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Solvolysis Reactions and Force Field Calculations with Epimeric Cyclohexane Derivatives[1)]

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Reactions of the epimeric 4-*tert*-butylcyclohexyl tosylates in hexafluoroisopropyl alcohol (HFIP) (**1e**, **1a**) allow for the first time to observe S_N1-type non-stereospecific substitution, whereas conventional solvents including even trifluoroethanol yield S_N2-type inversion by solvent assisted pathway ($\triangleq k_s$). Large differences are found between the epimers in the solvent participation, measured kinetically by the Schleyer-Bentley equation. This, as well as the even enhanced elimination with the equatorial isomer **1e** as compared to **1a** (98% vs. 96% in HFIP) points to the occurrence of non-chair intermediates from **1e**-derivatives, and to more E_2- than E_1-type reactions. Kinetic measurements, including those of *cis*-3,5-dimethylcyclohexane esters (**2a**, **2e**) and 3α/3β-(tosyloxy)androstanes (**3a**, **3e**) show little differences between the equatorial esters in agreement with MM2 calculations, which establish small strain energy variations between the differently substituted twist-boat intermediates. Large differences, however, of up to 500% are measured between the axial esters (**1a**, **2a**, **3a**), although the alkyl substituents are remote from the leaving group and do not alter the chair geometry. These variations, which demonstrate the severe limitations of the Winstein-Holness equation for solvolysis reactions, are explained by MM2 calculated significant strain differences between the educts and the corresponding substituted cyclohexenes.

Solvolysereaktionen und Kraftfeld-Rechnungen mit epimeren Cyclohexanderivaten[1)]

Reaktionen der epimeren 4-*tert*-Butylcyclohexyltosylate (**1e**, **1a**) Hexafluorisopropylalkohol (HFIP) ermöglichen erstmals die Beobachtung von S_N1-artigen, nicht stereospezifischen Substitutionen, während konventionelle Solventien, unter Einschluß sogar von Trifluorethanol, S_N2-artige Inversionen durch einen solvensgestützten Mechanismus ($\triangleq k_s$) ergeben. Die Epimeren zeigen hier große Unterschiede in den nach Schleyer-Bentley et al. erhaltenen k_s/k_c-Werten. Dies sowie die sogar verstärkte Eliminierung bei der Reaktion äquatorialer Epimerer (**1e**: 98%, **1a**: 96%, in HFIP) läßt auf das Auftreten von Nicht-Sessel-Formen aus **1e** schließen sowie auf eher E_2- als E_1-artige Übergangszustände. Kinetische Messungen, einschließlich solcher mit *cis*-3,5-Dimethylcyclohexanestern (**2a**, **2e**) und 3α/3β-(Tosyloxy)androstanen (**3a**, **3e**) zeigen kleine Unterschiede zwischen den äquatorialen Estern, in Übereinstimmung mit MM2-Rechungen, welche ebenfalls kleine Variationen der Spannungsenergie zwischen den verschieden substituierten Twist-Boot-Intermediaten ergeben. Dagegen zeigen die axialen Epimeren (**1a**, **2a**, **3a**) erhebliche Unterschiede von bis zu 500%, obwohl die verschiedenen zusätzlichen Alkylgruppen entfernt von der Abgangsgruppe stehen und die Sesselgeometrie nicht stören. Die mit **1a**, **2a**, **3a** beobachteten Variationen, welche die nahezu prohibitive Limitierung der Winstein-Holness-Gleichung bei Solvolysen demonstrieren, lassen sich mit MM2-berechneten erheblichen Spannungsdifferenzen zwischen den Edukten und den entsprechenden substituierten Cyclohexenen erklären.

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The mechanism of nucleophilic displacement reactions in substituted cyclohexanes has been the subject of many investigations[2,3], which include detailed product[4] and kinetic[5] analyses as well as studies of solvent effects[6]. Several fundamental problems, however, are still open and are addressed to in the present study: (1) Even substitution reactions in weakly nucleophilic solvents have hitherto shown to proceed only with inversion[2,3,4]; the extremely weak nucleophile HFIP[7] may for the first time allow to study less stereoselective S_N1-processes. (2) Reactivity differences between epimers should be accessible to molecular mechanics calculations[8] and should also shed light on the applicability of the Winstein-Holness equation[9]. (3) The possible influence of alkyl substituents used commonly as conformation locking groups must be clearified. (4) The occurrence of non-chair intermediates in the reaction from equatorially substituted cyclohexanes renders the concept of E_1-mechanisms here doubtful and can also be evaluated with MM calculations.

Results

The reaction of the axial cyclohexyl sulfonate **1a** in hexafluoroisopropyl alcohol (HFIP) represents an example of almost non-predominant inversion with a secondary ester (Table 1). Trifluoroethanol (TFE) still shows mainly S_N2-type reaction (Table 1), in agreement with earlier findings[7a,f,g,10]. This corresponds to the increasing occurrence of solvent-separated ion pairs, which are more favoured in the reaction of axial (≙ **1a**) than of equatorial (≙ **1e**) leaving groups[5]. In line with earlier findings[4] and predictions[5], **1e** shows more inversion, although increasing retention products are observed with decreasing solvent nucleophilicity (Table 1).

Table 1. Solvolysis products from *trans*-(**1e**)- and *cis*-(**1a**)-4-*tert*-butylcyclohexyl tosylates[a]

ROTs	Solvent	Elimination	Δ^1	Δ^2	Δ^3	Subst.	ROR′ **1e** X = OH	ROR′ **1a** X = OH	Other
1e	H_2O[b]	40	0.3	6	94	60	4	90	5
	TFE[c]	65	0.6	2	97.3	35	3	85	12
	HFIP[d]	96.5	1	6	93	3.5	12	50	38
1a	H_2O[b]	56	0.3	4.7	95	44	80	15	5
	TFE[c]	82	0.2	1.3	98.5	18	50	17	32
	HFIP[d]	98	0.7	3.7	95.6	2	40[e]	30[e]	30[e]

[a] In %; Δ^1, Δ^2, Δ^3: *tert*-butylcyclohexenes (±0.2%; Σ = 100%); substitution products (Σ = 100%) (for errors and assignment problems with other substitution products see Experimental Section). – [b] In 80% acetone/water (= 80 + 20, v/v) at 70 ± 5°C. – [c] In 97% trifluoroethanol (97 TFE + 3 H_2O, w/w) at 70 ± 5°C. – [d] In 97% hexafluoroisopropyl alcohol (97 HFIP + 3 H_2O, w/w) at 60 ± 5°C. – [e] Larger error of ±8% due to low S/N ratio in the ^{13}C NMR spectrum.

Schleyer, Bentley et al.[7a] have proposed eq. (1), containing k_s/k_c as a measure of nucleophilic solvent assistance in a ROTs reaction, with rate constants k_{ROTs}

in a given solvent SOH, and in an extremely weak nucleophile S'OH, using 2-adamantyl tosylate (AdTs) as a standard without nucleophilic participation.

$$k_s/k_c = \frac{(k_{ROTs}/k_{AdTs})_{SOH}}{(k_{ROTs}/k_{AdTs})_{S'OH}} \quad (1)$$

Using HFIP as S'OH and literature values for AdTs[7a] as well as for ROTs in 50% ethanol[5] we obtained k_s/k_c ratios for **1a** and **1e** (Table 2), which demonstrate that epimers can show substantial differences in solvent participation. The high k_s/k_c ratio for **1e** as opposed to **1a** would be in line with an increased S_N2-process on the equatorial ester with the predominantly observed inversion. It would, however, also agree with an attack on intimate as opposed to separated (with **1a**) ion pairs, particularly in view of the absence of rate-product correlations in such reactions[6].

The high k_s/k_c value for **1e** would be at variance with expected higher hindrance at the axial rear side of the leaving group in a cyclohexane chair form, and clearly points to the occurrence of non-chair twist conformations. Similarly, the even larger proportion of elimination (Table 1) with **1e** as compared to **1a**, which should be much more suited for anti-periplanar proton abstraction than the **1e**-chair form, speaks for such twist-boat intermediates. That cyclohexanes with equatorial leaving groups indeed react via non-chair forms has been found earlier by *Shiner*[11] and *Saunders*[12] et al. and was demonstrated by us recently even for 3β-tosyloxy steroids[13] (see below).

The Rôle of Substituents as Conformational Locking Groups and the Limitation of the Winstein-Holness Equation

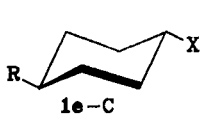
The *tert*-butyl group has been used to stabilize cyclohexane conformations in solvolytic studies under the premise that it will not influence to a significant degree the mechanisms and rates[2,3,9]. Our previous results show that this assumption may well be correct for solvolysis in the conventional, more nucleophilic solvents, where the observed substitution products and the k_s/k_c values indicate predominantly bimolecular k_s processes for *both* epimers. With decreasing solvent nucleophilicity, however, the participation of k_c or k_Δ processes[7a] increases and, as evident from the products (Table 1), varies for the *cis*- and *trans*-isomers. At least the elimination, which at the same time increases to up to 98% in HFIP, is known to differ significantly in the conformational requirements between the stereoisomers. Cyclohexanes with equatorial substituents must convert to twist-boat forms, whereas axial leaving groups are ideally oriented for elimination. In consequence, substituents may leave the solvolysis of cyclohexanes with axial leaving groups almost unaffected, but can well influence the ease of twist-boat formation from the equatorially substituted compounds.

In order to clearify such possible differences we calculated with the MM2 force field[14] the strain energy differences ΔSI (C, TB) between chair C forms with e-substituents and twist-boat forms TB with nearly anti-periplanar orientations of leaving group to a β-hydrogen, and compared ΔSI (C, TB) for cyclohexanes

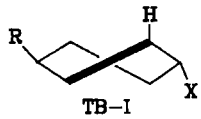
with and without 4-*tert*-butyl groups (R = CMe_3 and R = H). The leaving group X was simulated by a methyl group, which for unhindered positions does not lead to significant deviations[1] and will have even less influence on ΔSI for R = CMe_3 or R = H.

The twist-boat intermediates obtained by force field minimization show X−Cα−Cβ−H arrangements which do not quite reach 180° (Scheme 1); a calculated strain energy profile (Fig. 1), however, demonstrates that relatively little additional energy would be needed to approach an almost ideal antiperiplanar elimination geometry. Noticeably, the introduction of a *trans*-4-*tert*-butyl group, or even annelation to the steroid B-ring in **3e**, does not lead to a destabilization of the twist-boat intermediate, compared to unsubstituted cyclohexane (see Scheme 1).

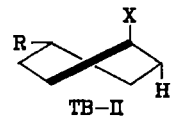
Scheme 1. Geometries and strain energy differences (ΔSI) between cyclohexane chair forms (C) with equatorial leaving group X and twist-boat intermediates (TB)[a]



1e–C

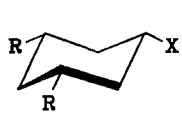


TB–I

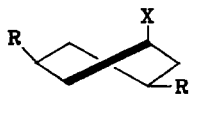


TB–II

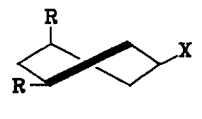
R = CMe_3	φ	59°	145°	170°	
	ΔSI(C,TB)	–	6.0	6.6	ΔG^* 23.75
R = H	ΔSI(C,TB)	–	5.9	7.2	ΔG^* 23.87



2e–C



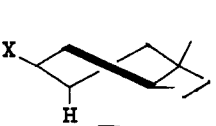
TB–I



TB–II

R = Me	φ	59°	168°	142°	
	ΔSI(C,TB)	–	8.4	8.4	ΔG^* 24.00

3e



TB

Andro-	φ	59°	180°	
stanes	ΔSI(C,TB)	–	6.6	ΔG^* 23.85

[a] From MM2 calculations (see Table 5), except **3e**-TB (MM1 calculation)[13], for X = Me as leaving group model; X = OH leads to similar differences between **1e** and **3e** (Table 5).

φ: Torsional angle X−C−Cβ−H (°); ΔSI (kcal/mol);
ΔG^*: Exp. free activation energy in HFIP at 25°C (Table 2) (kcal/mol).

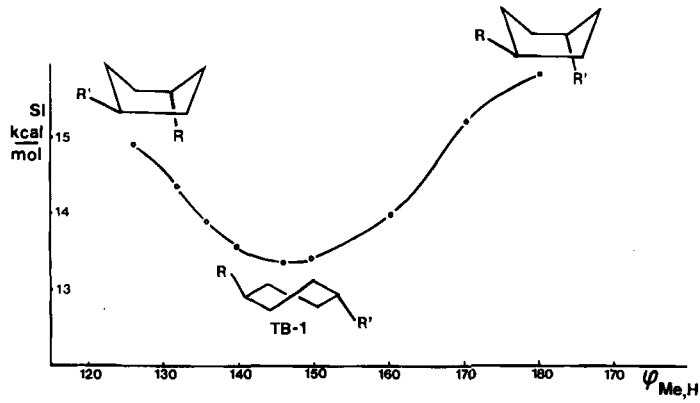


Fig. 1. Strain energy profile for *trans*-1-*tert*-butyl-4-methylcyclohexane

In contrast, *cis*-3,5-disubstituted cyclohexane can form suitable twist-boat intermediates only at the expense of approximately 2.5 kcal/mol additional strain energy (see Scheme 1), and thus is expected to react slower than the other cyclohexanes, which is indeed borne out by experiment (Table 2). Although 1,3-hydride shifts in the 1,3-dimethylcyclohexanes are favoured[7g], this is kinetically unsignificant as elimination dominates by 98% in HFIP and is accompanied by little 1,3-hydrogen shift[7g].

Table 2. Solvolysis kinetics of cyclohexyl tosylates in HFIP[a]

Compound	$k_{25} \cdot 10^5$ (s^{-1})	ΔG^*_{25} (kcal/mol)	ΔH^* (kcal/mol)	ΔS^* (cal/deg. · mol)	k_s/k_c
1e	2.38	23.75	18.1	−19	224[b]
1a	7.25	23.09	20.1	−10	20[b]
2e	1.54	24.00	–	–	–
2a	2.87	23.64	19.0	−16	–
3e[c]	2.00	23.85	18.8	−17	–
3a[c]	16.6	22.61	21.6	−3	–

[a] **1** 4-*tert*-butylcyclohexanes, **2** *cis*-3,5-dimethylcyclohexanes, **3** 3β/3α-androstanes, with alternatively eq or ax tosyloxy substituent. Average errors: k and ΔG^* (at 25°C) ±0.5%; ΔH^* ± 2%; ΔS^* ± 3 e.u.; k values for (3 to 5) different temperatures see Table 3. Measurements in hexafluoroisopropyl alcohol + water = 97 + 3 (w/w). – [b] From k in 50% ethanol/water[5] and in HFIP at 45°C. – [c] Measurements by *N. Becker*, Dissertation, Universität Saarbrücken 1985.

In contrast to the cyclohexanes with equatorial tosyloxy groups (**1e**, **2e**, **3e**) the axial counterparts **1a**, **2a**, **3a** show rate variations of up to 500%. This cannot be due to different X−Cα−Cβ−H torsional angles, which are invariably close to 180° (±5°), or to a change of, e.g., solvent participation. *Casadevall* et al.[6] have observed k_s/k_c variation only by substituents in β-, but not in not hindering γ-position. The transition states, however, will also resemble the olefins; we have

approximated these possible strain difference contributions by calculation of ΔSI (RX – en) between the sp^3-educts and the corresponding substituted olefins (Scheme 2). The decrease of experimental ΔG^* values from **2a** to **1a** to **3a** by up to 2 kcal/mol is indeed reflected in the calculated SI-gain from educt to olefin, which also reaches approximately 1.8 kcal/mol more for the steroid **3a** (Scheme 2). Thus, not only the predominant Δ^2-olefin formation over Δ^3 from 3-substituted steroids can be explained by the force field model[7g], but also the higher reactivity of the steroid. Only the 4-*tert*-butyl substituent has a smaller influence on ΔSI (RX – en) of 0.35 kcal/mol (by comparison with the unsubstituted cyclohexyl system, with X = CH_3 as leaving group model). In consequence, only for this case, and only approximately, the Winstein-Holness equation can apply. *Hückel* et al. have already observed noticeable solvolytic differences between cyclohexanes with equatorial alkyl groups in 3- and 4-position; they concluded that the Winstein-Holness equation should not be used in such cases[15a,b,c], which obviously also include related decalin or steroid frameworks. *Hückel* also concluded already in 1959, that the cyclohexane chair changes its form during solvolysis[15d].

Scheme 2. Axially substituted cyclohexanes[a]

	1a	**2a**	**3a**
ΔG^* (kcal/mol)	23.09	23.64	21.60
k (10^5 s^{-1})	2.9	7.2	16.6
$\Delta\Delta G^*_{a-e}$	0.66	0.36	1.24
ΔSI_{a-e}	1.70	1.84	1.86 (for X = Me)
ΔSI_{a-e}	0.53	[b]	0.59 (for X = OH)
ΔSI (RX – en)	2.28	1.49	3.26 (for X = Me)[c]
ΔSI (RX – en)	1.30	[b]	2.10 (for X = OH)[c]

[a] ΔG^* and k: solvolysis data with X = OTs in HFIP at 25°C; $\Delta\Delta G^*_{a-e}$: difference ax R'OTs – eq R'OTs; ΔSI_{a-e}: strain energy (MM2 calculations) between ax and eq X; ΔSI (RX – en): between axially substituted system and the corresponding olefin in its lowest energy conformation. SI (RX – en) values for cyclohexane without additional substitution: 1.94 (with X = Me); 0.87 (with X = OH); ΔSI_{a-e} 1.78 (X = Me); 0.57 (X = OH). SI values and details see Table 5. – [b] Not calculated. – [c] For the Δ^2 olefin; Δ^3 olefin see Table 5.

Table 3. Rate constants for solvolysis in HFIP at different temperatures (°C)[a] (in 10^5 s^{-1})

1e	20.7: 1.48	30.3: 4.37	40.5: 11.6	49.3: 25.8
1a	20.0: 3.83	30.3: 15.4	40.5: 38.9	49.3: 103.0
2e	–	30.0: 2.7	–	50.0: 11.0
2a	–	30.0: 5.37	40.0: 12.4	50.0: 40.4

[a] See foot notes to Table 2. For androstanes (**3e**, **3a**) see *N. Becker*, Dissertation, Universität Saarbrücken 1985.

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Experimental Part

NMR-Spectra: Bruker HX 90/WH 90 (^{1}H: 90 MHz, ^{13}C: 22.2 MHz) or AM 400 instruments (^{1}H: 400 MHz, ^{13}C: 100.1 MHz). Some ^{13}C-shifts were determined graphically in the product mixtures and are therefore accurate to only $\pm$0.1 ppm; others (olefins) $\pm$0.02 ppm (Table 4).

Product Analysis: Typically 40 mmol of tosylate in 20 ml of solvent with 45 mmol of pyridine was solvolyzed for 15–20 half-life times in sealed ampoules (temperatures see Table 1). After cooling 10 ml of carbon disulfide or trichlorofluoromethane was added; the solution was washed first with dilute hydrochloric or acetic acid, then with water, and dried over sodium sulfate. The solvent was distilled off to 90%, and the remaining solution first analyzed by GLC (5% diethyleneglycol succinate on Chromosorb PAW 60/80, 2 m + 1/4") and, for the HFIP-reaction, by ^{13}C NMR at 100 MHz. For ^{13}C NMR measurements carried out before the AM400 instrument became available (reactions in acetone/water and in TFE) the olefins were distilled off (to at least 90%) over a 20 cm Vigreux column, and the residual solution, containing mostly substitution products, was measured by ^{13}C NMR spectroscopy at 22.2 MHz.

The olefins were identified by GLC and ^{13}C NMR shift (Table 4a) comparison to olefin mixtures obtained from epimeric 4- and 2-*tert*-butylcyclohexyl tosylates upon base treatment. The alcohols (see Table 1) were compared by GLC and ^{13}C NMR with authentic samples. Other substitution products were identified largely on the basis of the ^{13}C NMR shifts of the functional Cα-carbon atoms, which agreed within the expected error with shifts calculated with literature increments (Table 4b); all other signals in the vicinity of calculated shifts were present in the observed spectra, but could not be unambigously assigned due the heavily overlapping lines. The substitution product assignment was supported by GLC, which, however, led only to partial resolution of the TFE- and HFIP-ethers. GLC of TFE-products showed 4 peaks I–IV with the following areas (in %) (from **1e**/**1a**, respectively) I (70/27); II (83/18); III (5/7); IV (4/49); similarly for substitution products in HFIP: I (35/10); II (24/3); III (21/9); IV (20/17). The comparison with ^{13}C NMR signal areas and between the main products from **1e** and **1a** establishes that for TFE-ethers II = **1a**-OR; IV = **1e**-OR, and for HFIP-ethers I = **1e**-OR; II = **1a**-OR. The ^{13}C NMR spectra from TFE-products showed additional Cα-signals at 81.4 and 80.7 ppm, from HFIP-products at 81.9

Table 4. ^{13}C NMR shifts of solvolysis products

Table 4a. *tert*-Butylcyclohexenes[a)]

	Δ^1	Δ^2	Δ^3
C1	145.40	128.04	127.58
C2	117.58	129.28	126.87
C3	25.74*	46.21	26.97
C4	24.76*	27.69*	44.46
C5	23.79$^+$	26.19*	24.24
C6	22.88$^+$	23.14	22.62
C7	35.36	32.82	34.45
C8,9,10	29.18	25.41	27.30

Table 4b. Etherification ^{13}C NMR shifts ($\delta_{ROR'} - \delta_{ROH}$)[b]

	R′ = CH_2CF_3[c]			R′ = $CH(CF_3)_2$[d]		
	eq	ax	Ref.[7g]	eq	ax	Ref.[7g]
Cα	6.05	9.75	10.1	12.95	13.0	13.0
β	−3.95	−2.9	−3.6	−3.75	−3.7	−3.7
γ	−0.9	−1.2	−0.8	0.1	−1.1	−0.7
δ	−0.4	[e]	−0.3	0.7	[e]	−0.5

[a] In ppm from int. TMS; measured in $CDCl_3$ (10 ± 5%); exchangeable assignments: *, + Assignment based on related compounds[16]. – [b] Only signals of the predominating ethers (**1e**, **1a**) could be evaluated; shift differences to the parent alcohol[17] in ppm; measurements: [c] In $CFCl_3$ (10 ± 5%); OCH_2 66.1 ppm (J_{CF} = 33 Hz); CF_3 125.3 ppm (J_{CF} = 270 Hz), for e and a isomers. – [d] In $CDCl_3$ (3 ± 2%); OCH 74.4 ppm (J_{CF} = 32 Hz); CF_3 121.5 ppm (J_{CF} = 290 Hz) for e and a ethers. – [e] Not assigned. – Ref.[7g] refers to values measured with the conformationally inhomogeneous cyclohexyl ethers.

and 77.8 ppm, which, together with the GLC observation, indicate the formation of at least 3 different hydride shift substitution products; these, however, amount to only ≈5% (in TFE) and ≈1% in HFIP and were not analyzed further. The accuracy of the substitution product composition (Table 1) varies from ±2% (for small amounts, such as **1e**-ROR′ from **1e**-ROTs in TFE) to ±5% for larger amounts (50–90%).

Kinetic measurements were carried out by conductometry as described earlier[1] using, however, an automatical measuring system (MESY), based on a 8 bit microcomputer (Apple II+), suitable interfaces, timer, and A/D converter. The system allows for digital registration of up to 8 simultaneous experiments in time sharing mode, using up to 500 points for each run (vertical resolution with, e.g., a 12 bit converter 11 ppm), for the elimination of spurious signals, for the subsequent manipulation of the evaluated data, as well as for the application of least square analysis on the basis of integrated rate equations.

Compounds were either commercially available or prepared by literature procedures[2].

Table 5. MM2 calculated strain energies (kcal/mol)[a]

	X = Me[a]		X = OH[a,b]		Olefin I[c]	Olefin II[c]
	e-X	a-X	e-X	a-X		
Cyclohexane	2.51	4.29	2.65	3.22	2.35	–
TB	8.39	9.68				
1	7.35	9.05	7.54	8.07	6.77	10.06
TB	13.34	13.92				
2	2.24	4.08	–	–	2.59	6.25
TB	10.66	10.67				
3[d] TB	27.01	28.87	27.12	27.71	Δ^2: 25.61	Δ^3: 27.13

[a] In chair form; for X = Me also in twist-boat forms (TB). – [b] With 3 C_α-OH rotamers weighted, except for **3** (SI of the most stable conformation). – [c] Lowest (I) and next higher (II) energy structure. – [d] From *U. Buchheit*, Dissertation, Universität Saarbrücken 1985.

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