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Consequences of Strain for the Structure of Aliphatic Molecules

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By Christoph Rüchardt* and Hans-Dieter Beckhaus

Dedicated to Professor Rolf Huisgen on the occasion of his 65th birthday

The chemist is accustomed to deriving structures and preferred conformations of organic compounds from rigid molecular models and standard values for bond lengths, bond angles, and torsional profiles. In the case of strained compounds, this rigid structural model has to be abandoned and replaced by a flexible one which takes individual conditions of strain into consideration. It is shown, on the basis of new experimental structural data, that the force field method is suitable and highly reliable for the calculation of structural parameters and preferred conformations of strained compounds. It is, therefore, capable of replacing the rigid molecular model. Furthermore, the systematic analysis of strain induced angle and bond deformation gives a new pivot for the development of a qualitative discussion of deformation in strained molecules and hence for improved conformational analysis.—In the course of this work we were able to isolate two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane; this is the first isolation of a rotamer pair of an aliphatic hydrocarbon.

1. Introduction

Probably the most important concept in the whole of chemistry is that of molecular structure. The properties of matter are connected with it, and discussions of reactivity are based on the molecular structures of the reaction partners.[1,2] Hence, the development of structural models is of central importance.

Additivity rules have been developed for a uniform description of the structural data[3] and thermodynamic quantities of numerous organic compounds.[4,5] These enable a calculation of molecular properties from increments for the atoms and groups involved. In this context, standard bond lengths and bond angles are used, and ideal con-

formations with a staggered arrangement of the groups on neighboring tetracoordinated carbon atoms with a 60° torsional angle are assumed. Individual deviations from the standard values caused by conjugational effects can be taken into account with the aid of correction factors[5] as regards both geometry and thermodynamic properties.

Structural models based on this simple concept allow the discussion of reactivity without having to analyze experimentally the structures of whole series of compounds. However, this simple additive and hence rigid structural model rapidly reaches its limits when used to explain steric effects on reactivity.[6–8] The deliberately pragmatic concept "steric effects" incorporates phenomena arising from individual structural properties of the reactants and the activated complexes. If the result of a steric effect is a change in the activation enthalpy,[9] it can be described by the model quantity "strain enthalpy H_s".[10] This is defined as the difference between the enthalpy of formation of a real

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molecule, ΔH_f° (g), and a norm or standard value ΔH_f^N calculated from group increments.[10]

Strain can result, for example, from ring formation or repulsion between non-bonded atoms and is associated with changes in the geometric parameters of a molecule, i.e. bond lengths, bond angles, and torsional angles, with respect to the standard values.[11,12] Therefore, the rigid structural model breaks down in the treatment of steric effects,[13] and the question is posed as to the alteration of bond lengths and bond angles under the influence of strain.[6-8,11,12] Consequences for the conformational behavior can also be expected as a result of the deformability of the molecular framework; the fundamental rules of conformational analysis are based on the rigid structural model.

The study of steric influences is of increasing importance not only in organic chemistry. Studies of the relationships between structure and activity of drugs attest to intermolecular effects as one of the reasons for the high selectivity of biochemical recognition processes, which have been described, inter alia, as docking processes between an active substance and its receptor.[14,15] As another example, special material properties of polymers resulting from preferred conformations in a polymer chain should be mentioned. These in turn are determined by steric effects.[16] In these and many other cases only a flexible structural model which requires variation of the structural parameters as well as knowledge of the dynamic behavior of organic molecules subjected to internal or external strain, is applicable.

Hitherto, the investigation of highly strained compounds has largely been confined to monocyclic and polycyclic small ring compounds,[11] the rigid skeletons of which permit the evaluation of angle deformations and preferred conformations. In this review we summarize the structural investigations of highly branched open chain carbon skeletons, which are in part characterized by very high strain enthalpies. Therefore, the extent and consequences of the deformability of these molecular structures are particularly readily perceived.[17-31] Because of the inherent flexibility of the open chain framework, predictions about the extent and nature of the deformation can hardly be made in the realm of classical conformational analysis.[13]

In order to answer the question posed, experimentally derived structural parameters of strained compounds are required. These also permit an extension of the parameter basis of empirical force field methods[32-34a] to include strongly deformed and highly strained compounds. Their application to strongly deformed molecules permits an evaluation of the usefulness of the various empirical force fields as regards dynamic behavior and deformability of molecular structures under the influence of strain. Therefore, these evaluations will also answer the question whether the rigid structural and thermodynamical increment model for aliphatic molecules can be replaced. In this context *Mislow*'s comparison of the X-ray structure of the propeller-like molecules trimesitylmethane and the result of a force field calculation was a pioneer work.[34b]. The increasing use of empirical force field (EFF) calculations in the quantitative analysis of structure reactivity relationships[1s] makes a demanding test all the more essential. We will use the experimental structural data of strained representatives of the classes of compounds 1—8 (Table 1) as test cases.

C_q-C_q skeleton

1-4, 8

C_t-C_t skeleton

5-7
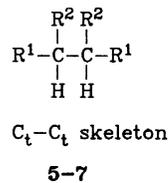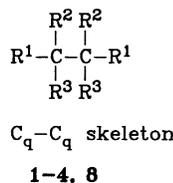
1, R^1, R^2, R^3 = alkyl
2, R^1, R^2 = alkyl; R^3 = phenyl
3, R^1, R^2 = alkyl; R^3 = CN
4, R^1 = alkyl; R^2 = alkyl or phenyl; R^3 = COOCH$_3$

5, R^1, R^2 = alkyl
6, R^1 = alkyl; R^2 = aryl
7, R^1 = alkyl; R^2 = 1-cyclohexenyl
8, R^1 = phenyl; R^2 = OCH$_3$; R^3 = CN

2. Synthesis

The sixfold (C_q-C_q) and fourfold (C_t-C_t) symmetrically substituted ethanes **1—8** were mostly synthesized by dimerization of the "half" molecules. These were obtainable either by Wurtz type reactions[26,36-39] [e.g. Reaction (a),[26] (b),[19]] or by dimerization of thermally or photochemically generated radicals from azoalkanes[20,28,36] [Reaction (c),[36] (d),[28] (e),[40]], or by dimerization of radicals generated by hydrogen abstraction [Reaction (f)[41]].
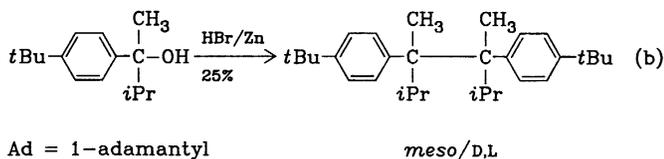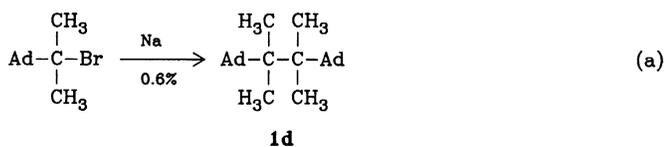
(a)

1d

(b)

Ad = 1—adamantyl   *meso*/D,L

(c)

10

(d)

3b

(e)

5g

(f)

meso/D,L

8

530

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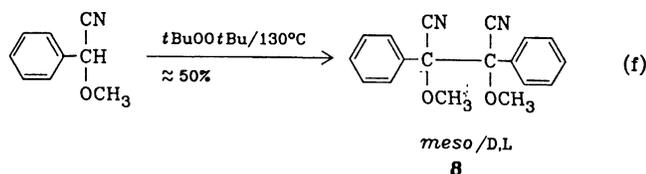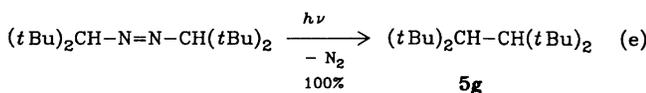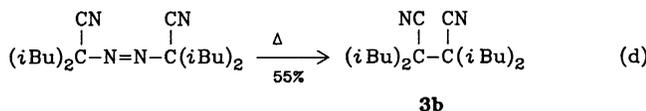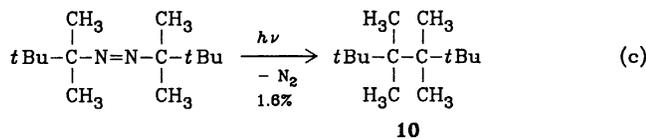
Moreover, oxidative coupling reactions have been used [Reaction (g)[29,42]].

(g)

4b
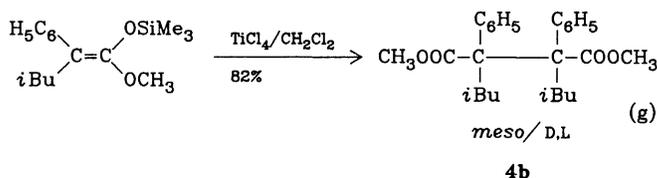
In general, the yields were higher for phenyl-[19,39] or cyano-substituted[28] compounds than for unsubstituted alkanes[36] because in the latter case radical disproportionation often predominated. The highest yields were obtained when β-hydrogen atoms were absent in the radicals concerned, because in these cases disproportionation was no longer possible.[20,40] The peroxide-induced oxidative dimerization gave, as expected, particularly good yields of dimers when capto-datively substituted radicals were involved.[43] The *oxidative* dimerization of enolates or enol ethers proved less broadly applicable than expected.[29] The reductive dimerization of geminal dibromides [Reaction (h)[44]] proved to be an excellent strategy for the synthesis of the highly strained molecules tetra-*tert*-butylethane (3,4-di-*tert*-butyl-2,2,5,5-tetramethylhexane), **5g**,[44] [H_s(exp) = 66.3 kcal/mol] and 1,2-diadamantyl-1,2-di-*tert*-butylethane (3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane) [**5**, R^1 = 1-adamantyl, R^2 = *t*Bu; H_s(MM2) = 72.9 (*meso*) or 73.3 (D,L) kcal/mol].[40]

(h)
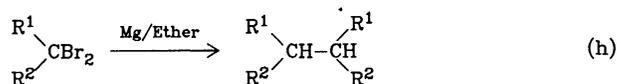
5g, $R^1 = R^2 = t$Bu (13%)
5e, f, R^1 = 1−adamantyl, $R^2 = t$Bu, *meso*/D,L (21%)

3. Force Field Calculations of Strained Molecules

Strain enthalpies of interest for the discussion of strain effects on structure were obtained by force field calculations[7b] on numerous representatives of compound classes **1**—**8** and compared with experimental values derived from combustion calorimetry.[7b] In general, the agreement between calculated and experimental values was excellent; only in the case of the most highly strained compounds, e.g. tetra-*tert*-butylethane **5g**,[44] was a discrepancy of a few kcal/mol found. The validity of the calculated strain enthalpies was also seen in the successful quantitative analysis of the thermal decomposition of the compound classes **1**—**8**.[6,7] Here, radical formation is associated with a decrease in strain and a gain in conjugational energy. These results have been reported elsewhere.[7]

Force field calculations not only give heats of formation, ΔH_f°(g), but also predict structural data for organic compounds.[32] The reliability of the computational results is well documented within the range of parametrization, not however for compounds which, because of high strain, fall outside this range. This is the case for most of the compounds given in Table 1.[7]

The potential of the force field method in structure determination can be evaluated by comparison of its predictions with the experimental structural data for highly strained compounds; these have been worked out in recent years by crystal structure analyses. In Table 1, only selected characteristic structural parameters are given from which the influence of strain on the structure can be derived. These are, on the one hand, the bond lengths from the central carbon atom in the ethane skeleton (C_e), and, on the other, the bond angles at the central atoms C_e and the carbon atoms in the α position C_α. The bond lengths C_e–C_e and C_e–C_α are lengthened to up to 164 pm—in the record case, 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d**, there are three neighboring bonds of this length. The bond angles at the tetracoordinated carbon atoms in these positions are also increased to a maximum of 123°. These are clear signs of significant molecular strain.

We have carried out calculations of the strain and structures for all compounds in Table 1 using the MM2 force field of *Allinger*.[45] Of the several force fields tried for **1b**, this one gave results in closest agreement with the experimental data.[22] We have extended the force field with the necessary parameters to include alkyl benzenes,[46] nitriles,[28] and carboxylic acid esters,[29] and correspondingly modified the MM2 program for alkylcyclopropanes.[18]

The structural data obtained with the extended MM2 force field just described are given in Table 1 together with the experimental results. Furthermore, for each compound the calculated strain enthalpy H_s is given.[7b] A comparison shows that even pronounced molecular deformations created through high molecular strain are well reproduced by the calculation. Only the values calculated for extremely elongated bonds are somewhat too short (see e.g. **2d**, **4a**, **4b**, **5c**). If packing effects on the crystal structure are also taken into account (this, of course, not being possible in the force field calculations on isolated molecules) the data in Table 1 demonstrate the high reliability of the EFF calculations for the structural types investigated here. This could not have been predicted, since up until now highly strained compounds such as those given in Table 1 had not been used in the parametrization of the MM2 force field.[32,45] The reliability of the MM2 force field in calculating structures of sterically strongly deformed compounds justifies the use of computational structural data in the discussion of the relationships between structure and strain.

4. The Breakdown of the Additive Structural Model through Strain Induced Deformation

The results in Table 1 clearly show that in the case of strained compounds whose heats of formation no longer can be verified by simple increment calculations, also the

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Table 1. Selected structural data for highly branched ethanes **1–8** from crystal structure analysis and force field calculations [a].

$$R^1-\underset{\underset{R^2}{|}}{\overset{\overset{R^3}{|}}{C_e}}-\underset{\underset{R^2}{|}}{\overset{\overset{R^3}{|}}{C_e}}-C_\alpha-C_\beta$$
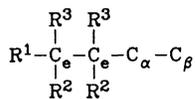
	R¹	R²	R³	Configuration	H_s [b] [kcal/mol]	Bond lengths [pm] $d(C_e-C_e)$	$d(C_e-C_\alpha)$ [c]	Bond angles [°] $(C_e-C_e-C_\alpha)$ [c]	$(C_e-C_\alpha-C_\beta)$ [c]	Torsional angles [°] $(C_\alpha-C_e-C_e-C_\alpha)$ [c]	Ref.
1a [d]	Me	Me	Me	—	6.9 (6.9)	158.2 (157.7)	154.2 (154.3)	111.0 (111.8)	— —	175±7 (164)	[47]
1b	cHex	Et	Me	meso	34.8 (34.8)	162.6 (163.0)	160.2 (159.2)	112.1 [e] (112.0)	117.5 (117.3)	180 (180)	[22]
1c	cPr	cPr	cPr	—	17.9 [f] (23.4)	163.6 (161.5)	153.2 (155.2)	108.9 (109.9)	124.6 (123.7)	180 (180)	[18]
1d	1-Ad	Me	Me	—	— [f] (42.1)	163.9 (164.0)	164.7/164.0 (164.5)	117.6 (120.9)	—	162 (162)	[26]
2a	Ph	Me	Me	—	11.1 (12.0)	158.5 (157.4)	154.5 [e] (155.5)	110.8 (110.6)	—	180 (180)	[19]
2b [g]	Ph	Et	Et	—	24.9 [h] (27.4)	162.2/163.5 (162.1)	153.6–157.1 [e] (156.8)	109.0–109.6 (107.9)	113.9–119.9 [e] (119.0)	164/180 (180)	[19]
2c	Ph	–(CH₂)₇–		—	45.0 (42.1)	162.2 (161.8)	155.2 (154.1)	109.0 (108.9)	118.5/119.0 [e] (118.5)	180 (180)	[20]
2d	Ph	nBu	nBu	—	22.7 [h] (22.3)	163.8 (161.2)	155.4 (154.6)	108.7 (108.2)	119.1 [e] (120.9)	180 (180)	[27]
3a	iBu	Me	CN	meso	— (12.9)	155 (158)	153 (156)	114.2 (112.0)	122.9 (119.8)	180 (180)	[28]
3b	iBu	iBu	CN	—	25.9 (23.8)	160 (160)	155/156 (156)	112.7 (107.5)	117.8/118.9 (119.5)	180 (180)	[28]
4a	Ph	Et	CO₂Me	D,L	— (21.0)	163.5 (160.4)	156.2 (154.6)	108.1 (109.4)	116.2 [e] (119.6)	175 (176)	[29, 30]
4b	iBu	Ph	CO₂Me	meso	— (24.9)	163.7 (161.2)	156.3 (156.8)	111.2 (112.2)	121.1 (122.8)	44 (48)	[29, 30]
4c	iPr	Et	CO₂Me	D,L	— (36.4)	162.0 (161.8)	157.8 (158.8)	115.3 (—)	— —	172 (164)	[31]
5a [d]	Me	Me	H	—	2.7 (2.7)	154.6 (154.9)	153.9 (153.8)	111.3 (113.9/109.2)	—	— (70)	[46, 48]
5b	cHex	cHex	H	—	— (20.1)	157.7 (158.1)	156.8 (156.7)	113.1 (115.8)	—	69 (58)	[21, 37]
5c	tBu	cHex	H	meso	— (34.5)	160.2 (158.5)	159.4/158.9 (158.3/158.6)	123.5/115.1 (123.7/118.8)	119.6/121.3 [e]	129 (117)	[22, 37]
5d	tBu	cHex	H	D,L	— (28.1)	158.9 (158.0)	154.8/156.2 (157.5)	113.3/113.9 (115.8)	120.4/120.9	139 (147)	[22, 37]
5e	1-Ad	tBu	H	D,L [i]	— [f] (57.5)	162.1 (161.5)	162.9 (162.3)	120.0 [e] (119.1)	—	115 (113)	[30, 40]
5f	1-Ad	tBu	H	D,L [i]	— [f] (58.1)	163.1 (162.1)	162.8/163.5 [e] (160.8/161.2)	120.8/120.6 (119.3/120.9)	—	52 (52)	[30, 40]
5g	tBu	tBu	H	—	66.3 (57.7)	— (161.4)	— (15.1/161.2)	— (117.6/119.8)	—	— (65)	[37, 44]
6a [g]	tBu	Ph	H	meso	— (14.7)	157.7/157.3 (156.1)	159.9/158.2 (157.2)	116.0(116.8 (118.7)	—	180 (180)	[23]
6b	tBu	Ph	H	D,L	— (18.4)	158.9 (155.9)	156.9/158.3 (156.8)	114.0/115.2 (117.1)	—	—	[23]
6c [g]	tBu	Mesityl	H	meso	— (31.7)	155.2/151 (157.2)	161.1/163 (157.9)	111.8/111.2 (121.2)	—	180 (180)	[24]
6d	tBu	Mesityl	H	D,L	— (35.1)	158 (158.2)	161 (158.4)	116.6 (121.0)	—	138	[24]
7 [k]	tBu	1-c-Hexenyl	H	meso	— (20.1)	157.0 (156.2)	160.0 (156.2)	115.6 (120.5)	—	180 (180)	[25]
8	Ph	OCH₃	CN	meso	— (12.8)	157.8 (157.3)	152.7 (152.8)	111.9 (109.6)	—	180 (180)	[30, 41]

[a] Computational value using the MM2 force field according to *Allinger* et al. [45] with extensions [28, 29, 46]. [b] Experimental values from enthalpies of combustion and sublimation (MM2 computational values in parentheses) [49]. [c] C_α belongs to the group R¹ unless otherwise indicated. [d] Electron diffraction experiments. [e] C_α belongs to the group R². [f] Ring strain is subtracted: H_s(cyclopropane) = 28.12, H_s(adamantane) = 7.9 kcal/mol. [g] Two independent molecules are present in the crystal. [h] Derived from the *p-tert*-butyl derivate. [i] See Figures 4 and 5 for a designation of the rotamers **5e** and **5f**. [k] Calculated using the force field described in reference [49].

structural parameters strongly deviate from the norm, i.e. bond angles, bond lengths, and torsional angles. However, common traits can be perceived from the structures of the strained four- and six-fold substituted ethanes. These can be used as guidelines in the interpretation of the structures of other branched molecules. The generalizations reached

in the rigid structure model by the standardization of bond lengths and bond angles have been lost again in favor of individual structural parameters for each molecule. Such phenomena are successfully taken into account by the force field method, which therefore pragmatically becomes the basis for a flexible structural model. The realization that molecular strain can be spread over large areas rather than localized in individual bond lengths or angles, is almost trivial but extremely important in this context. Many internal coordinates change in order to evade repulsive van der Waals interactions between neighboring atoms within the molecule. Each individual deformation is compensating for only a small part in the total strain. For example, the elongation of a C—C bond to 160 pm is calculated as requiring an energy of less than 2 kcal/mol.[50]

4.1. Angle Deformation

From vibrational spectroscopy it is known that angle deformation is energetically more favorable than bond elongation: the stretching vibrations have larger force constants. Furthermore, and more importantly, a bending vibration is more effective in separating two groups than is simple bond stretching. *The preference for angle deformation over bond stretching* is impressively demonstrated in Table 1 by comparison of the fourfold substituted ethanes (C_t—C_t series 5—7), with the sixfold substituted ethanes (C_q—C_q series 1—4). In the first series the four residues evade mutual repulsion by increasing the C_e—C_e—C_α angle at the central tertiary carbon atom and simultaneously decreasing the C_e—C_e—H angle. This is much more difficult to achieve for the six residues in the C_q—C_q systems 1—4 because each C—C—C angle enlargement results in compression of another C—C—C angle in the center of the molecule (see however 1d). The C_q—C_q systems, therefore, evade repulsion by more pronounced bond extension.

Table 2. Strain and angle opening caused by geminal repulsion in methanes 9 with two, three or four substituents (EFF calculations) [a].
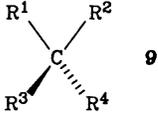
	R^1	R^2	R^3	R^4	α [°]	H_s [kcal/mol]
9a	Me	Me	Me	Me	109	0.0
9b	Me	Me	H	H	113	0.0
9c	Ph	tBu	H	H	114	0.7
9d	Et	tBu	H	H	117	1.6
9e	tBu	tBu	H	H	125	7.4
9f	tBu	tBu	Me	H	121	13.9
9g	tBu	tBu	Me	Me	118	21.6

[a] Calculated according to the MM2 force field [45, 53, 54] extended to include alkyl benzenes [46].

The interplay between the relative space-filling property of the four residues at a four-coordinated carbon atom and the deformation of its geminal bond angles is seen in the case of the alkylated methanes 9 in Table 2. It is noteworthy that the central carbon atom in neopentane, 9a, having four identical residues (R^1—R^4 = CH$_3$), adopts the ideal tetrahedral structure. The central C—C—C angle in propane, 9b, is increased to 113° by the small repulsion between the two methyl groups. Thus, the C—C—C angle deformation in 9 depends less on the total strain and more on the difference in size between the four residues R^1—R^4. Di-*tert*-butylmethane (2,2,4,4-tetramethylpentane), 9e, has a relatively small strain energy of 7 kcal/mol and has a C—C—C angle of 125° (according to crystal structure analysis: 124—126°).[51,52] 9e represents a rare case of a single internal coordinate carrying a high proportion (ca. 40%) of the total strain; according to MM2 ca. 3 kcal/mol is required for this degree of angle deformation.[45b]

The space-filling property of a group, which is decisive in geminal repulsion, is strongly dependent on shape, as seen in the comparison between ethyl and phenyl groups in 9c and 9d (Table 2). The larger and heavier phenyl group leads to less strain and a smaller C—C—C angle than does the smaller ethyl group in the presence of a geminal *tert*-butyl group.

The result is that the bond angles of the tetravalent carbon atom easily adapt to the space-filling requirements of the four substituents.

If the angle deformations of the highly branched ethanes shown in Table 1 are considered in this context, then again a clear correspondence with size and shape of the substituents R^1, R^2, and R^3 is seen. The large difference in size between H and an alkyl group results in the particularly large angle deformations already mentioned in the C_t—C_t-ethanes. It is somewhat smaller in the diarylethanes 6 and in dicyclohexenylethane 7. Thus, the 1-cyclohexenyl residue, which is joined through a trigonal carbon atom, is more similar to the planar phenyl group than to the cyclohexyl ring as regards geminal repulsion. The quaternary centers in the C_q—C_q series 1—4 are, in general, less distorted, but here, too, differences in size determine the distortion pattern. In the most strongly strained compound 1d the central bond angle is increased to almost 120°.

As shown for di-*tert*-butylmethane 9e in Table 2, a secondary CH$_2$ center is particularly easily deformed as a result of steric pressure from geminal groups. The large C—C—C angles at the α-carbon atoms in the alkyl side chains of 1 are also a consequence of this phenomenon.

Increased angles caused by geminal repulsion decisively determine the conformational behavior of branched hydrocarbons. This will be further elaborated in depth in Section 5.

4.2. Bond Elongation

The steric repulsion in compounds 1—7 leads not only to angle deformation but also to bond lengthening. As expected from the preceding discussion, bonds between more highly alkylated, e.g. quaternary, carbon atoms are more strongly affected than those between tertiary or even secondary carbon atoms. This is shown in the graph in Figure 1. The correlation between central C—C bond length and strain enthalpy shows a steeper slope for C_q—C_q than

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for C_q–C_t alkanes, and the smallest slope is found for the C_t–C_t series.
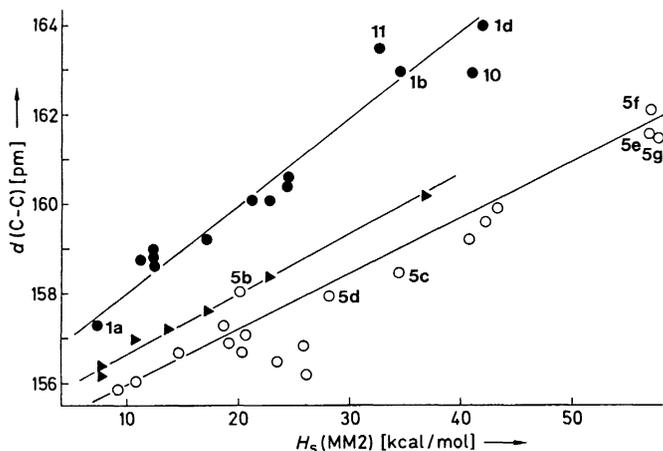
Fig. 1. Dependence of C–C bond length, d(C–C), on molecular strain, H_s(MM2), in various alkanes. O R^1R^2CH–CHR^1R^2 (C_t–C_t) [37, 40], ● $R^1R^2R^3C$–$CR^1R^2R^3$ (C_q–C_q) [36, 40], ▲ $(CH_3)_3C$–CHR^1R^2 (C_q–C_t) [53].

In the first two of these series, the length of the central C–C bond is surprisingly linearly dependent on the total strain of the system. Apparently, the two molecular halves constitute approximately equal steric domains and lead to qualitatively similar and only quantitatively different deformation of the molecules within each series. The proportion of the total strain manifested in the form of bond elongation is either constant or linearly related to the total strain within each series. Exceptions are found in the C_q–C_q series only for most highly strained compounds, viz. 2,2,3,3,4,4,5,5-octamethylhexane **10**, 3,3,4,4-tetraethylhexane **11**, and 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d**. This is not surprising considering that in these C_q–C_q alkanes strongly deformed C_q–C_q–C_α or C_q–C_α–C_β bond angles are also present (see Table 1 and Section 4.1).

1d   **10**

$(C_2H_5)_3C$–$C(C_2H_5)_3$ **11**
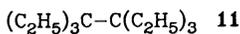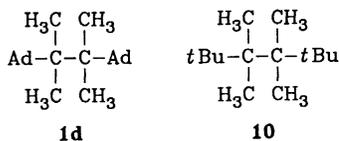
Ad = 1–adamantyl

The longest C–C bonds ever measured experimentally in acyclic systems are found in 2,3-di(1-adamantyl)-2,3-dimethylbutane **1d** (164.7, 164.0, and 163.9 pm).[12] Moreover, these bonds are immediate neighbors[26] (Table 1). The good agreement between experimental and calculated (MM2) values is noteworthy. The central C_q–C_q bond in the structurally related octamethylhexane **10**[36] is comparatively shorter (MM2 value 162.9 pm). Apparently, the more flexible *tert*-butyl group permits a stronger molecular deformation by means of angle opening than does the polycyclic adamantyl skeleton. The question as to the inher-

ent limit of bond elongation has often been posed and finds a general answer here: the multifarious deformability of alkyl chains prevents further elongation of bonds in acyclic molecules. Of the total strain in **1d** (over 40 kcal/mol) only about 3 kcal/mol is manifested in the form of elongation of the central bond to a total of 164 pm.[45b, 50] Thus, even in the C_q–C_q ethanes, only a very small part of the total strain is reflected in the lengthening of the central bond.

In contrast to the C_q–C_q and C_q–C_t series, a less direct relationship between central bond length and strain enthalpy is found in the C_t–C_t series[37] (Fig. 1). In particular, the compounds with linear side chains have shortened central bonds because strain is readily relieved through angle deformation at the methylene groups in the side chains (see Section 4.1).

As already shown in another connection, the linear correlation for the C_q–C_q series (Fig. 1) is also valid for phenyl, cyano, and otherwise substituted compounds,[7] although with a somewhat larger spread. In this context it is of interest that comparatively short central C–C bonds are found in the compound classes **3** and **12** with planar phenyl or linear nitrile groups. Apparently, these substituents increase the opportunities for angle deformation.

12   **3**
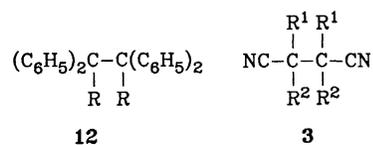
In view of these findings it is understandable that the length of a bond is no criterion for its strength.[7] The bond broken in a homolysis reaction is the one leading to the less strained and more stabilized radical, as evidenced by us in detailed kinetic studies. Also in compound **1d** the somewhat shorter central bond is clearly weaker than the longer neighboring C_e–C_α bond.[26]

5. Preferred Conformations

Angle deformation caused by repulsion between geminal groups has direct consequences for the preferred conformations.[6, 37] Although the angle deformations typical for the C_t–C_t alkanes **5** (see Section 4.1) decrease geminal repulsion, they increase vicinal repulsion in the *anti* conformation as seen from the Newman projection of the en-

13   **14**   **15**
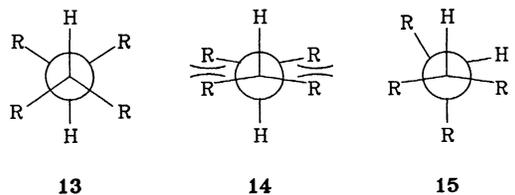
vironment of the C_t–C_t bonds in **13** and **14**. In the conformation **15** with *gauche* hydrogens, the groups R can adopt positions minimizing both vicinal and geminal repulsion. Thus, according to force field calculations, the *anti* ro-

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tamer of 1,2-di-*tert*-butyl-1,2-dicyclohexylethane (3,4-dicy-
clohexyl-2,2,5,5-tetramethylhexane) is 10 kcal/mol less sta-
ble than the preferred *gauche* conformation.[22,37] This dif-
ference is even more extreme in the case of tetra-*tert*-bu-
tylethane 5g[33,44,55] or the isomeric 3,4-di(1-adamantyl)-
2,2,5,5-tetramethylhexanes,[40] which prefer *gauche* confor-
mations similar to 15 in which vicinal hydrogens and R-
groups are almost eclipsed. It is still an open question why
structures with non-alternating Newman projections have
not been found so far. Their occurrence in tetra-*tert*-butyl-
ethane, 5g, was suggested originally by *Mislow* et al. on the
basis of earlier force field calculations.[55c] Even in 2,3-di-
methylbutane, 5a, the *gauche* conformation 15 (R=CH$_3$)
is slightly preferred.[37,48] If the two residues in a C$_t$—C$_t$ al-
kane 5 differ in the space-filling properties, the D,L dia-
stereomer 16 turns out to be more stable than the *meso*
form 17.

16 (D,L)   17 (*meso*)
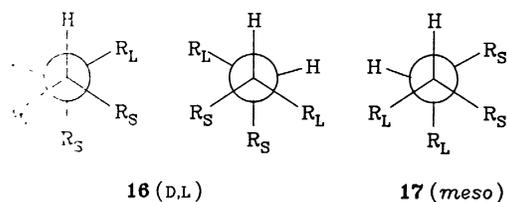
This is because in the preferred conformation of the D,L
diastereomer 16 the two large substituents R$_L$ are flanked
by the steric vacancy caused by the small hydrogen atoms.
In the *meso* compound 17 only one of the large groups R$_L$
can adopt this preferred position, the other one being in a
gauche relationship to two R residues. Accordingly, D,L-
1,2-dicyclohexyl-1,2-di-*tert*-butylethane, 5d, is thermody-
namically more stable than the *meso* diastereomer 5c by
6 kcal/mol.[22] These conformation-controlling factors,
which have already been identified earlier for C$_t$—C$_t$ al-
kanes and phenyl-substituted analogs,[6,37] are more gener-
ally applicable than hitherto believed.

With respect to the central bond, a total of five stag-
gered, alternating rotamers are possible for a symmetri-
cally substituted ethane[56] having three substituents of dif-
ferent steric requirement (R^1, R^2, and R^3, designated L, M,
and S). Two of these rotamers (I and II) correspond to the
meso form (*erythro*), and three (III—V) to the D,L (*threo*)
form. These are shown in Newman projections with a
schematic representation of the steric requirements in Fig-
ure 2. The expected increase of the L—C—M angle, and de-
crease of the L—C—S and M—C—S angles at the central
carbon atoms (cf. Section 4.1) have been taken into ac-
count in these projections.

The consequences of this angle increase are readily seen
in Figure 2. Judging from the repulsion between the
groups, rotamer I in the *meso* series clearly appears less fa-
vorable than rotamer II. The deformation of the central
carbon atom in I causes a closer approach of the medium-
sized substituents, M, to the large ones, L. In II, however,
the increased bond angle between the L and M substit-
uents leads to relief of vicinal interaction between these
groups.
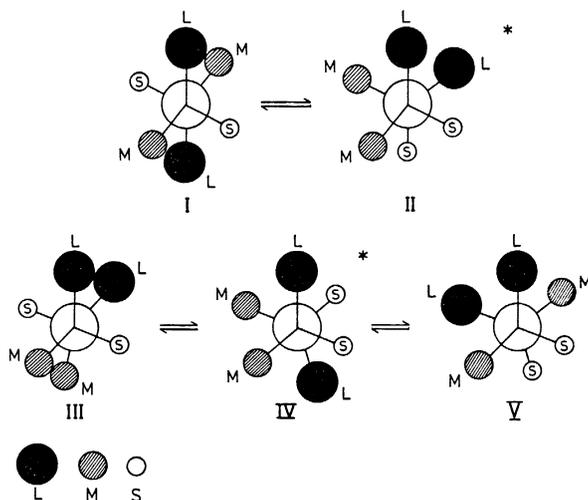
Fig. 2. Model for conformational analysis of C—C single bonds taking into
account geminal repulsion between groups of different sizes (L = large,
M = medium, S = small). I—II: *meso*; III—V: D,L. In each case, only one
enantiomer of III—V is shown. * Denotes the preferred conformation.

Thus, although conformer I with the large substituents L
anti to each other is slightly preferred as long as ideal te-
trahedral geometry is maintained, this conformer becomes
less favorable when increasing differences in size cause an
increased deformation of the central bond angles.

By analogy, IV is seen to be the preferred conformation
in the lower row of Figure 2. Here, too, the two large sub-
stituents L profit from less vicinal repulsion of the smallest
substituents as a result of opening of the L—C—M bond
angle. Of all the rotamers shown, IV should be the most
stable. Consequently, the D,L diastereomer becomes more
stable than the *meso* form.

Further predictions can be made for particular combina-
tions of groups. If two of the groups are identical or effec-
tively identical, the differences between II, IV, and V van-
ish (see 5e and 5f in Table 1 and Fig. 2).

The differences between the conformers become less
pronounced as the differences in size between the groups
R diminish. This is particularly true for IV and V, the
meso-2,3-diisobutyl-2,3-diphenylsuccinic ester 4b (L = *i*Bu,
M = Ph, S = COOMe) exists in the *gauche* conformation II
in clear agreement with the model.[29,30] Also, with respect
to the total strain, the methoxycarbonyl group proved to be
"smaller" than the phenyl group.[29] Force field calcula-
tions indicate that the *anti* form I is less stable by 1.7 kcal/
mol.[29]

18   19

Another special case obtains in the C$_q$—C$_q$ series when
two large substituents R^1 are combined with two small
ones, R^2 and R^3. Here, conformation 18 is, of course, pre-
ferred, because the large groups L are *anti*, but the tor-
sional angle between these groups is not 180° but signifi-

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cantly less (165—175°; see Fig. 2). Thus, conformations corresponding to **IV** are present, and surprisingly enough this is also the case when R^2 and R^3 are methyl groups, as in **1a** and **1d** (cf. **19**). Apparently, the methyl groups in **19** differ as regards their vicinal repulsion. A sterically less demanding pair (Fig. 2) gets closer together and reduces the total strain, as shown earlier.[57] This is due to the fact that methyl groups do not behave as spheres; in contrast, their interlocking ability allow them to reduce repulsion pairwise.

Phenyl groups influence the conformations of substituted ethanes in a different manner. Their disk shape allows them to avoid geminal repulsion more easily, and hence the bond angles at the ethane carbons are much less deformed (see Table 2). In the C_q—C_q series the 1,2-diphenylethanes **2** with *n*-alkyl side chains adopt the *anti* conformations **I** or **III** with normal torsional angles of 180° between the phenyl groups. Similarly, in the C_t—C_t series, the diarylethanes **6** carrying smaller alkyl groups (methyl to isopropyl), follow the usual conformational rules: *meso* and D,L configurations prefer the conformations **I** and **III**, respectively, the hydrogen atoms being *anti*; the *meso* form is somewhat more stable than the D,L form.[13] Only *tert*-alkyl groups (**6a**—**6d**) increase the geminal repulsion to such an extent that the *gauche* conformation **IV** becomes preferred in the D,L series because of increased angle deformation. In contrast, the *meso* form maintains the *anti* conformation **I** and remains more stable than the D,L form.[13, 14]

6. Rotational Barriers and the Isolation of Stable Rotational Isomers

The height of the barrier toward rotation around the central bond of an ethane is not a simple function of the total strain or the sum of the volumes of the groups. Six-fold substituted C_q—C_q ethanes show rather uniform rotational profiles, and the rotational barriers are generally not high ($\Delta G^* \leq 13$ kcal/mol; see Fig. 3). Secondary groups can co-rotate (like cogwheels) in the course of a rotation around the central bond. This can result in a complex change of the enthalpy as a function of the inner movements during rotation.[58] This is very nicely illustrated by the rotation profile of the isopropyl derivative in Figure 3.

C_t—C_t ethanes with large substituents have very steep torsional profiles.[23, 24] In tetra-*tert*-butylethane, **5g**, the barrier toward rotation around the central bond is even higher than that for dissociation.

Starting with this phenomenon and using a strategy based on orienting force field calculations, the compounds **20** and **5e, f** were synthesized[40] [see Reaction (h)]. NMR-spectroscopy demonstrated that in both cases three isomers were formed, assigned as the three rotamers **II** (*meso*), **IV**, and **V** (D,L) (Fig. 2). The two conformationally stable rotamers D,L-**5e** and D,L-**5f** could even be separated by manual crystal selection, and after purification by fractional crystallization were subjected to crystal structure analysis[30, 40] (see Fig. 4). **5e** corresponds to the *anti* conformation **IV** and **5f** to the *gauche* conformation **V** when L = 1-adamantyl, M = *tert*-butyl, and S = H.

Fig. 3. Rotational potentials for the C_q—C_q bonds in hydrocarbons $R(CH_3)_2C$—$C(CH_3)_2R$ according to MM2 calculations [57].

Fig. 4. Structures and Newman projections of the two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane with important bond lengths [pm] and angles [°] derived from crystal structure analysis [30, 40]. Ad = 1-adamantyl. The (*S*,*S*)-enantiomers are shown.

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The assignment of the rotamers made previously by NMR was based on a characteristic difference between the *tert*-butyl groups *gauche* or *anti* to the methine C−H bond. The former possess lower rotational barriers ($H_{rot} = 3$ kcal/mol), as is also observed for tetra-*tert*-butylethane, **5g**; the latter have higher barriers ($H_{rot} = 8$ kcal/mol), both being MM2 calculated values[40,44,55] (Fig. 5).

$$\Delta H_{rot}^{\ddagger} \simeq 8 \text{ kcal/mol}$$

$$\Delta H_{rot}^{\ddagger} \simeq 3 \text{ kcal/mol}$$

5g

$(R,R)-\textbf{5e}$ $(R,R)-\textbf{5f}$ *meso*
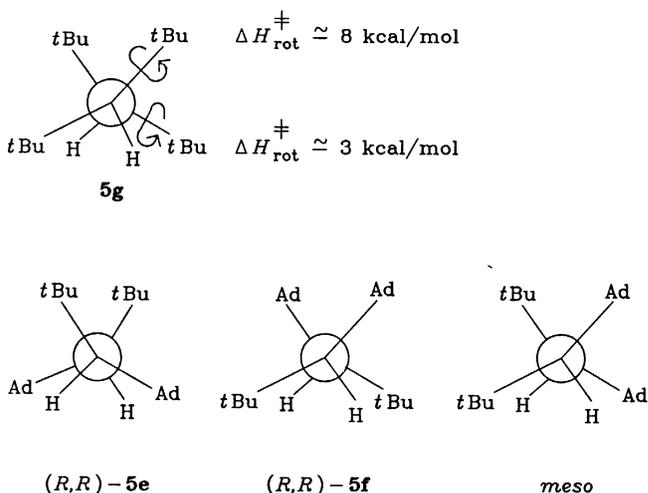
Fig. 5. Newman projections of tetra-*tert*-butylethane (**5g**), the two rotamers of D,L-3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexanes [40, 59] (illustrated: (R,R)-enantiomers) and the corresponding *meso*-compound. Ad = 1-adamantyl.

To the best of our knowledge, **5e** and **5f** are the first examples of stable rotameric aliphatic hydrocarbons.[60] Their strongly deformed structures, in particular the Newman projections, eminently confirm the rules for conformational analysis of C−C single bonds, derived for $C_t−C_t$ hydrocarbons in the present work, and applicable also to other compounds.

7. Conclusion and Outlook

Starting with the work of *D. H. R. Barton*,[61] the development of general rules of conformational analysis with the aid of geometrically standardized molecular models has made possible a unifying description of an unusual wealth of questions relating to structure and reactivity. Strained molecular structures, however, are at the limit of applicability of simple conformational analysis, and standard bond lengths, bond angles, and torsional profiles are no longer valid. The conformational analysis of each strained molecule becomes an individual problem, in the solution of which the force field method has proved well suited.

The knowledge of structural data for a variety of strained compounds also makes it possible to give new and refined guidelines for qualitative conformational analysis. Here, the consequences of angle enlargement caused by geminal repulsion between large groups are particularly decisive for the conformation. If angle enlargement is energetically unfavorable, bond lengthening will be the dominating outcome of strain. However, strain is always dis-

tributed over many structural coordinates, so that the degree of distortion of individual bond angles and bond lengths is limited. The influence of a substituent on the conformation depends less on the size than on the shape of the substituent.

The possibility of calculating unusual molecular geometries using the force field method is of importance not only for the determination of intramolecular but also intermolecular interactions. After all, van der Waals interactions can influence the nature of the accessible reaction channels[62] and hence the selectivity, e.g. in radical recombination[63] or in asymmetric synthesis.[35] Their importance should be even more far reaching in biological recognition processes.[14,15,64-65]

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[59] (R,R)-**5e** and (R,R)-**5f** are rotamers and at the same time diastereomers which do not differ in their absolute configurations. The signs of the torsional angles between equal groups are, however, either positive (P) or negative (M) in both rotamers; see also V. Prelog, G. Helmchen, *Angew. Chem. 94* (1982) 614; *Angew. Chem. Int. Ed. Engl. 21* (1982) 567; for (S,S)-**5e** und (S,S)-**5f** (Fig. 4), the signs are reversed (M and P, respectively). (S. W. Bähr, H. Theobald, *Organische Chemie,* 1st edit. Springer Verlag, Berlin—Heidelberg—New York 1973, p. 97).

[60] For isolable rotamers see also J. S. Lomas, P. K. Luong, J.-E. Dubois, *J. Org. Chem. 42* (1977) 3394; B. Tiffon, J. S. Lomas, *Org. Magn. Reson. 22* (1984) 29; M. Oki, *Angew. Chem. 88* (1976) 67; *Angew. Chem. Int. Ed. Engl. 15* (1976) 87; S. Murata, S. Kanno, Y. Tanabe, M. Nakamura, M. Oki, *Bull. Chem. Soc. Jpn. 58* (1984) 525, and references cited therein.

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[62] See also J. D. Dunitz, *Phil. Trans. R. Soc. London B272* (1975) 99.

[63] A. Peymann, *Diplomarbeit,* Universität Freiburg 1983; H.-D. Beckhaus, A. Peymann, unpublished work.

[64] See, e.g., W. Graham, L. Mangold, *Endeavour, New Ser. 7* (1984) 2.

[65] J. M. Blaney, P. K. Weiner, A. Dearing, P. A. Kollmann, E. C. Jorgenson, S. J. Oatley, J. M. Burridge, C. C. F. Blake, *J. Am. Chem. Soc. 104* (1982) 6424.

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