Conformation Design of Hydrocarbon Backbones: A Modular Approach**

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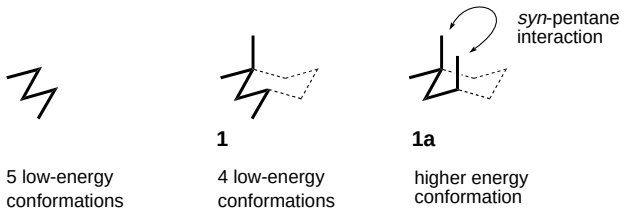
Abstract: A modular approach towards a conformation design of hydrocarbon backbones is described. The idea is to attach substituents (e.g., methyl branches) to a hydrocarbon backbone in such a manner that they create destabilizing *syn*-pentane interactions in all but one diamond-lattice backbone conformation. This creates a substantial (>7 kJ mol^{-1}) energy gap between the lowest energy conformer and the higher energy conformers. In consequence, the lowest energy conformer will be populated to a high extent (e.g., $>80\,\%$). Small hydrocarbon modules that fulfil this requirement have been identified in a systematic manner, highlighting the role of inductor groups to control the conformation at neighboring skeletal bonds. These modules can in turn serve as inductor groups for more extended hydrocarbon chains, or they may be combined with one another to form larger monoconformational hydrocarbon structures.

Keywords: ab initio calculations · conformation analysis · heterocycles · hydrocarbons · steric hindrance

Introduction

Unbranched hydrocarbon chains have an enormous number of populated low-energy conformers.[2, 3] This number can be reduced by substituents that introduce steric strain in certain conformers. This is achieved most effectively[4] if these substituents create destabilizing *syn*-pentane interactions,[5] which add 7 – 9 kJ mol^{-1} to the energy of a given conformer. The population of the remaining low-energy conformers is thereby increased (see Scheme 1).

We are interested in defining substitution patterns on a hydrocarbon chain that would thus destabilize all but one conformer, which would remain free of *syn*-pentane interactions. This conformer would then be the only low-energy conformer and should be highly preferentially populated. If this conformer is populated to $>80\,\%$, we call the compound or a particular segment of a compound monoconformational.[6, 7]



Scheme 1. Methyl substitution at C2 of pentane reduces the number of low-energy conformers of 2-methylpentane to four, because conformation **1a** is destabilized by a *syn*-pentane interaction.

As a first step, we want to identify small segments of a hydrocarbon backbone, segments that, by virtue of their substituent pattern, have only a single low-energy conformation. As a next step we shall consider how these segments may be connected with one another to result in larger hydrocarbon backbones, which should ideally maintain the property of preferentially populating a single conformation.

Discussion

1. Basic types of monoconformational skeletons: The smallest hydrocarbon segment to be considered is 2,3-dimethylbutane (**2**).[8] When rotating about the central 2,3-bond, **2** has three rotamers that are located at energy minima, **2a – c** (Scheme 2). Rotamer **2c** is the lowest energy conformer. Energies of **2a** and **2b** are calculated to be slightly (ca. 1.5 kJ mol^{-1}) higher, because one of the methyl groups is exposed to a double *gauche* interaction with two other methyl groups. To render the 2,3-dimethylbutane backbone monoconformational, two out of the three conformations of **2** have to be destabilized selectively, for example by introducing *syn*-pentane interactions. For instance, if it were possible to place an additional methyl group at C1 of **2**, with the methyl group kept in an antiperiplanar orientation to the neighboring C2 methyl group, that is, **3**, *syn*-pentane interactions would be created in conformers **3b** and **3c**, but not in **3a**. Likewise, if it were possible to fix the additional methyl group at C1 of **2** in a

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[**] Flexible Molecules with Defined Shape, Part IX. For Part VIII, see ref. [1].

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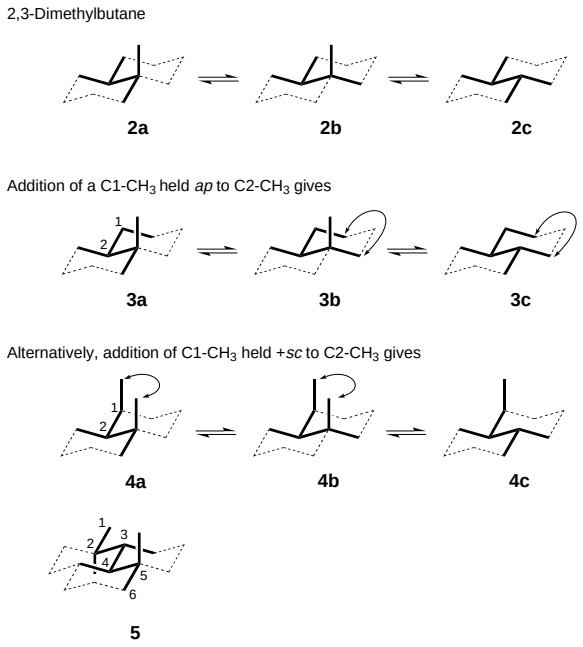
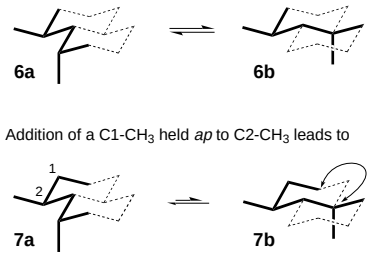


Scheme 2. 2,3-Dimethylbutane is rendered monoconformational by a substituent held in a defined spatial arrangement.

*+sc** position relative to the methyl group at C2, this would lead to *syn*-pentane interactions in conformers **4a** and **4b**, but not in **4c**. In consequence, a monoconformational situation would be created in compounds **3** and **4** regarding rotation of the C2/C3 bond. In these cases the inductor group, the methyl group at C1, controls the conformation at a single skeletal bond.

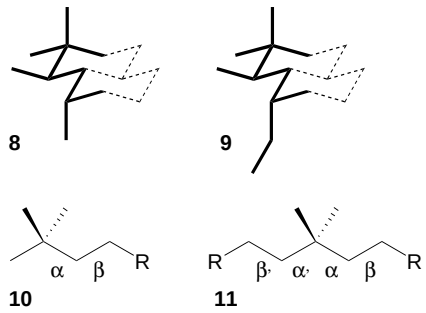
A surprisingly simple way to reach such an arrangement is to combine two units of 2,3-dimethylbutane into 2,3,4,5-tetramethylhexane (**5**). Analysis of its skeleton shows that rotation about any skeletal bond creates a *syn*-pentane interaction. The inherent conformation design is as follows: As C3 – CH_3 is antiperiplanar to C4 – CH_3, this arrangement controls the conformation at the C4 – C5 bond. As C5 – CH_3 is synclinal to C4 – CH_3, this arrangement controls the conformation at the C3 – C4 bond. The situation at the C2 – C3 bond is the same as that at the C4 – C5 bond for symmetry reasons. Compound **5** should therefore be monoconformational. MM3 calculations[9] predict the conformation shown for **5** to be populated to 80 %. The imperfect conformational preference can be attributed to the fact that the low-energy conformer of **5** is destabilized to some extent by the eight *gauche* interactions present.

A hydrocarbon backbone in which monoconformational behaviour can be induced at *two* skeletal bonds is 2,4-dimethylpentane (**6**). Its skeleton has just two enantiomorphous low-energy conformations, **6a** and **6b**,[10] because all other diamond lattice conformations suffer from *syn*-pentane interactions. If a methyl group is placed at C1 of **6** to give **7** it could destabilize conformation **7b** by a *syn*-pentane interaction, provided it can be held in a local *ap* arrangement relative to the neighboring C2 methyl group. This would leave **7a** as the only low-energy conformation (Scheme 3). One



Scheme 3. 2,4-Dimethylpentane is rendered monoconformational by a substituent held in a defined spatial arrangement.

obvious way to reach the situation projected in **7b** is to utilize a *tert*-butyl group as indicated in **8** (Scheme 4). The *tert*-butyl group can rotate freely, but as the three rotamers are



Scheme 4. 2,4-Dimethylpentane is rendered monoconformational by a *tert*-butyl substituent at the chain end.

energetically degenerate, there will always be one methyl group in the required position. Compound **8** has been calculated by MM3 to populate a single conformation to 91 %. The related compound **9** has been studied experimentally:[11] Calculated and experimentally measured optical rotations have been discussed in the context of the prevalence of a single conformation. In a way, this is a manifestation of the long-known *tert*-butyl effect,[12] according to which a *tert*-butyl group at the end of a linear alkyl chain, as in **10**, forces the bond β into an antiperiplanar arrangement with respect to the *tert*-butyl group, as the other two rotamers at bond β would suffer from *syn*-pentane interactions. In terms of designing hydrocarbon backbones which have a preferred conformation, this also holds if the chain continues on both sides of a quaternary center, as in **11**. Then the two bonds β and β' will be forced into an antiperiplanar arrangement with respect to the quaternary center. However, the population of several conformations still remains possible for the bonds α and α'.[13] Therefore, conformation control by quaternary centers is limited to cases in which the quaternary center is

[*] Backbone conformations are designated by the terminology of Cahn and Prelog.[24] *ap* refers to an antiperiplanar arrangement of four backbone atoms considered, dihedral angle $\approx 180°$, *+sc* to a dihedral angle of ca. $+60°$, *– sc* to one of ca. $-60°$. A backbone arrangement in which a *+sc* bond is followed by a *– sc* bond (or vice versa) generates a destabilizing *syn*-pentane interaction. Such a conformation is not a minimum on the energy surface but relaxes to one with dihedral angles of ca. 90°,[2] which is still destabilized relative to a diamond-lattice type conformation that contains only backbone dihedral angles close to $+60, -60$, and 180°.

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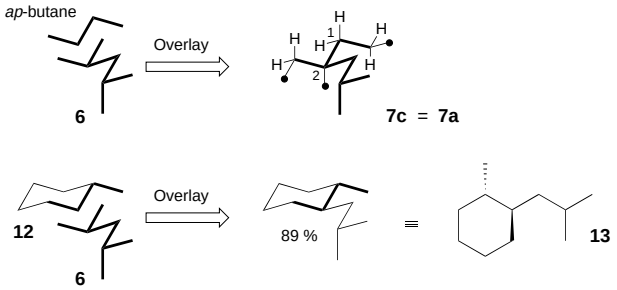
placed at the end of a chain as in **10** or if it forms part of a cyclic system that defines the conformations at bond α.

2. Inductor groups based on methylcyclohexane skeletons: The situation projected in **7** can be described in terms of an *ap*-butane chain superimposed with two skeletal bonds onto the skeleton of 2,4-dimethylpentane (**6**). An *n*-butane chain in an *ap* conformation is contained in the chair conformation of methylcyclohexane (**12**), as depicted in Scheme 5. Therefore, a monoconformational situation can be reached by suitable superimposition of a methylcyclohexane structure onto that of 2,4-dimethylpentane. This has to be done in such a fashion that no additional *syn*-pentane interactions are created; that

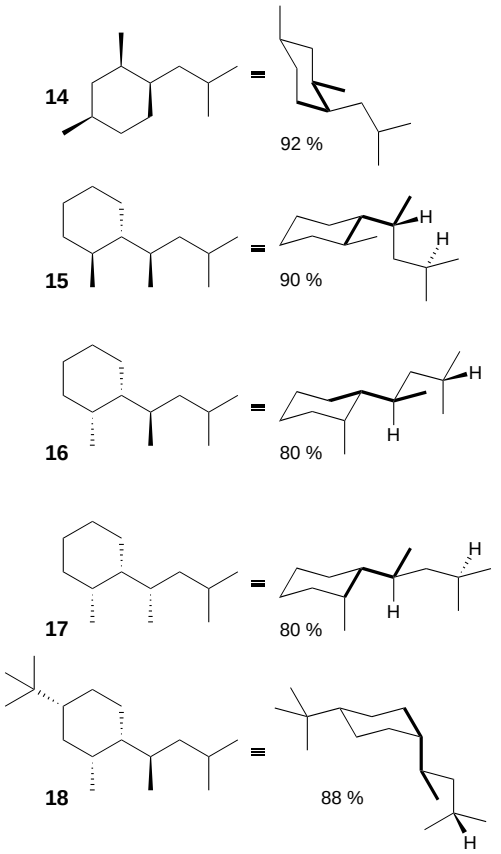


Scheme 5. Rendering 2,4-dimethylpentane monoconformational by overlay with an *ap*-butane chain.

is, an overlay with methylcyclohexane of the C–H bonds marked in **7c** is possible, whereas overlay on the C–H bonds marked with a black dot would lead to additional *syn*-pentane interactions and would thereby preclude generation of a monoconformational situation. Thus, structure **13** depicts one possibility to overlay **12** with **6** to give a monoconformational entity. The *ap*-butane segment is highlighted in **13**. Moreover, the calculated (MM3) percentage of the conformer shown in the total conformer population at 298 K is indicated.

Further monoconformational structures can be obtained by superimposing a (substituted) methylcyclohexane in other ways with two or more skeletal bonds onto **6** while avoiding the creation of additional *syn*-pentane interactions. Structures **14**–**18** illustrate the available possibilities (Scheme 6). The further substituents on the methylcyclohexane part of **14** and **18** are necessary to hold the methylcyclohexane in a particular chair conformation equivalent to holding the *n*-butane chain in the desired *ap* conformation.

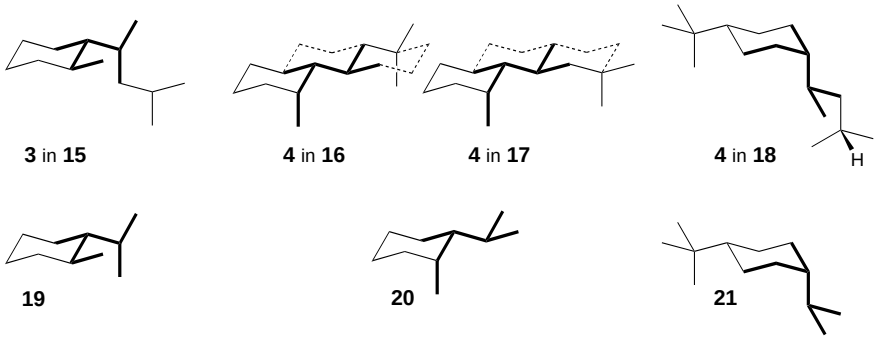
The structures **13**–**18** illustrate how a methylcyclohexane unit can serve as an inductor group for a 2,4-dimethylpentane skeleton. Structures **15**–**18** illustrate a further aspect: they all contain a 2,3-dimethylbutane segment (**2**) held in a single conformation, be it through the substitution pattern delineated in **3** (**15**) or in **4** (**16**), (**17**), (**18**). One can therefore infer that the monoconformational 2,3-dimethylbutane units **3** and **4** may also serve as inductor groups when superimposed with at least two skeletal bonds onto



Scheme 6. Calculated conformer preferences for 2,4-dimethylpentane chains with an attached methylcyclohexane inductor group.

2,4-dimethylpentane. To illustrate how the monoconformational nature of **15** to **18** can be interpreted by the presence of the 2,3-dimethylbutane inductor groups, these inductor groups are highlighted in **19**–**21** in Scheme 7, before superposition with the 2,4-dimethylpentane skeleton. The monoconformational nature of derivatives of **19**[14] and **20**[14] has been discussed with reference to ^{13}C NMR spectra, and that of **21**[15] has been discussed before on the basis of MM calculations.

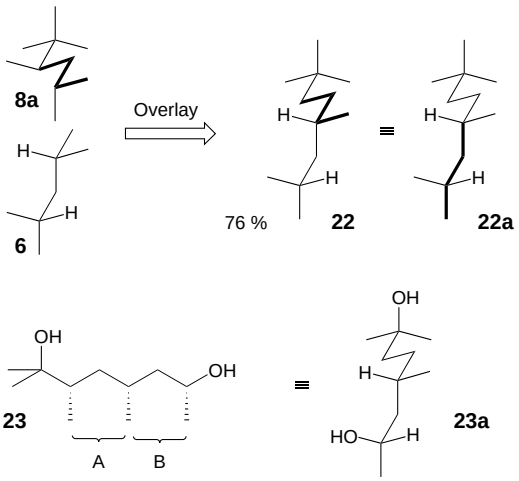
At this point we have already identified a substantial set of monoconformational structures, such as **5**, **8**, and **13**. These structures in turn may serve as inductor groups to render a neighboring hydrocarbon segment monoconformational, as



Scheme 7. Conformationally constrained 2,3-dimethylbutane segments highlighted in the compounds **15**–**18** calculated to be monoconformational.

described in section 3. They may also be directly combined with one another to result in larger hydrocarbon structures with high conformational preferences, as delineated in section 4, thus allowing a modular approach to conformation design.

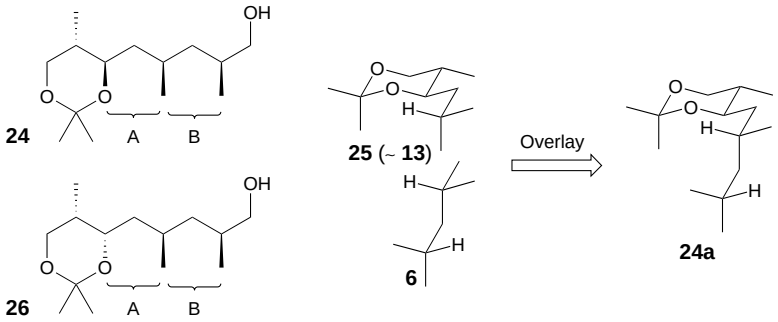
3. Sequential induction of conformation along a hydrocarbon chain: The monoconformational nature of the hydrocarbon building blocks **8**, **13**–**18**, discussed above, arose by attachment of an inductor group to a biconformational 2,4-dimethylpentane unit, rendering it monoconformational. It is an intriguing thought that structures **8** or **13**–**18** could themselves be used as inductor groups for another 2,4-dimethylpentane unit. Conformational induction in a first 2,4-dimethylpentane unit comes about (Scheme 5) by particular overlay with a butane chain in an *ap* arrangement, namely **7a**. This could be realized in practice by using, for example, a *tert*-butyl group as seen in **8**. The single low-energy conformation of **8** contains a second *ap*-butane unit, **8a** (Scheme 8). Two-bond overlay of **8a** with



Scheme 8. Conformation control by sequential overlay of 2,4-dimethylpentane segments.

another unit of **6** generates **22**, which should be monoconformational. Compound **22** contains a further *ap*-butane structure, **22a**. Therefore **22** could serve as an inductor group for yet another 2,4-dimethylpentane segment to be attached. While the conformational properties of **22** have not been studied yet experimentally, data are available for the related diol derivative **23**.[16] Analysis of the ^{1}H NMR coupling constants suggests that in **23** the conformation shown in **23a** is populated with a 7:1 preference in segment A and a 7:1 preference in segment B. Moreover, the conformation **23a** is the one present in crystalline **23**. This demonstrates that a single inductor group, the *tert*-butyl group, controls the conformation in segment A, and that the latter in turn controls the conformation in segment B to a considerable extent.

An inductor group **25** analogous to **13** is present in **24** (Scheme 9).[17] Determination of the $^3J_{H,H}$ coupling constants



Scheme 9. Conformation control of neighboring dimethylpentane segments by a methylcyclohexane-type inductor group.

in the NMR spectra indicated a 3:1 preference in segment A and a 2.2:1 preference in segment B of **24** for the conformation shown in **24a**.

Both in **23** and **24** the conformation control manifest from the NMR spectra was lower than that calculated for the pure hydrocarbon parent structures. Replacement of a CH_2 or CH_3 group by a smaller oxygen atom leads to a lower energy penalty for undesired conformations with a *syn*-pentane interaction involving oxygen, because a O-C-C-C-CH 1,3-parallel ($\geq$ *syn*-pentane) interaction is less destabilizing than the corresponding HC-C-C-C-CH situation.[18]

When the relative configuration of the stereocenters is changed from that in **24** to that in **26**, ^{1}H NMR coupling constants indicate that segment A in **26** has a substantial (85:15) conformational preference, but that segment A has no inductive effect on the conformation of the neighboring segment B. This demonstrates that transfer of conformation induction from a given 2,4-dimethylpentane segment to a neighboring one, as illustrated for the induction from segment A to segment B in **23** or **24**, is subject to quite stringent structural requirements.

Examples **23** and **24**, in which sequential conformation induction could be demonstrated, correspond structurally to isotactic polypropylene (**27**, Scheme 10). The principles governing the induction of conformation along a hydrocarbon chain may be discussed with reference to structure **27**. Each of the 2,4-dimethylpentane segments A–C of **27** is biconformational a priori. If the group R in **27** is an inductor group, for example a *tert*-butyl group, this would induce an *ap* backbone conformation at bond α. Therefore an *ap* $+sc$ conformation will prevail in segment A. Permutation of the biconformational nature of the segments B and C would then lead to the four possible backbone conformations shown for **27** in Scheme 10. Since bond β is held in a $+sc$ conformation, a $-sc$ conformation at bond γ would lead to a destabilizing *syn*-pentane interaction. Hence, segment B should become monoconformational in an *ap* $+sc$ conformation. This way bond δ is held in a $+sc$ conformation. Therefore, the same argument shows that segment C should also adopt an *ap* $+sc$ conformation as well. This shows how a single inductor group R could control the backbone conformation of an extended structure such as **27**.

When the substitution pattern of the hydrocarbon chain does not conform to that of isotactic polypropylene, as in **28** or **29**, a similar analysis shows that the same conformation

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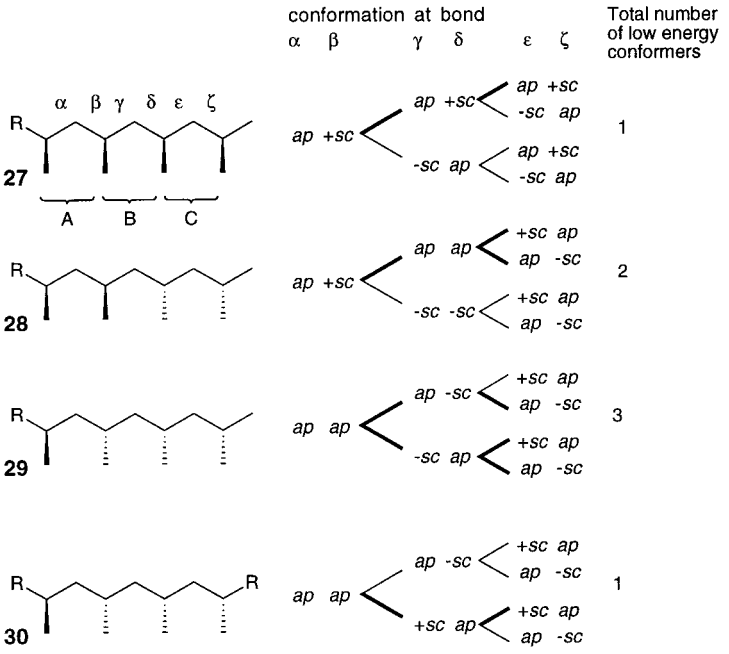


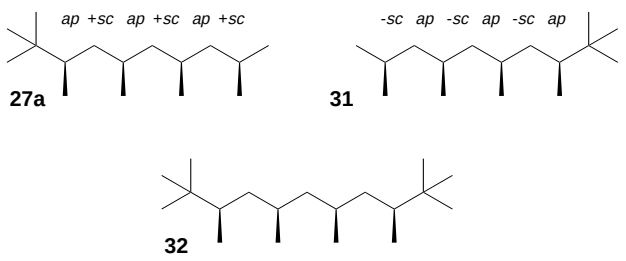
Scheme 10. Conformation control along a polypropylene chain.

induction as in **27** operates in segments A and B of **28**, inducing an *ap* conformation at bond δ. Following an *ap* conformation at bond δ in segment C of **28**, both an *ap* as well as a $+sc$ conformation at bond ζ would be free of *syn*-pentane interactions. Hence, segment C remains biconformational, as in the situation found in **26**.

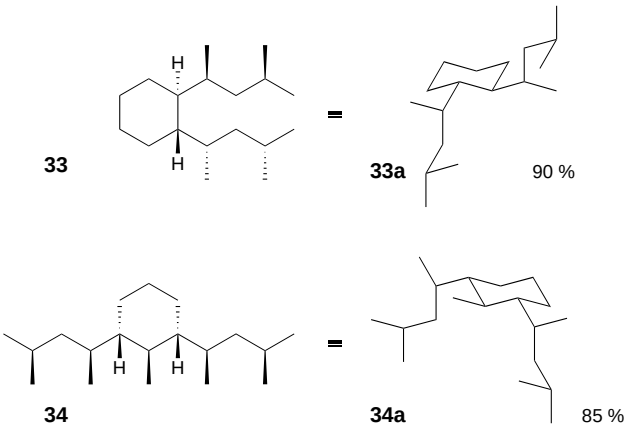
If the isotactic sequence of 2,4-dimethylpentane segments is interrupted closer to the inductor group, as in **29**, segment B remains biconformational and, in consequence, permits segment C to remain biconformational as well. Therefore, conformation induction of an inductor group on a 2,4,6,…*n*-polymethylated hydrocarbon chain reaches only as far as the substituent pattern remains isotactic. There is no conformation control downstream of any syndiotactic segment interposed. Note the syndiotactic nature of segment A in **26**.

In a situation such as **29** with only a single break in tacticity, there is the possibility of achieving conformation control by introducing a second inductor group at the other end of the chain. A *tert*-butyl group at the right-hand end of the chain, such as that in **30**, would permit only an *ap* conformation at bond ζ and would destabilize two of the three low-energy conformations of **29**, rendering **30** monoconformational. It should be noted at this point that double conformation induction with an inductor group at each end of a hydrocarbon chain is *not* possible in cases with a completely isotactic substitution pattern: for instance, an inductor group at the left end of **27** (**27a**, Scheme 11), induces a right-handed helical folding of the chain. An inductor group at the right end of **27**, as in **31**, induces a left-handed helicity of the backbone. The two modes of induction are therefore incompatible with one another and there are no low-energy conformations of the diamond-lattice type available for structure **32**.

Rather than placing an inductor group at the end of a hydrocarbon chain, it may be more advantageous to control the conformation of two hydrocarbon chain segments simultaneously by a single inductor group placed in the middle of a chain. This is illustrated for a methylcyclohexane inductor group in structures **33** and **34** (Scheme 12).

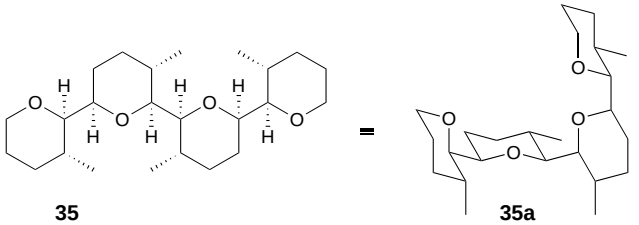


Scheme 11. End-group conformation control in isotactic polypropylene.



Scheme 12. Calculated efficiency of bidirectional control of conformation of 2,4-dimethylpentane segments.

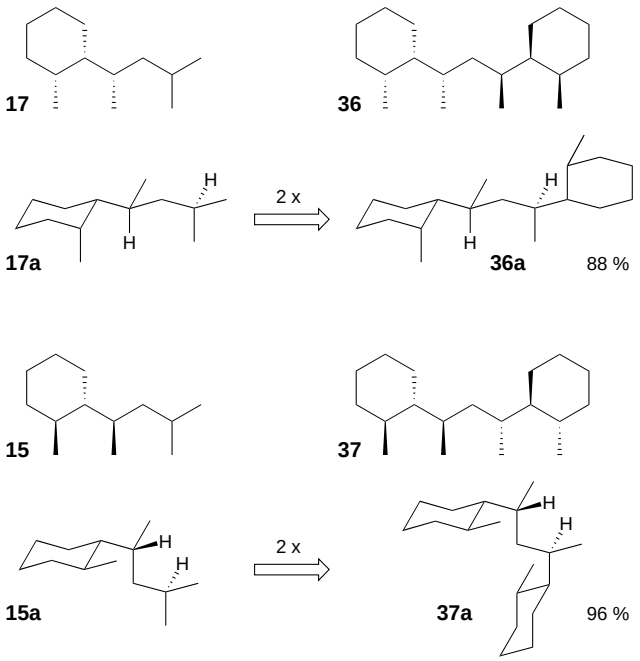
4. Conformation control of larger molecular backbones by combination of monoconformational hydrocarbon segments: In the previous sections we have presented a variety of monoconformational hydrocarbon structures in which the conformation at up to 8 rotatable bonds has been controlled. It is immediately apparent that overlay with at least two skeletal bonds of two or more of such building blocks such as **13**–**18** without creation of extra *syn*-pentane interactions should result in even larger monoconformational backbone entities. This kind of conformation design has been perfectly illustrated by W. C. Still[19] in his conception and realization of a monoconformational chelating polyether structure **35** (Scheme 13). It is apparent that **35** consists of four units of the type **19**, which share two skeletal bonds. One has to note, however, that **35** contains not **19** itself, but an oxygen



Scheme 13. Design of monoconformational polyether structures based on the overlay of *trans*-1-methyl-2-isopropylcyclohexane-type segments.

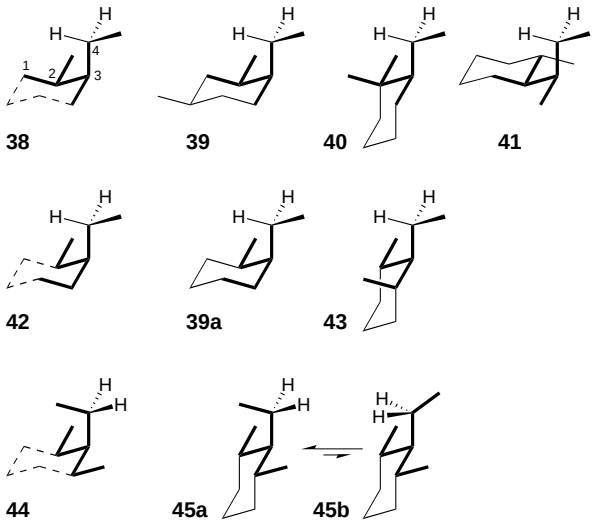
analogue, a tetrahydropyran ring instead of a cyclohexane ring. The conformational preferences in **35** may therefore be not as marked as in the cyclohexane series, because, as stated before, destabilization of undesired conformers by a O-C-C-C-CH 1,3-parallel (*syn*-pentane type) interaction is less than that by the HC-C-C-C-CH (*syn*-pentane) interactions.[18] Nevertheless, it appears that nature frequently chooses such tetrahydropyran rings as building blocks in her conformation design.[6]

When nature relies on the combination of monoconformational building blocks to attain larger monoconformational backbone structures, one is tempted to explore the scope and limitations of such a modular approach to conformation design based on building blocks. For instance, 6-bond overlap of two monoconformational entities **17** should lead to the monoconformational skeleton **36**, or 6-bond overlap of two entities of **15** should lead to the skeleton **37**, for which a very high conformational preference is calculated (Scheme 14).



Scheme 14. Calculated conformational preferences for larger molecular skeletons derived by overlay of monoconformational units.

Rather than examining numerous possible permutations, we would like to address the question of whether control of conformation is possible in hydrocarbon chains in which the branching points are further apart than a 1,3 interval. In order to reach such a goal by overlay of monoconformational building blocks, we first have to search for entities in which an ethyl group is held in a defined conformation. Such structures may be derived from 2,3-dimethylbutane (**2**) when the latter is in a fixed conformation: If a methyl group is attached either to C1 or to C4 of **2**, as it is in **38**, the ethyl unit generated will be held in a defined conformation (Scheme 15). Examples in which the 2,3-dimethylbutane segment and, hence, the ethyl side chain are held in a defined conformation are given by the structures **39**–**41**. In **39** and **41** a further methyl group was



Scheme 15. Structural possibilities for the confinement of ethyl group rotation to a single conformation.

needed to hold the 2,3-dimethylbutane unit in the necessary conformation. An ethyl group will also be held in a defined conformation when attached to a pentane chain that is fixed in an *ap* +*sc* conformation, as is the case in **42**. Representative entities calculated to be monoconformational with such a chain in a defined spatial arrangement are given by **39a** and **43**.

There is a third possibility, **44**, for control of the conformation of an ethyl group: this possibility is embodied in structure **45**. The enthalpic preference of the ethyl side chain to adopt the conformation shown in **45** may not be as high as the one in **39**–**41** or **43**, because the terminal methyl group suffers two *gauche* interactions in conformation **45a**. Therefore, compounds of the type **45** may have a tendency also to populate conformers with eclipsed arrangements of the ethyl side chain, **45b**.[20]

This identification of the building blocks **39** **41**, **43**, and **45** with an ethyl group held in a single conformation allows us to address the design of a conformation-controlled 3,4-unsubstituted hexane chain: This could be achieved by a combination of two of the building blocks **39**–**41**, **43**, or **45** overlaid on the ethyl groups. Thus, for example, combination of two units of **40** leads to **46**, which should be monoconformational, since two out of the three diamond lattice type rotamers about the highlighted 3,4 bond of the hexane chain in **46** have destabilizing *syn*-pentane interactions (Scheme 16). Therefore **46** is calculated to have a respectable tendency to populate a single conformation.

The hydrocarbon entity **45** has some features in common with a *tert*-butyl inductor group: for instance, if the side chain in **45** is lengthened by one methylene group, as in **47**, bond β is confined to a single conformation (Scheme 16). In contrast to **10**, bond α is also held in a single conformation, therefore the propyl chain of **47** is held in a defined spatial arrangement. Combination of two units of **47** overlaying the propyl groups then leads to compound **48**, for which MM3 calculations predict a remarkable preference for a single conformation. In this conformation, a pentane chain substituted only at the 1- and 5-positions is held in a defined arrangement as shown.

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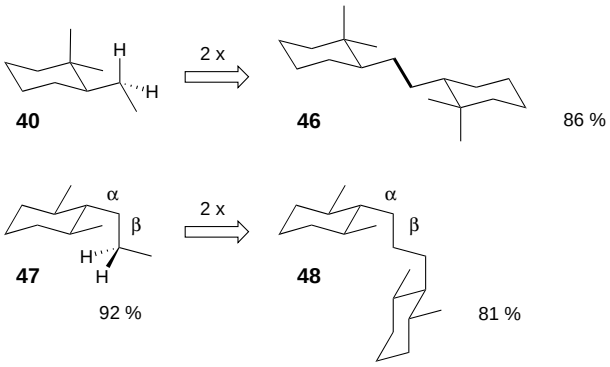
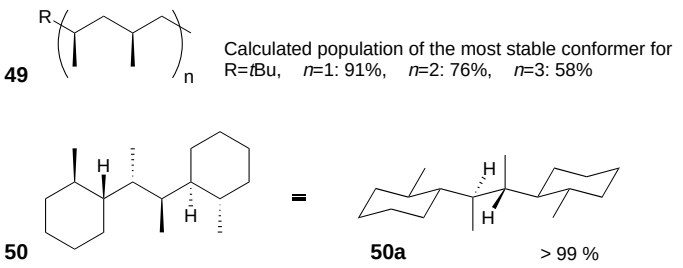


Scheme 16. Calculated preferences for monoconformational butane and pentane chains with conformation-inducing end groups.

5. Persistence length of conformation control: In the previous section we have shown that larger flexible hydrocarbon backbones can be designed by combination of diverse monoconformational building blocks in which all but one of the conformations suffer from destabilizing *syn*-pentane interactions. This may nourish the dream that by multiple combination of such building blocks large structures should become accessible in which just a single conformation would be populated to a high extent. But there is an intrinsic limitation as to the number of rotatable bonds that may be held in a single conformation by destabilizing undesired conformers by means of *syn*-pentane interactions. The limitation may be illustrated with reference to structure **49** (Scheme 17): Upon elongation of **27** by further 2,4-dimethyl-



Scheme 17. Flexible structures with very high calculated preferences for a single conformation.

pentane segments to give **49**, the energetic distance between the global minimum conformation and structures with partially relaxed *syn*-pentane interactions is unaffected. However, the number of such higher energy conformers with a single partially relaxed *syn*-pentane interaction increases for **49** with $n(n+1)$. Hence, the more rotatable bonds that are present in a given structure, the higher should be the number of conformers with relaxed *syn*-pentane interactions that lie over the global minimum by a constant value. On Boltzmann averaging over the conformer energies and numbers, the population of the global minimum conformation will accordingly become smaller and smaller.

One can also describe the situation in other terms: While each segment **49** is a priori biconformational, adoption of a single conformation in **49** implies that in each of the n segments, a single rather than two conformations are populated. The price for conformational order in **49** is then a loss in entropy. The penalty for violating conformational order at one point is the enthalpy difference between a local diamond-lattice type backbone arrangement and one with a partially relaxed *syn*-pentane interaction, that is, a skewed conformation. This corresponds to an enthalpy term of ca. 7 kJ mol^{-1}.[2] Therefore, any conformation control by an inductor group should have a finite persistence length; see the the conformer population calculated for **49** with $n = 1$ to 3.

Is conformation design of monoconformational entities therefore limited to molecules with few rotatable bonds when based on the avoidance of *syn*-pentane interactions? All that matters is the penalty term for violating conformational order. If the penalty in ΔH can be raised, the persistence length of conformation control could be longer. From this consideration, monoconformational structures in which rotation into an undesired conformation creates not only a single but rather two *syn*-pentane interactions become of interest. A case in point is structure **50** (Scheme 17): its global minimum is calculated to lie more than 18 kJ mol^{-1} lower in energy than any other conformer. This indicates the direction in which to proceed for conformation design of flexible hydrocarbon skeletons with unusually strong preferences for a single conformation.

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