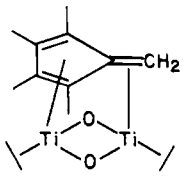
is essentially a single σ bond, without significant contribution from the olefinic structure



The Ti(1)-C(10) distance of 3.205 (6) Å and the normal Ti(1)-C(7) distance of 2.402 (6) Å indicate that there is no interaction between the methylene group and Ti(1). The ring A-Ti(1)-ring B angle of 140.6°[9] is close to the 145.8° and 145.6° observed in $(Cp^*_2Ti)_2N_2$.[10] The bridging CH_2 therefore produces little distortion of the Cp^*_2Ti unit. However, the angle between the Ti(1)-O(1)-O(1′) and Ti(2)-O(1)-O(1′) planes is 158.8°, producing an extremely short Ti-Ti distance of 2.725 (2) Å [compare this to the 3.336 (4) Å in $(\eta^5\text{-}C_5H_5)_2Ti\text{-}\mu\text{-}(\eta^1\text{:}\eta^5\text{-}C_5H_4)\text{-}Ti(\eta^5\text{-}C_5H_5)$ for which a single Ti-Ti bond is proposed,[3] or the shortest Ti-Ti distance previously observed, 2.891 (1) Å in $(C_5H_5)_6Ti_6O_8$].[11] However, there can be no Ti-Ti bond, since we are dealing formally with Ti(IV), d°. The folding is produced by the strong C(10)-Ti(2) bond.

If the usual electron counting rules are followed, Ti(1) has 16 electrons and Ti(2) only 12. The extreme electron deficiency of Ti(2) manifests itself in the highly unsymmetrical Ti-O distances to the bridging oxo ions: Ti(1)-O is 1.961 (3) Å whereas Ti(2)-O is only 1.789 (3) Å.

It is becoming apparent that N_2O functions as a source of a bridging O atom in its reactions with Cp_2M derivatives of the early transition metals. In addition to the present work, examples have now been found for Ti,[5] V,[4] and Mo and W.[12] These aspects as well as the reactivity of I are being further investigated.

Acknowledgment. We thank the National Sciences and Engineering Research Council of Canada and the University of New Brunswick Research Fund for financial support of this work.

Supplementary Material Available: Tables of fractional atomic coordinates, thermal parameters, and bond distances and structure of I (5 pages). Ordering information is given on any current masthead page.

(9) The ring A-Ti(1)-ring B angle is defined by using the center of the rings A and B as terminus.
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Conformational Mobility in 1,4-Bridged Cyclooctanes. ^{13}C NMR Evidence for Facile Chirality Inversion

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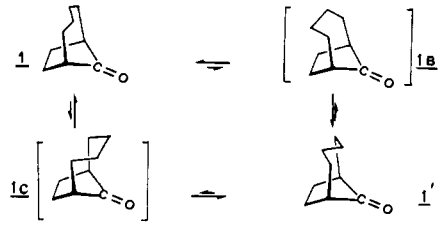
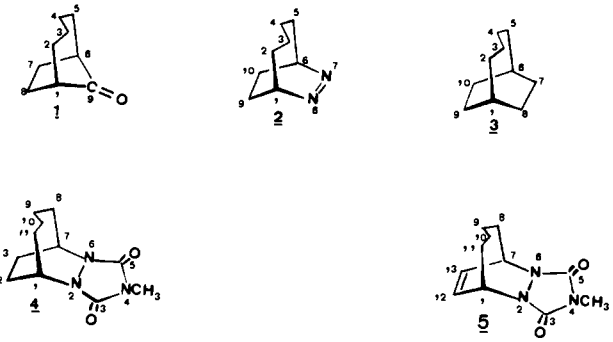
The family of cyclooctane conformers has been investigated both theoretically by means of semiempirical strain energy calculations[1] and experimentally by dynamic NMR (^1H, ^{19}F, and ^{13}C)[2] and X-ray diffraction.[3] Universal agreement exists concerning the cyclooctane minimum energy conformation, which has been shown to be the boat-chair (BC). 1,4-Bridged cyclooctanes **1-5** are expected to retain some of the flexibility of the cyclooctane system but are also expected to behave similarly to cyclohexenes[4] as far as the dynamics of the four-membered bridge is concerned.[5] In order to elucidate the structure and dynamics of 1,4-bridged cyclooctanes, we synthesized compounds **1**,[8] **2**,[9] **3**,[10] **4**,[11] and **5**[11] and investigated their 25.2-MHz ^{13}C NMR spectra (^1H noise decoupled) as a function of temperature.

Scheme I





All compounds produced slow-exchange ^{13}C NMR spectra which are in agreement with 1:1 mixtures of the chiral structures **1-5** and their mirror images **1′-5′**. In the fourth column of Table I the change in the molecule's symmetry group during the exchange-producing process is given. In the fifth column the chemical shifts at two representative temperatures are displayed and exchanging signals are grouped together. Line-shape analyses were performed[12] by employing suitable exchanging sites, and with these calculated first-order rate constants, activation parameters were obtained which are given in Table II.

In Scheme I a probable reaction sequence for the conformational mobility of **1** is displayed. **1** has the choice of racemizing

†The Technological Institute, Gregersensvej, DK2630, Tåstrup, Denmark.
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(5) It has been suggested[6] that the *N*-phenyl derivative of **5** should exist as a mixture of diastereomeric "boat" conformers which interconvert rapidly at room temperature. Lehn and Wagner,[7] on the other hand, argue that the $-(CH_2)_4-$ bridge in this system probably adopts a conformation in which H/H eclipsing is minimized but do not specify the structure.
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Scheme II

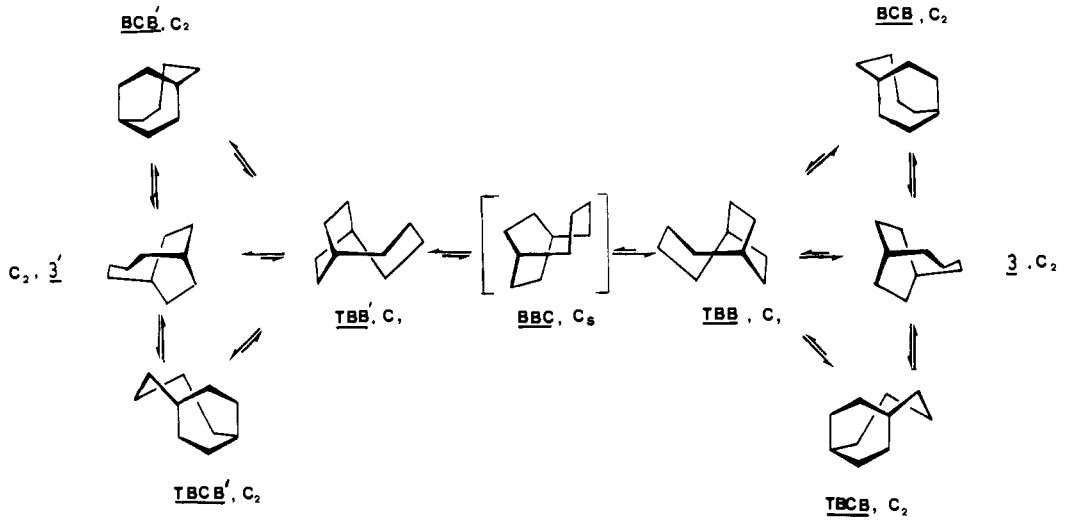

Table I. ^{13}C NMR Chemical Shifts of Compounds 1-5 at Two Representative Temperatures

compd	temp, °C	solvent	change of symmetry group	chemical shifts, ppm downfield from Me_4Si (assignments)
1/1'	-113.8	$CF_2HCl/C_6D_5CD_3$	$C_1 \rightarrow C_s$	228.4 (9); 47.2 (1/6); 31.6; 27.7; 25.7
	-139.0	(3:1)		228.4; 48.6, 45.7; 31.1, 30.0; 31.1, 24.5; 27.1, 23.7
2/2'	-68.0	$CHCl_2F/CD_3COCD_3$	$C_1 \rightarrow C_s$	62.2 (1/6); 32.5; 23.6; 19.6
	-122.0	(1:1)		62.5, 61.2; 34.2, 29.8; 23.3, 22.6; 21.5, 17.1
3/3'	-68.2	propane/$(CD_3)_4Si$	$C_2 \rightarrow C_{2v}$	39.7 (1/6); 30.3; 28.0; 26.5 (7/8/9/10)
	-111.1	(5:1)		39.5; 30.1; 27.9; 27.9, 24.9
4/4'	22.5	CBr_2F_2/CD_2Cl_2	$C_1 \rightarrow C_s$	149.5 (3/5); 47.9 (1/7); 34.7 (12/13); 24.6 (N-CH_3); 23.4; 22.8
	-113.3	(1:1)		149.0; 49.6, 46.8; *a*; 25.3; *a*; *a*
5/5'	22.5	CBr_2F_2/CD_2Cl_2	$C_1 \rightarrow C_s$	149.5 (3/5); 127.4 (13/13); 50.3 (1/7); 34.2; 25.2 (N-CH_3); 23.5
	-34.7	(1:1)		148.5, 148.3; 129.3, 124.3; 50.5, 49.0; 35.7, 32.2; 25.3; 23.5, 22.3

[a] Signals too broad to determine chemical shift accurately.

Table II. Eyring Parameters for the Conformational Mobility of Compounds 1-5

rate process	$\Delta G^{\ddagger}$ [a-c]	$\Delta H^{\ddagger}$ [a-c]	$\Delta S^{\ddagger}$ [a,b,d]
$1 \rightleftarrows 1'$	6.2 ± 0.1	6.8 ± 0.1	2.0 ± 0.4
$2 \rightleftarrows 2'$	8.8 ± 0.2	6.9 ± 0.3	-6.3 ± 1.5
$3 \rightleftarrows 3'$	8.4 ± 0.2	7.8 ± 0.2	-1.7 ± 1.3
$4 \rightleftarrows 4'$	9.4 ± 0.1	6.9 ± 0.2	-8.4 ± 1.1
$5 \rightleftarrows 5'$	11.1 ± 0.1	11.7 ± 0.2	2.0 ± 1.0

[a] At 25 °C. [b] Deviations are standard deviations. [c] In kcal/mol. [d] In eu.

via two diastereomeric transition states, namely, **1B** or **1C**. It is difficult to decide on the basis of available force-field data on cyclooctane[13] and cycloheptanone[14] which transition state is the preferred one. The barrier height to ring inversion in **1**, $\Delta G^{\ddagger}$ = 6.2 kcal/mol, may be compared to the one in cyclohexene, which was found to be 5.2 kcal/mol at -164 °C.[15]

The interrelationship of various conformers of **3** is given in Scheme II. One possibility is that **3** exists as a mixture of conformers, namely, **3**, BCB, and TBCB and their respective mirror images, all possessing C_2 symmetry (Scheme II). The interconversion of these three conformers must still be fast at -160 °C according to the ^{13}C NMR measurements. This is in agreement with the calculated barrier height for the chirality inversion in perhydro[0.0]paracyclophane, which is less than 2 kcal/mol.[16] Alternatively, the ^{13}C NMR spectrum at -160 °C could result from two or only one populated conformer of C_2 symmetry but not from conformer TBB (C_1 symmetry). The observed barrier height (see Table II) can be understood by solely taking the cyclooctane potion of **3** into account[13] and neglecting the contribution of the $-CH_2CH_2-$ bridge. On the assumpation that BBC is the transition state and TBB a high-energy intermediate on the energy hypersurface, a barrier of ca. 8 kcal/mol in agreement with the observed value can be calculated. This value is also very similar to the barrier to ring inversion in cyclooctane.

The barrier heights for ring inversion in compounds **2** and **4** lie in the same range as the one found for **3**. Two situations are possible: (i) only one conformer, characterized by eclipsed hydrogens on carbon atoms 9/10 and 12/13 of **2** and **4**, respectively, is present due to the constraint imposed by the azo or urazole moieties and nonbonding interactions, or (ii) an equilibrium exists between diastereomeric conformers ("twisted" and "eclipsed"), which is still fast on the NMR time scale at the temperatures employed. A study on *cis*-1,2-diazacyclooctene[17] furnished a barrier to ring inversion of $\Delta G^{\ddagger}$ = 8.1 kcal/mol which is very similar to the value for **2**. In contrast to our results for **2**, recent force-field calculations of the related 7,8-diazabicyclo[4.2.1]-non-7-ene have predicted that the boat form was of the lowest

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energy.[18] The ring inversion barrier is somewhat higher in **5** than in **4** (see Table II). This could be due to the restraint caused by the double bond. For cyclooctene, experiments[19] and force-field calculations[20] resulted in a smaller activation barrier for the ring inversion ($\Delta G^{\ddagger}$ = 8.2 kcal/mol).

Acknowledgment. We thank Professors F. A. L. Anet, J. F. M. Oth, and J. D. Roberts for helpful discussions and the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung for their financial support.

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Solid-Phase Synthesis of Hentriacontanucleotide

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Solid-phase synthesis is very attractive when preparing polynucleotides of defined sequences, since the synthesis of polypeptides (~30 amino acids) has been very successful on various polymer supports.[1] There were some difficulties in bringing fruitful results with solid-phase synthesis in the polynucleotide field. This relative lack of success was probably due to inefficient coupling methods in forming an internucleotidic phosphate bond between two nucleoside derivatives. Although the classical phosphodiester method to make phosphate bonds is powerful and accurate,[2] it has certain inherent disadvantages, including low yields in the coupling reaction. Accordingly, solid-phase synthesis of polynucleotides by the phosphodiester method was not successful.[3] Recent improvements by several groups in the phosphotriester approach have changed this situation drastically.[4] When a slight excess of one coupling unit is used, it is practical to drive a coupling reaction almost to completion by a liquid-phase synthesis, forming a phosphotriester bond.[5] Very recently we introduced a new strategy, a block coupling phosphotriester approach on a polymer support to synthesize oligodeoxyribonucleotides of defined sequences.[6] We now report the synthesis of a hentriacontanucleotide, d(TGGTGCACCTGACTCCTGAGGAGAAGTCTGC), on the poly(acrylyl morpholidate) support **6b** by using a similar strategy. The essential features of the approach are very simple: (a) sequential addition of appropriately protected trinucleotide blocks **7** to the solid-support **6b** in the presence of a coupling reagent, 2,4,6-triisopropylbenzenesulfonyl tetrazolide (TPSTe), (b) masking of any unreacted 5′-hydroxyl group with acetic anhydride, and (c) removal of the dimethoxytrityl group from the polynucleotides bound to the support to afford a new 5′-hydroxyl function for the next coupling reaction.

Table I

step	solvent or reagent	amount, mL	shaking, min	no. of operations
1	2% BSA	10	0.5	1
2	$CHCl_3$-MeOH (7:3 v/v)	10	1	2
3	pyridine	10	1	2
4	trimer (5 equiv) in pyridine	10	coevaporation	2
5	TPSTe (15 equiv) and pyridine	8	180	1
6	pyridine	10	1	2
7	10% Ac_2O in pyridine	10	60	1
8	pyridine	10	1	2
9	$CHCl_3$-MeOH (7:3 v/v)	10	1	2

In Scheme I, the outline of the approach is described. The commercially available Enzacryl Gel K-2 **1** (Aldrich) was derivatized with ethylenediamine in ethylene glycol to the amino support **2** (0.20 mmol/g of the amino function) as published.[7] 5′-*O*-Dimethoxytrityl deoxynucleoside **3** was reacted with succinic anhydride (1.5 mol equiv) in the presence of 4-(dimethylamino)pyridine (1.5 mol equiv) in pyridine at room temperature overnight to give the monosuccinate derivative **4** in ~80% yield. When **4** was treated with pentachlorophenol (1.1 mol equiv) and dicyclohexylcarbodiimide (3 mol equiv) in dimethylformamide (DMF) at room temperature for 20 h, the activated ester **5** was obtained in ~90% yield. Treatment of the amino support **2** with this ester **5** (2.5 mol equiv) and triethylamine (2.75 mol equiv) in DMF, shaking at room temperature for 20 h, gave the dimethoxytrityl support **6a**. Any unreacted amino group **2** was masked by treatment with phenyl isocyanate (10% solution in pyridine) at room temperature for 1 h and the dimethoxytrityl group was removed by treatment with a 2% solution of benzenesulfonic acid (BSA) in $CHCl_3$-MeOH (7:3 v/v) at room temperature for 30 s. The amount of released dimethoxytrityl group from the support **6a** was estimated by an absorption spectrum in a 1% BSA solution in $CHCl_3$ [λ_{max} 507 nm, ϵ_{max} 92 100 M^{-1} cm^{-1}] and is in agreement with that of the nucleoside liberated from the support **6b** by treatment with aqueous ammonia (28%) at 50 °C overnight (0.177 mmol/g of the nucleoside). Each trinucleotide addition cycle started from step 4 (Table I), coevaporation of the support **6b** (0.80 g) and the trinucleotide **7** (5 mol equiv) in pyridine twice to remove hydroxylic solvents. TPSTe[8] (15 mol equiv) and anhydrous pyridine (8 mL) were added to the residue, and the reaction mixture was shaken for 3 h (step 5) and filtered. The support was washed with pyridine twice (step 6) and treated with a 10% solution of acetic anhydride in pyridine for 1 h to mask the unreacted 5′-hydroxyl group (step 7). The mixture was filtered and washed successively with pyridine (step 8) and $CHCl_3$-MeOH (7:3 v/v, step 9). The dimethoxytrityl function was removed from the polynucleotide bound to the support by treatment with a 2% BSA solution in $CHCl_3$-MeOH (7:3 v/v, step 1) for 30 s at room temperature. The new coupling cycle was resumed after washing the support with $CHCl_3$-MeOH (step 2) and pyridine (step 3). The first coupling unit, a derivative of the trinucleotide **7** (B_1 = C^{Bz}, B_2 = T, and B_3 = $G^{i\text{-}Bu}$ in Scheme I), was coupled to the 5′-hydroxyl N-benzoylated deoxycytosine polymer **6b**, and nine other trinucleotides with the desired sequences ($A^{Bz}G^{i\text{-}Bu}T$, $A^{Bz}G^{i\text{-}Bu}A^{Bz}$, $A^{Bz}G^{i\text{-}Bu}G^{i\text{-}Bu}$, $C^{Bz}TG^{i\text{-}Bu}$, $C^{Bz}TC^{Bz}$, $TG^{i\text{-}Bu}A^{Bz}$, $A^{Bz}C^{Bz}C^{Bz}$, $TG^{i\text{-}Bu}C^{Bz}$, and $TG^{i\text{-}Bu}G^{i\text{-}Bu}$) were sequentially used to synthesize the 31-mer. The average coupling yield estimated by the absorption spectrum of the dimethoxytrityl

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§Wakunaga Pharmaceutical Company, Ltd., Hiroshima, Japan.
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