH_3$ signals: δ 144.3 (Cl') and 135.7 (*p*-C), 129.9, 128.15 (*o*-C, *m*-C), 21.55 (CH_3), identical for the epimers (±0.1 ppm). [e] Signals not detectable due to C1 D. [f] *tert*-Bu signal at 0.88 ± 0.02 ppm. [g] Trifluoroethyl ethers: functional $^2H/^1H$ 0.2 ppm upfield from ROH; OCH_2CF_3 signal at 3.71 ppm (q, $^3J = 8.8$ Hz). [h] Signals of olefins from 2 and 3 (X = Ts) solvolysis.

of transannular shift preceding elimination can be evaluated by comparison of overall olefin content, as obtained by GLC, and nonrearranged olefin content as obtained from integration of the vinylic signals in the ^2H NMR spectrum. The structures of the olefins were only partially assigned. 1-*tert*-Butylcyclooctene was excluded by comparison with an authentic sample; 1,2 and eventually 1,3 hydrogen shift products in the olefins could be observed by the corresponding allylic and homoallylic ^2H NMR signals. The product distributions thus calculated (Table II) were secured (then with a higher accuracy) for hydrolysis products by preparative GLC separation and subsequent ^2H and ^{13}C NMR measurements.

Discussion

S_N1 reactions of aliphatic compounds are usually characterized by a substantial amount of inversion.[13] Predominant front side displacement has been reported in some cases;[14] in contrast to our model, however, energetically close and easily interconvertible stereoisomeric intermediates do not occur in these systems. The present investigation shows that the conformationally very flexible cyclooctyl cations can retain their configurational identity before undergoing substitution, even after transannular rearrangement.

A rationalization of the observed stereospecificity on the basis of conformational effects requires activation energies for both nucleophilic attack and 1,5 hydride shift of the cationic intermediates (corresponding to **2** and **3**) to be lower than their interconversion barrier.[15] This is not unlikely since fast pseudorotation of the cyclooctane ring will not interconvert the substituents,[16] and comparable inversion barriers for cyclooctanone[10a] and monosubstituted cyclooctanes[17] were reported to be as high as 7 kcal/mol. Saunders and Stofko[18] have estimated barriers for 1,5 hydride shifts of less than 6 or 7 kcal/mol from NMR observations under conditions suitable for stable carbocations; these barriers are expected to be even lower in medium rings with possible 1,5-proximity. Exclusive frontside attack of cyclooctyl cations or ion pairs leading to retention is reasonable since the backside of the reaction center can be protected by the vicinity of transannular CH_2 groups. Force field calculations of cyclooctanones[19] indicate a distance of only 2.85 Å between C^α and the pseudoaxial hydrogen at C^ϵ in a boat-chair conformation such as **2**-BC (Chart I).

Alternatively, the formation of hydrogen-bridged carbocations **7** and **8** can be responsible for the observed stereospecificity, in analogy to other bridged cationic intermediates.[13a,20] We would then have to our knowledge the first case of retention due to hydrogen participation. Kirchen und Sorensen[21] recently presented compelling NMR evidence for the formation of stable 1,5-hydride-bridged cyclooctyl cations under conditions suitable for

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free cations of long lifetime. The strong and stereospecific isotope effect found by Parker and Watt[3] indicates that in cyclooctane solvolysis reactions transannular hydrogen participation contributes to the rate and product determining steps. That the substitution products show the absence of both the usually favored[22] 1,2-shift and also of the 1,3-shift, which would lead to a tertiary cationic center, is again in accord with 1,5-bridged intermediates or at least transitions states of low energy. These would also account for the almost invariable 50% D Scrambling, which means complete 1,5-shift in substitution products observed with both epimers, showing the absence of counterion control. It should be noted that internal return via ion pairs (corresponding to **2** and **3**) is excluded by the observed stereospecific products obtained from each epimeric tosylate.

Change of solvent nucleophilicity has an unusually small effect on the product composition, which is in agreement with the exceptionally low solvent assistance found in cyclooctyl tosylate solvolysis.[6] It is remarkable that, even in trifluoroethanol, the lifetime of a cyclooctyl cation formed in an S_N1 process is too small to allow for any conformational isomerization. Only in basic aqueous solution can direct nucleophilic attack compete with the 1,5-shift, as evident from the reduced rearrangement; that the amount of retention is not lowered simultaneously indicates that at least not all substitution occurs via a 1,5-bridged intermediate.

As far as the olefins could be analyzed, elimination proceeds largely via 1,5-hydrogen-shifted intermediates, as does substitution; 1,3- and 1,4-shifts are believed to be unimportant since none of the corresponding 1-*tert*-butylcyclooctene has been observed. That 1,2 hydride shift leads only to elimination can be due to a different geometric situation of the corresponding ion pair which favors elimination more than substitution or a 1,5-hydrogen shift.

The particular geometry responsible for the observed 1,5 hydride shift must resemble conformations such as **2**-BC and **3**-BC and not the solid-state conformation **6** which lacks the required proximity of C^{α} and the transannular hydrogen at C^{ϵ}. It is noteworthy, that molecular mechanics calculations on cyclooctanone[5,10b,19] predict a particularly stable conformation with the trigonal carbon at the same position as the leaving group in **2**-BC and **3**-BC, which would bring the cationic center close to the transannular C^{ϵ} group. Furthermore, our earlier calculations[5] suggest that, indeed, only the one trigonal intermediate of lowest strain energy is formed by starting from different sp^3 ground states in medium-ring reactions.

Considerable solvolysis rate differences have already been reported between epimeric 5-*tert*-butyl-[2c] (factor of 35:1) or 5-phenylcyclooctyl tosylates[2b] (5:1) and discussed in terms of steric differences in the transition state or of transannular hydrogen participation, since the faster reacting isomer was always the one yielding transannular rearranged product. The epimeric 3-*tert*-butylcyclooctyl tosylates **2** and **3** (X = OTs) both undergo a 1,5 hydride shift to the same degree, yet their rates in ethanol/water differ by a factor of 15:1; consequently, hydrogen participation cannot be inferred from such rate differences. Since bridging is effective to the same degree for both epimers, at least in the product step, the solvolysis activation energy difference should be sought in strain energy differences of both ground and transition states. A full exploration by force field calculations[5] would require consideration of many contributing conformers and eventually bridged transition-state models. Preliminary calculations[19] suggest that the strain energy in different *tert*-butylcyclooctane boat–chair conformers varies over 2 kcal/mol, whereas a methyl group in corresponding different positions leads only to a variation of 0.25 kcal/mol.

Experimental Section

NMR spectra were recorded in the PFT mode on a 21.14-kG Bruker HX-90 system (^1H, 90 MHz; ^2H, 13.82 MHz; ^{13}C, 22.62 MHz) under ^1H noise decoupling for ^2H and ^{13}C observation. Resolutions of 0.5 Hz and <1 Hz could be attained for ^{13}C (10-mm tubes) and ^2H (5-mm tubes) NMR data, respectively.

3-*tert*-Butylcyclooctanone (1) was obtained from cycloocten-2-one and *tert*-butylmagnesium chloride in 62% yield: ^{13}C NMR (80% with C_6F_6, tentative assignments in the order C1–C10) 214.80, 42.69, 47.61, 33.70, 22.12, 26.09, 25.18, 29.08, 44.18, 28.11 ppm.

$LiAlH_4$ or $LiAlD_4$ reduction of 1 in ether at 37 °C was performed according to the literature;[7] yield 78% (mixture of alcohols; see Table I).

Reduction with Ni/H_2 was carried out on 4 g (22 mmol) of ketone **1** with 1.5 g of Urushibara nickel in 250 mL of methanol at 110 atm of H_2 and 90 °C during 18 h. After filtration and solvent removal, the residual oil was destilled [bp 136–137 °C to (16 mm)] to yield 2 g (50%) of alcohols (Table I).

Reduction of 1 with $Li/NH_3/EtOH$. Compound **1** (2 g, 11 mmol) was dissolved in 50 mL of dry ammonia, 30 mL of ether, and 8 mL of ethanol at −78 °C. After addition of 1 g of lithium, the mixture was stirred for 1 h at −78 °C and then allowed to come to room temperature. The then ammonia-free solution was treated with 100 mL of water and dilute HCl, washed, and dried over Na_2SO_4. For the product composition, see Table I.

L-Selectride[8] Reduction of 1. Compound **1** (1 g, 5.5 mmol) in 5 mL of tetrahydrofurane was added dropwise at −78 °C to 10 mL of a 1 M solution of lithium tri-*sec*-butylborohydride (10 mmol) in THF. After 3 h at −78 °C and 2 h at 20 °C, 10 mL of H_2O and 50 mL of H_2O_2 (30%) were added, the solution was washed and dried, and the residue after solvent removal was analyzed by GLC (see Table I).

Separation of the epimers 2 and 3 was achieved with colums, e.g., 200-cm length and 7.5-cm diameter, of neutral silica gel with methylene chloride. Crude product mixture (5 g) from the reductions yielded, e.g., 1.3 g of **2** (X = OH) (97% **2**, 1% **3**, 2% impurities), 1 g of **3** (X = OH) (90% **3**, 0.5% **2**, 9% impurities), 1 g of **2**/**3** mixtures, and 1 g of impurities (ketone etc.).

Tosylates from 2 and 3 were prepared by reaction of 1 mol of ROH with 1.1 mol of TsCl in 10 mol of pyridine first at 0 °C and then for 20 h at 20 °C. The solutions were worked up by addition of ether, washing with very dilute HCl and $NaHCO_3$, drying over Na_2SO_4, and evaporation of the solvent at reduced pressure.

***p*-Nitrobenzoates (2 and 3, X = $O_2CC_6H_4NO_2$)** were prepared from the alcohols by reaction with equimolar amounts of *p*-nitrobenzoyl chloride in pyridine similarly to the method for the tosylates; mp (recrystallized from ethanol) 94 °C (cis isomer), 81–82 °C (trans isomer). ($C_{19}H_{27}NO_4$, cis) C, H, N.

Methyl ethers 2 and 3 (X = OCH_3) were prepared from the alcohols with diazomethane/BF_3: ^{13}C NMR (20% in $CFCl_3$) C1–C10 for **2** 83.45, 34.77*, 44.52, 34.38*, 31.10, 29.00, 22.94, 33.67*, 25.22, 27.43 (*t*-Bu); for **3** 80.14, 34.38*, 41.66, 34.25*, 30.16, 29.70, 23.53, 33.99*, 26.58, 27.62 (*t*-Bu).

Solvolysis Products. The tosylates **2** and **3** (X = OTs) were solvolyzed under conditions given in Table I, and worked up by adding one part H_2O to one part reaction mixture and extracting three times with two parts of ether or carbon disulfide. The organic phase was washed with dilute HCl and $NaHCO_3$ solutions and dried over Na_2SO_4. The solvent was distilled off and the residue analyzed by GLC and NMR. In some control experiments CCl_4 was used as the solvent, and the extract was used directly for analysis in order to avoid loss of olefins during the workup.

The GLC analysis (5 m × $^1/_4$ in 10% Carbowax 4000 on Chromosorb PAW 80/60, 170 °C, flow rate 55 mL/min of N_2) yielded from *cis*-(*trans*)-ROTs hydrolysis the following [retention time, percent from cis isomer (from trans)]: olefins I at 3.7 min, 4.5 (3.5); II at 4.0 min, 5 (63.5); III at 4.8 min, 52 (4); trans alcohol, 21.3 min, 0.5 (26); cis alcohol, 22.9 min, 34 (0.5); impurities (ketone etc.), 3–5%. The olefins I–III distribution from acetolysis and trifluorethanolysis differed by <±5%; the *cis*- and *trans*-trifluoroethyl ethers had identical retention times (9.7 min).

^{13}C NMR signals (if not reported in Table III) are as follows: olefin II, 129.2, 130.77, 25.61, 26.13, 27.82, (*t*-Bu), 28.73, 29.38, 50.70 (*t*-Bu) ppm; olefin III (measured in mixture with II plus I), 129.41, 132.00, 26.39, 27.04, 27.75, 27.95 (*t*-Bu), 30.15, 32.41, 46.00 (*t*-Bu) ppm.

^{13}C NMR, ^1H NMR and IR spectra of the separated epimers **2** and **3** (X = OH) are given in the supplementary material.

1-*tert*-Butylcyclooctanol (4) was obtained according to the literature:[23] ^{13}C NMR (50% C_6F_6, C1–C7) 77.89, 32.47, 2342*, 29.08*, 25.83, 39.56 (*t*-Bu), 26.55 (*t*-Bu) ppm.

2-*tert*-Butylcyclooctanol (5) was prepared via hydroboration of 1-*tert*-butylcyclooctene. The olefin was obtained by heating 1.35 g (7.3 mmol) of 1-*tert*-butylcyclooctanol with 1.5 g (17 mmol) oxalic acid and 50 mg of hydroquinone to 150 °C at 20 mmHg; 1 g (91%) of product distilled off at 115–117 °C: ^1H NMR ($CDCl_3$) δ 1.03 (*t*-Bu), 1.5–2.1 (CH_2), 5.38 (C=CH); ^{13}C NMR (25% in $CDCl_3$) C1–C10 148.01,

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121.06, 29.51*, 31.14*, 26.11**, 26.55**, 27.08**, 26.55**, 36.58 (*t*-Bu), 29.81 ppm (*t*-Bu) (no other isomer detectable).

Compound **5** was obtained by reaction of 10 mL of 1 M (10 mmol) B_2H_6 solution in THF with 0.63 g (3.8 mmol) of olefin at 0 °C for 3 h, addition of 20 mL of H_2O, 20 mL of 3 N NaOH, and 20 mL of H_2O_2 (30%), extraction with pentane (2 × 50 mL), and destillation (57% yield). GLC showed the presence of two epimers (I and II) in 27 ± 4% and 73 ± 4% yields which were separated on a silica gel column (180 × 2.5 cm) with chloroform. Anal. ($C_{12}H_{24}O$, I and II) C, H.

^{1}H NMR ($CDCl_3$) for I δ 0.94 (*t*-Bu); 3.83 ppm, $b_{1/2}$ = 14 Hz (H_x); for II δ 0.85 (*t*-Bu); 3.98 ppm, $b_{1/2}$ = 10 Hz (H_x).

^{13}C NMR (5-10% in $CDCl_3$ with 10% C_6F_6) C1-C10 for I 71.82, 54.01, 31.33*, 26.84**, 23.07**, 26.19**, 26.71**, 33.02*, 36.86 (*t*-Bu), 28.27 ppm (*t*-Bu); for II 70.39, 41.86, 34.06*, 29.18**, 23.33**, 26.52**, 27.36**, 37.31*, 35.16 (*t*-Bu), 26.91 ppm (*t*-Bu).

Solvolysis rates were determined automatically[24] by continuous titration with 0.015 N NaOH in 80% ethanol to pH 7.

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Supplementary Material Available: IR and ^{1}H NMR spectra of the separated epimers **2** and **3** (X = OH), ^{13}C spectrum of a mixture of **2** and **3** (X = OH), and ^{2}H NMR spectrum of a solvolysis mixture (4 pages). Ordering information is given on any current masthead page.

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(25) **Note Added in Proof**: J. E. Nordlander et al. have observed similar stereoselective reactions by using deuterated cyclooctyl sulfonates. We thank Professor Nordlander for communicating the results prior to publication and discussions.

Kinetic Isotope Effect Study of the Solvolysis of Neophyl Arenesulfonates[1]

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Abstract: Carbon-14 and deuterium kinetic isotope effects (KIE) have been determined in the solvolysis reactions of para-substituted neophyl arenesulfonates. Large α-carbon KIE [1.094 in acetic acid (AcOH), 75 °C; 1.141 in trifluoroacetic acid (F_3AcOH), 0 °C] and medium Ph-1-carbon KIE (1.023 in AcOH; 1.035 in F_3AcOH) were observed for the unsubstituted neophyl brosylate; larger α-carbon and smaller Ph-1-carbon KIE were observed for a substrate with a more electron-donating substituent, and the reverse trend was found for electron-withdrawing substituents. These results, together with small β-carbon KIE (1.014 in AcOH and in F_3AcOH) and medium α-deuterium KIE (1.214 in AcOH; 1.247 in F_3AcOH, both per D_2), suggest that the reaction proceeds via a k_Δ mechanism in which the neighboring phenyl group participates in the rate-determining ionization step and that the transition state (TS) shifts to a more reactant-like structure as the electron-donating character of the substituent increases. The calculations of the KIE were carried out within the framework of transition state theory, in order to test these mechanistic conclusions, assuming a bridged TS structure with the neighboring phenyl group acting as an internal nucleophile displacing the leaving group. Cutoff models containing 10 atoms were used for both the reactant and TS, with structural parameters and force constants of the TS related to those of the reactant by empirical expressions relating geometry and force constants to bond orders. The bond orders of the five reacting bonds and a reaction coordinate consistent with S_N2 character at C_α constitute the independent parameters; consequently, families of solutions are found for which calculated KIE reproduce experimental values. The solutions are represented as regions on an O'Ferrall-Jencks reaction diagram; by requiring that the properties of the transition states vary smoothly with the Hammett σ parameter for substituents on the phenyl ring, a series of transition-state structures are found in which the C_α-leaving group bond is more than half-ruptured and the phenyl group is much less than half-transferred. The C_β-phenyl bond is largely intact and the C_α-phenyl bond develops at the expense of the π-electron density of the aromatic ring, similar to a bridged phenonium ion. The results are consistent with the qualitative nature of the transition state deduced from kinetic studies and provide strong support for the view that the neophyl arenesulfonates react via the k_Δ pathway.

Studies on neighboring-group participation in solvolysis reactions were initiated by Winstein[3a] nearly four decades ago, and many studies have been carried out since then.[3b,c] The 2-arylalkyl system, for which the term "anchimeric assistance" was first used,[4] has been of special interest in this field. The question of whether the neighboring aryl group accelerates the solvolysis rate by anchimeric assistance in the 2-arylalkyl system has now been shown[3b,c] to depend upon the structure, the substituents on the aromatic ring and at the β position, and the solvent. The 2-arylethyl sulfonates, the simplest of the 2-arylalkyl systems, have been shown to react either by an anchimerically assisted pathway (k_Δ) or by an unassisted pathway (k_s) (Scheme I), depending upon the substituents R, the aromatic substituent, and the solvent. The first

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(1) Part 11 of a series of neighboring group participation in solvolyses. For part 10, see Ando, T.; Yamawaki, J.; Saito, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 2348.

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