Flexible Molecules with Defined Shape, II[1]

Control of *n*-Heptane Conformer Populations by Methyl Substitution or Ring Annulation

Reinhard W. Hoffmann*, Thomas Sander, and Martin Brumm

Fachbereich Chemie der Philipps-Universität Marburg,
Hans-Meerwein-Straße, W-3550 Marburg a.d. Lahn

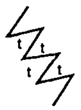
Received April 10, 1992

Key Words: Conformations / Conformational Preferences / Alkanes, branched / Calculations, force-field

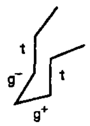
The conformations of a flexible *n*-heptane chain are considered. Six-membered ring annulation at the inner bonds leads to 1,3-disubstituted cyclohexanes, at the outer bonds to dicyclohexylmethane derivatives. Force-field calculations show that these molecules maintain the conformational mobility of the heptane chain to a large degree, yet some populate one particular conformer to more than 80% (up to 99% in the case of **17**). The predominant conformers of the molecules described here allow to represent each of the regular (diamond lattice type) conformations of a heptane chain. Moreover, for the open-chain heptane derivatives the effect of methyl substitution on the conformational preferences has been examined. Finally, the adamantane derivative **32** has been identified in giving the heptane chain a 93% preference for the tg^+g^+t-conformation.

The shape of a molecular backbone, be it rigid or flexible, is responsible for the spatial disposition of any functional groups attached. When dealing with flexible molecular backbones, e.g. linear saturated hydrocarbon chains, the distance between the termini of the chain, or other attached functionalities, as well as their vectorial arrangement will be different for different conformers. The effective (time averaged) disposition of the chain ends, or of two attached functional groups, then depends on the conformer population, which is a function of the relative energy of the various conformers. A situation valuable for molecular design would be one in which a flexible chain has only one or two low-energy conformations, which should be populated at least in excess of 80%. Such molecules will remain fully flexible, but nevertheless have in a weighted time average a well-defined shape.

Here we would like to discuss, to what extent the conformational equilibria of an *n*-heptane chain can be shifted by adding substituents in order to favor just one particular folding of the molecular backbone. The conformer populations of short-chain *n*-alkanes have been investigated by various computational techniques before: *n*-pentane[2–6]; *n*-hexane[5]; *n*-heptane[5,7].



1



2

The *all-trans* conformer, cf. **1**, has been found to possess the lowest energy, followed by rotamers having an increasing number of *gauche* interactions. Rotamers having a g^+g^--sequence of dihedral angles, cf. **2**, are among the high-energy conformations, which actually tend to relax the unfavorable *syn*-pentane interactions by opening of the dihedral angles[3,5,7]. But even these relaxed conformations remain of high energy, i.e. 1.4 to 3.0 kcal above the lowest energy *all-trans* conformation. Thus, molecules tend to avoid such g^+g^--conformations, which are destabilized by *syn*-pentane interactions[8].

This is the clue to favoring certain conformations of a molecular backbone: Substituents may be placed at the molecular backbone in such a way that they will cause unfavorable *syn*-pentane interactions between the substituents or with the backbone in all but one particular conformation. This will then by necessity be the only low-energy conformation populated.

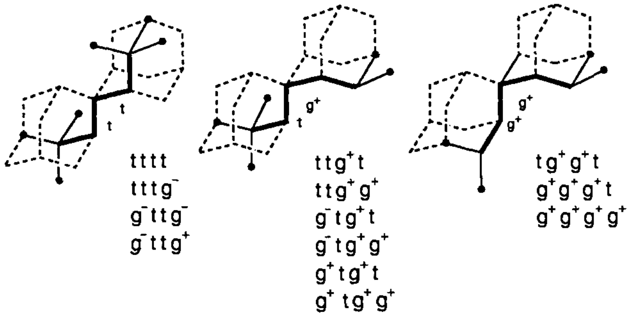
This principle is well-documented in many natural products, exhibiting flexible backbones, yet populating only few conformations of this backbone[9]. Thus, by a judicious placement of substituents on a hydrocarbon chain, the number of available low energy conformations may be substantially reduced[2,6,10].

Modelling of Various Conformations of a C_7-Chain

The conformations of *n*-heptane are described by a sequence of four dihedral angles. There exist 13 different conformations, which are free of skew or of g^+g^--interactions and which correspond to local energy minima. This number allows for enough variety, in order to test whether certain conformations could be rendered to be the predominant one, be it by methyl substitution or by ring annulations. Moreover, the *n*-heptane unit is long enough to be representative for conformations of segments of longer carbon chains. We therefore hope that the principles delineated here can be generalized for longer carbon chains.

0009–2940/92/1010–2319 $ 3.50+.25/0

The 13 conformations of the *n*-heptane chain mentioned above can be projected onto a diamond lattice in order to visualize them (mirror images of those conformations result, if the g^+-notation is changed to g^- and vice versa).



In order to evaluate the relative conformer energies and conformer populations, the force-field MM2[11] as implemented in the program package Macromodel[12] has been used. A spectrum of conformers were generated by changing each of the four initial dihedral values of the input in increments of 60° and letting the force field optimize the geometry to the nearest conformational energy minimum. After elimination of identical structures a set of conformers with their associated strain energies was generated. This output of Macromodel was than used to calculate a Boltzmann distribution at 293 K, taking into account the statistical weight of mirror images and degenerate conformations. In doing so, only conformations were considered whose strain energy was less than 12 kcal/mol over that of the lowest-energy conformer. The results are tabulated below, with the major conformer being depicted.

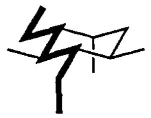
It may be argued that corrections for vibrational and zero-point energy contributions should additionally be made in our theoretical treatment. However, the MM2 force-field was developed to reproduce vibrationally averaged structures and energies[11] at room temperature. Therefore, a calculation of the different vibrational energies of the various conformers is not warranted. Finally, the significance and precision of the calculated conformer populations deserves a comment: In most cases reported below the most stable conformer is populated to $\geq 85\%$. The uncertainty of ca. 0.2 kcal/mol in the strain energies would e.g. effect a value of 85% to $\pm 5\%$. It is therefore clear, that the values reported below will reproduce the trends correctly without being numerically exact.

In the first round we simplified matters by annulating a cyclohexane ring to the C-3 to C-5 core of the *n*-heptane chain. This fixes the internal dihedral angles to *tt* for the diequatorially substituted cyclohexanes, and to *tg* for an equatorially/axially disubstituted cyclohexane. While ring inversion is possible for both series of compounds, only in the equatorially/axially disubstituted cases have the ring invertomers been considered to contribute to the conformational equilibrium.

1,3-Dialkylcyclohexanes

When dealing with *cis*-1,3-diethylcyclohexane, only rotation around the two semicyclic bonds is considered. Placement of two methyl substituents at the central carbon of a heptane chain causes these two bonds to rotate into a *trans*-conformation[13]. This way, due to the *gem*-dimethyl effect, the *tttt*-rotamer **3** can be made to predominate.

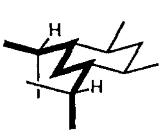
3 tttt 95%



4 g^+ttt 77%

5 g^+ttg^- 83%

6 g^-ttg^+ 83%

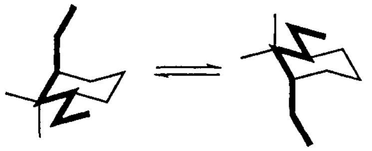


7 g^+ttg^+ 88%

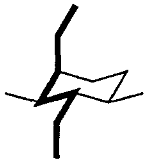
By suitably placing methyl substituents in equatorial or axial position on the cyclohexane ring it became possible to favor other conformers of the heptane chain having a central *tt*-arrangement. Compound **5** for instance is representative for an all-equatorially alkylated cyclohexane. Here, the side chains should alternatingly point upwards and downwards. Such compounds have been synthesized in the hope that they would form stable discotic mesophases[14]. As this requires an essentially flat arrangement of all side chains, these compounds failed to form discotic phases. The chain conformation of **6**, the g^-ttg^+-conformer, can be attained to a higher extent by placing the methyl substituents in the side chains, cf. **7**. Actually, **7** encompasses all *gttg*-possibilities, depending on which branch of the side chain is considered.

Likewise, all of the six possible heptane conformers having a central *tg*-conformation can be modelled by using a 1,3-*trans*-diethylcyclohexane skeleton. Again by placing methyl groups on the ring or at the side chains each of the possible side chain rotamers can be made to predominate. Of course, **8** will exist as a 1:1 mixture of degenerate ring invertomers.

The $g^-tg^-g^-$-conformation can be modelled both by the compounds **10** or **11**. The latter gives a slightly better bias, due to the *gem*-dimethyl effect. Side chain branching then



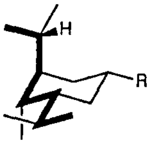
ttg^-t 44% **8** tg^-tt 44%



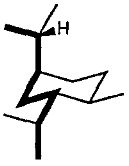
9 g^+tg^-t 83%

10 $g^-tg^-g^-$ 84%

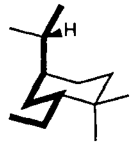
11 $g^-tg^-g^-$ 90%



12 ttg^-g^- 88%



13 $g^+tg^-g^-$ 93%

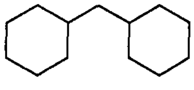


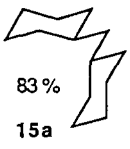
14 g^-tg^-t 95%

allows to model the remaining rotamers with a *tg*-central unit, cf. **12**–**14**. The conformational bias is strongest in **14**, which features a *gem*-dimethyl substitution. The latter three compounds may also be used to model the $g^-tg^-g^-$-conformation of a heptane chain with higher efficiency than does **10**. The conformational equilibria of **13** and **14** have been treated excluding ring inversion, which may be precluded by a further conformational anchor. If ring inversion in **13** and **14** is allowed for, the shown conformations will be populated to only 61 and 14%, respectively.

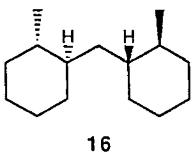
Dicyclohexylmethane Derivatives

Of course, if the three conformers of a heptane backbone are of interest, in which the central bonds have a g^+g^+-arrangement, six-membered ring annulation as a tool for stabilizing certain conformations may be applied only to the outer bonds of the heptane chain. For this reason we examined derivatives of the dicyclohexylmethane **15**. The Macromodel study shows that **15** should populate the C_2-symmetric conformer **15a** already to 82% even if the ring invertomers are included. This tendency may be further enhanced by methyl substituents on the ring.

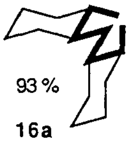

15



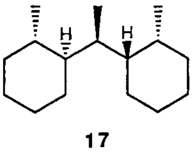
15a



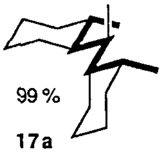
16



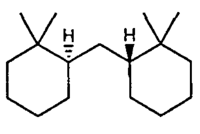
16a



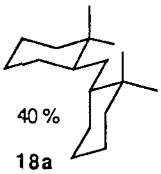
17



17a

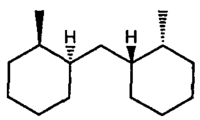


18

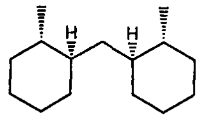


18a

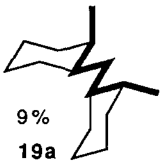
An outstanding example is given by **16**. This fully flexible molecule models not only the g^+ttg^+-chain indicated, but also the *tttt*-, *tttg*-, tg^+tg^+-, tg^+tt-, and tg^+g^+t-chains, if the C_7-chain is superimposed on this molecule in different orientations. A molecule of the same type is the less symmetrical **17** which essentially populates just conformation **17a**. This represents not only the g^+ttg^--chain as marked, but also the *tttt*-, *tttg*-, tg^+tg^--, and tg^+g^+t-chains very well. If the lower symmetry of **17** is of concern, the C_2-symmetrical **18** was considered as an adequate substitute. Surprisingly, the expected conformation **18a** was found not to be the most stable one. While being populated to 40%, a slightly distorted conformer (dihedral angles 178°, −77°, −77°, 178°) related to **18a** was found to be populated to 44%. Therefore, among the dicyclohexylmethane derivatives compound **17** remains at present the example with the strongest conformational bias. Permutation of the substitution pattern leads from **16** via **18** to **19** and **20**.



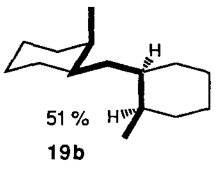
19



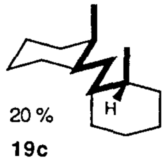
20



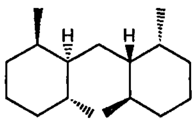
19a



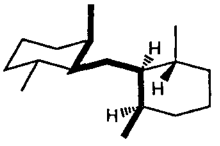
19b



19c



21



21a

The calculations show that the conformer **19a** corresponding to **16a** will not be populated to a large extent. The major conformer, albeit to only ca. 50%, should be **19b**, which corresponds to a $g^-g^-g^-g^-$-chain, as marked. The structure **19b** comprises also the $tg^-g^-g^-$- and the tg^-g^-t-arrangement of a heptane backbone. Thus, all three conformations of a heptane chain with a central g^+g^+ (or g^-g^-)-conformation can be modelled by **19**. To do this more effectively, the moderate preference for the conformation **19b** has to be enhanced. This may be achieved by placing two additional methyl groups on the system, as shown with **21**. Now conformer **21a** is favored to 93%. The molecule **21** is in so far remarkable, as 10 of the 13 regular (free of g^+g^- or skew) conformations of a heptane chain may be projected onto its preferred conformer **21a**. In **21**, ring inversion in both rings as well as rotation around the semicyclic bonds are easily possible. **21** thus represents a conformationally mobile skeleton, which nevertheless may be used to model extended carbon chains (*tttt*), U-turns (g^-ttg^+) or building blocks for helical molecules (g^-ttg^-).

It should be added that the σ-symmetric dicyclohexylmethane derivatives, such as **20**, do not have any conformation available, which is free of (relaxed) *syn*-pentane interactions. These structures are thus of higher energy and even while one conformation of **20** is favored by 83%, its dihedral angles (−178°, −100°, 164°, 177°) show that this conformation may not be projected upon a diamond lattice.

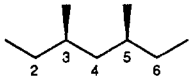
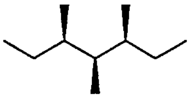
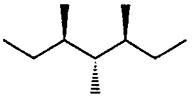
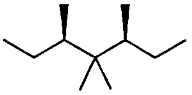
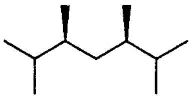
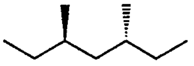
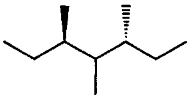
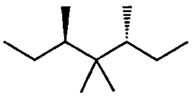
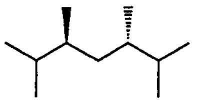
Methyl-Substituted Heptane Chains

In the previous section we discussed molecules in which the conformational flexibility was somewhat restricted by ring annulation. If a heptane chain carries only methyl branches, control of conformer population is much harder to attain. This can be illustrated starting from the meso-3,5-dimethylheptane (**22**). Macromodel calculations on the low energy conformations show that the core bonds of the molecule (the C-3—C-4 and C-4—C-5 bonds) populate the *gt*- or *tg*-conformations to 78%, whereas the terminal ethyl groups still enjoy considerable conformational freedom. This is in qualitative accord with the conformer populations reported for **22** using a "simulated annealing" approach[6]. Further methyl substituents as in **23**—**26** do increase the population of the most stable conformer, but not by a substantial amount. In **23** and **24** the methyl-substituents cause further gauche interactions and decrease the conformational preference of the core bonds for *gt*. Placement of the methyl substituents at the 2,6-positions of the heptane chain, as in **26**, is somewhat more effective to create a conformational bias of the chain.

When considering (±)-3,5-dimethylheptane (**27**) the extended core conformation *tt* should predominate, cf. ref.[6]. This core conformation allows for more conformational freedom of the terminal ethyl groups such that individual conformers are not populated by more than 13%. This holds also, when a third methyl group is placed at C-4. The lowest energy conformation has now the g^+g^+-conformation. This core conformation is shared by the predominant conformation of the *gem*-dimethyl-substituted derivative **29**. Actually, as with **18**, there is a cluster of slightly distorted conformers of the tg^+g^+t-type amounting to 45% of the conformer population. Finally, placing additional methyl groups in the 2- and 6-positions, cf. **30**, causes again the low-energy conformer to have the g^+g^+-core conformation. The *tt*-core conformations predominate among the remaining conformers. A comparison of the conformational preference of **30** with that of the structurally related **16** (93% *tt*-core conformation) and **19** (51% *gg*-core conformation) is instructive. It clearly matters, which of the terminal methyl groups is incorporated into the six-membered ring, when going from **30** to the related dicyclohexylmethane derivatives.

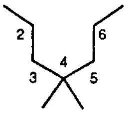
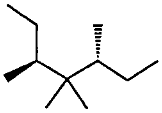
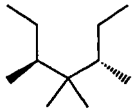
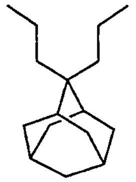
It has been pointed out by Alder[13] that *gem*-dimethyl substitution of a chain causes the next to neightboring bonds

Table 1. Conformational preferences of 3,5-dimethylheptane and derivatives

	Compound	Most Stable Conformer a)	Core Conformation i.e. Bonds 3-4-5
22		22 % $tg^{+}tg^{+}$	78 % ?gt?
23		25 % $g^{+}g^{+}tg^{+}$	58 % ?gt?
24		28 % $tg^{-}tg^{+}$	56 % ?gt?
25		39 % tgtt	73 % ?gt?
26		54 % $g^{+}g^{+}tg^{+}$	71 % ?gt?
27		13 % $g^{+}ttg^{+}$	58 % ?tt?
28		14 % $g^{+}g^{+}g^{+}t$	35 % ?tt?
29		19 % $tg^{+}g^{+}t$	46 % $?g^{+}g^{+}?$
30		17 % $g^{+}g^{+}g^{+}t$	55 % ?tt?

[a] Including enantiomorphous conformations.

Table 2. Conformational preferences of 4,4-dimethylheptane and derivatives

	Compound	Most Stable Conformer a)	Conformation of Outer Bonds, i. e. 2-3 and 5-6
31		46 % $tg^{+}g^{+}t$	94 % t??t
25		39 % tgtt	76 % t??t
29		19 % $tg^{+}g^{+}t$	79 % t??t
32		94 % $tg^{+}g^{+}t$	94 % t??t

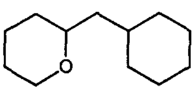
[a] Including enantiomorphous conformations.

to prefer a *trans* conformation. This has been seen in the "simulated anealing" calculations by Wilson[6] on **31**. Our Macromodel calculations on **31** verify this point, as the C-2–C-3 and C-5–C-6 bonds (the outer bonds) should populate to 94% the *t??t*-conformation. The core bonds show no marked preference, being 46% g^+g^+, 41% *tg*, and 5% *tt*. The preference regarding the core bonds can be altered by additional methyl substituents as in **25** or **29** (cf. Table 1). These additional methyl substituents cause a slight degradation in the conformational preference of the outer bonds as seen in Table 2.

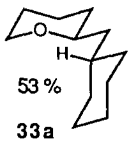
An ultimate molecule in conformational design is found in the heptane derivative **32**: The *gem*-dialkyl-substitution at C-4 causes the outer bonds to adopt the *t??t*-conformation to the same extent (94%) as in **31**. The branching inherent to the adamantane structure now also leads to a g^+g^+ (or g^-g^-) bias for the core bonds. Compound **32** features a seemingly uninhibited C_7-chain pinched at C-4. It is obvious that the chain enjoys maximal conformational flexibility, yet a set of two enantiomorphous conformers ought to be populated to more than 90%!

(Tetrahydropyranyl)methane Derivatives

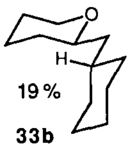
In order to extend the above evaluations, we became interested in compounds in which a CH_2 or CH_3 group is substituted by an ether oxygen. The following comparisons illustrate how this change affects the population of the preferred conformers.



33

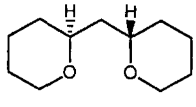


33a

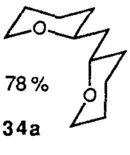


33b

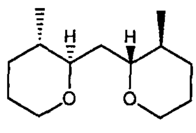
The calculated conformer equilibria for the *mono*-THP compound **33** show that an $O-C-C-C-H$ interaction in **33a** is by 0.6 kcal/mol more favorable than the $H_2C-C-C-C-H$ interaction in **33b**. The bis(tetrahydropyranyl)methane **34** therefore prefers the conformation **34a**, which allows for two of the more favorable $O-C-C-C-H$ interactions.



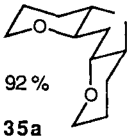
34



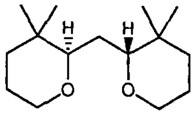
34a



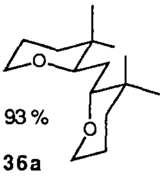
35



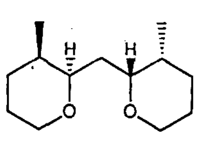
35a



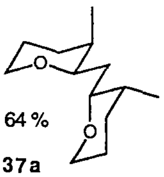
36



36a



37

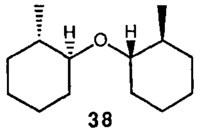


37a

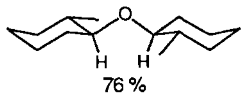
The 78% preference for **34a** may be reinforced by methyl substituents: compound **35** shows no significant differences in conformer populations compared to **16**. Compound **36** features a stronger conformational bias than **18**. On going to the stereoisomer **37**, it is now the conformation **37a**, corresponding to **19a** that is favored. In this case replacement of the $CH_2-C-C-C-H$ interaction in **19a** by an $O-C-C-C-H$ interaction has a noticeable effect. The particular conformation of **37** which corresponds to **19b** is now with a calculated population of 10% the second abundant rotamer.

A significant change in the nature of the conformers results when the central CH_2 group of **16** is changed to an ether oxygen, as in **38**.

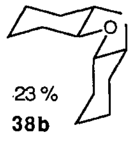
Now the molecule prefers the well-known skew conformation **38a** while the diamond lattice conformation **39b** is the second abundant one. Earlier MM2 calculations on diisopropyl ether have shown[15] that the energy difference between the σ-symmetric and C_2-symmetric conformations is small.



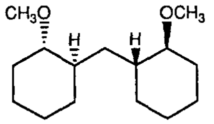
38



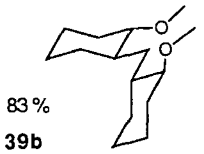
38a



38b



39



39b

If in turn the methyl groups in **16** are replaced by methoxy groups as in **39**, the conformational preference is slightly attenuated: **39a** is favored to only 83% as compared with **16a** (93%).

Calculations

The energies of the various conformers were calculated on a Silicon Graphics 4D/20-workstation by using Macromodel V3.1[12] in the following steps: An arbitrary starting conformation of the molecule was generated in the editor. The energy of this conformation was minimized to the nearest local minimum with the MM2-force field, using Polak-Ribiere conjugate gradient minimization. Next, a file containing 6^n starting conformers was generated by permutation of *n* torsional angles in 60° steps allowing for a minimum distance between nonbonded atoms of 0.5 Å. All these starting conformations were then minimized as above using Batch Min V3.1 as control operator. Of the conformations generated all those were eliminated whose energy was >12 kJ/mol above that of the lowest energy conformation.

For cyclohexane derivatives, for which it was expected that ring inverted conformations should be populated to a significant extent, the above steps were repeated by using ring-inverted starting geometries.

The files generated, containing the energies as well as the cartesian coordinates of all energy-minimized conformations were processed by a Fortran program which eliminated identical conformations, recognized enantiomorphous conformations and calculated the dihedral angles of the main carbon chain. Finally this program calculated the populations of the resulting conformers by a Boltzmann distribution for 20°C using the conformer energies and allowing for degenerate conformations. A typical printout of this treatment for **32** is shown below.

1. column: registration number of the particular conformer
2. column: dihedral angle 1–2–3–4
3. column: dihedral angle 2–3–4–5
4. column: dihedral angle 3–4–5–6
5. column: dihedral angle 4–5–6–7
6. column: energy of the particular conformer
7. column: number of degenerate conformers
8. column: conformer population at 293 K

```
1  −177.41  −56.37  −56.41  −177.42  131.790 kJ/mol  2  93.62%
2   175.84  −61.45  −44.49   −65.24  142.210 kJ/mol  4   2.60%
3  −175.35  −52.41  −55.18   −89.95  143.420 kJ/mol  4   1.58%
4  −101.85   58.95   65.52  −175.80  144.310 kJ/mol  4   1.10%
5  −170.73  −58.01   87.65  −171.39  144.500 kJ/mol  4   1.02%
```

Reproduction of the data discontinued at this point.

---

[1] For part I see: J. L. Broeker, R. W. Hoffmann, K. N. Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5006.

[2] S. Sykora, *Collect. Czech. Chem. Commun.* **1968**, *33*, 3514.

[3] A. Abe, R. L. Jernigan, P. J. Flory, *J. Am. Chem. Soc.* **1966**, *88*, 631.

[4] [4a] R. A. Scott, H. A. Scheraga, *J. Chem. Phys.* **1966**, *44*, 3054. – [4b] K. B. Wiberg, M. A. Murcko, *J. Am. Chem. Soc.* **1988**, *110*, 8029.

[5] S. Tsuzuki, L. Schäfer, H. Goto, E. D. Jemmis, H. Hosoya, K. Siam, K. Tanabe, E. Osawa, *J. Am. Chem. Soc.* **1991**, *113*, 4665.

[6] S. R. Wilson, F. Guarnieri, *Tetrahedron Lett.* **1991**, *32*, 3601.

[7] M. Saunders, *J. Am. Chem. Soc.* **1987**, *109*, 3150.

[8] [8a] P. Tevlin, S. Lafleur, L. E. H. Trainor, *Chem. Phys. Lett.* **1985**, *122*, 581. – [8b] P. W. Smith, W. C. Still, *J. Am. Chem. Soc.* **1988**, *110*, 7917.

[9] [9a] W. C. Still, P. Hauck, D. Kempf, *Tetrahedron Lett.* **1987**, *28*, 2817. – [9b] D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, D. J. Mathre, *J. Am. Chem. Soc.* **1991**, *113*, 7613. – [9c] P. K. Somers, T. J. Wandless, S. L. Schreiber, *J. Am. Chem. Soc.* **1991**, *113*, 8045.

[10] [10a] C. A. Kingsbury, *J. Chem. Educ.* **1979**, *56*, 431. – [10b] J. K. Whitesell, B. Hildebrandt, *J. Org. Chem.* **1985**, *50*, 4975.

[11] U. Burkert, N. L. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, ACS Monograph 177, **1982**.

[12] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440.

[13] R. W. Alder, C. M. Maunder, A. G. Orpen, *Tetrahedron Lett.* **1990**, *31*, 6717.

[14] K. Praefcke, P. Psaras, B. Kohne, *Chem. Ber.* **1991**, *124*, 2523.

[15] N. L. Allinger, M. Rahman, J.-H. Lii, *J. Am. Chem. Soc.* **1990**, *112*, 8293.

[170/92]

CAS Registry Numbers

1: 142-82-5 / *cis*-**3**: 142843-70-7 / **4**: 142843-71-8 / **7**: 142843-72-9 / **9**: 142843-73-0 / **10**: 142843-89-8 / **11**: 142843-74-1 / **12**: 142843-75-2 / **13**: 142843-76-3 / *trans*-**14**: 142843-77-4 / **15**: 3178-23-2 / **16**: 142843-78-5 / **17**: 142843-79-6 / (*R**,*R**)-**18**: 142843-80-9 / **19**: 142926-27-0 / **20**: 142926-28-1 / **21**: 142843-81-0 / (*R**,*S**)-**22**: 39056-18-3 / **23**: 52919-19-4 / **24**: 52919-16-1 / (*R**,*S**)-**25**: 142843-82-1 / (*R**,*S**)-**26**: 55258-14-5 / (*R**,*R**)-**27**: 122222-11-1 / (*R**,*R**)-**28**: 142926-29-2 / (*R**,*R**)-**29**: 142843-83-2 / (*R**,*R**)-**30**: 142867-27-4 / **31**: 1068-19-5 / **32**: 142843-84-3 / **33**: 134141-98-3 / (*R**,*R**)-**34**: 142843-85-4 / **35**: 142843-86-5 / (*R**,*R**)-**36**: 142843-87-6 / **37**: 142926-30-5 / **38**: 142926-31-6 / **39**: 142843-88-7