STUDIES ON CYCLOHEXANE DERIVATIVES

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Studies on cyclohexane derivatives

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Proefschrift

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CONTENTS

INTRODUCTION

This thesis is based mainly on investigations on cyclohexane, cyclohexene and cyclohexadiene derivatives the results of which have been published [1-6] or are in the press.[7,8] Another seven papers [9-15] in which the present author participated is also connected closely to the subjects to be discussed.

The preparation and properties of cyclohexane systems with carboxyl and/or alkyl substitution was a central theme in the investigations. Attention was drawn to, amongst others,
(i) the dependence of the ring conformation, i.e. the relative stability of both chair conformations and, in some cases, also of non-chair forms, on the ring substitution applied;[2,7,9]
(ii) the influence of alkyl substituents (at the 1-, 2-, 3- and 4-position) on the acidity of an equatorial or axial 1-carboxyl group;[6,7]
(iii) the assignment of configuration to the compounds studied; besides some chemical proofs of configuration[2,10-13] several other reliable configuration criteria have been developed;[1,5,7]
(iv) the efficiency, the selectivity and the mechanism of some of the preparative procedures applied.[1-4]

The cyclohexane and 1,4-cyclohexadiene derivatives entered the investigations through the last-mentioned studies. Cyclohexenes were found to play a role as intermediates in several catalytic hydrogenations of aromatic compounds,[1,2] whereas 2,5-cyclohexadiene-1-carboxylic acids[8] are intermediate products in a newly developed synthesis of 1-alkyl-substituted cyclohexanecarboxylic acids.
In the present summary the following order will be applied:
I Preparative Methods
II Assignment of Configuration
III Conformational Analysis; pK_a^*-measurements.

I. PREPARATIVE METHODS

1. Catalytic hydrogenation of benzene and cyclohexene derivatives

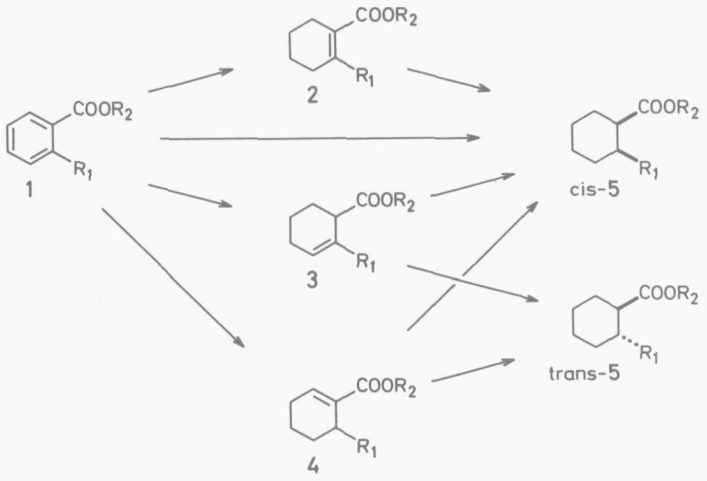
A very useful method for preparing cyclohexane derivatives is the heterogeneously catalyzed hydrogenation of the corresponding aromatic compounds.[16,17] Starting out from di- or trisubstituted benzenes, a mixture of stereoisomers is generally obtained showing that the process involves more than just all-cis addition of six hydrogen atoms from the surface of the catalyst to the adsorbed side of the ring.

To account for the contribution of two-side addition of hydrogen the following mechanisms have been suggested (i) 'roll-over' of adsorbed intermediate cyclohexenes[18,19] (ii) several ways of top-side addition of hydrogen to adsorbed unsaturated systems,[20,21] and (iii) desorption of intermediate cyclohexenes followed by readsorption with the other side of the ring.[22,23]

The reality of mechanism (iii) has been ascertained experimentally by us in the liquid-phase hydrogenation of some 2-alkylbenzoic acids and methyl 2-alkylbenzoates over rhodium and ruthenium catalysts. Scheme I gives (in a simplified formulation) routes towards cis- and trans-2-alkylcyclohexanecarboxylic acid [5] on the basis of cis-addition of hydrogen during each residence of the substrate molecules on the catalyst surface. Trans-isomer is formed then through the cyclohexenes [3] and [4]. It must be borne in mind, however, that transitions between the cyclohexenes [2]-[4]may occur by double bond migration on the catalytic surface.

The course of the hydrogenation of [1] (R_1 = t-Bu, R_2 = H) over rhodium at room temperature and atmospheric pressure is relatively clear as the aromatic acid [1] is found to be hydrogenated selectively with respect to desorbed intermediate cyclohexenes. About 75% of [1] adopts six hydrogen atoms during one residence on the surface yielding cis-[5], 23% desorbs as cyclohexene [4] yielding a 1 : 1 mixture of cis- and trans-[5] upon readsorption and hydrogenation. The cyclohexenes [2] and [3] were detected but play minor roles (< 1%) in the perceptible hydrogenation process. The graph of the reaction course (Fig. 1) reveals at once that for this case desorbing cyclohexene [4] is by far the main source of the trans-[5] formed.

An analogous course is observed for the hydrogenation of the corresponding methyl ester ([1], R_1= t-Bu, R_2 = Me) over rhodium



Scheme I

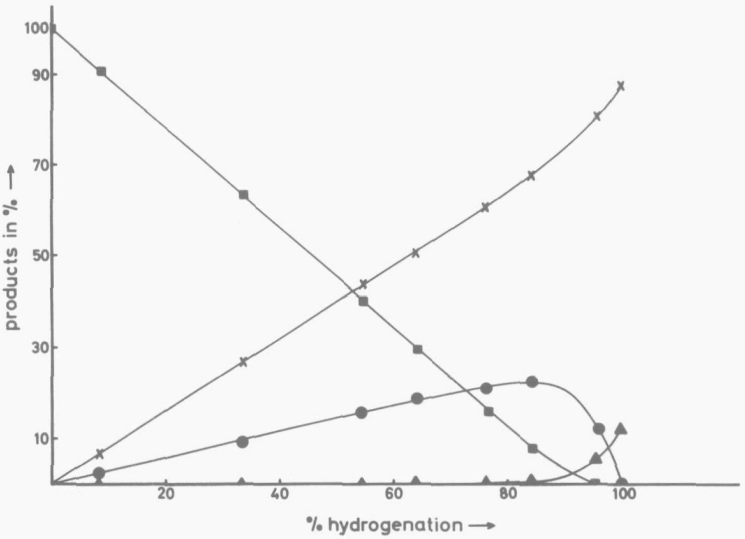


Fig. 1. Hydrogenation of 2-t-butylbenzoic acid (1.8 g) over 0.3 g of 5% rhodium on carbon in ethyl alcohol (60 ml) at 22° and 1 atm. ■, 2-t-butylbenzoic acid; ●, 6-t-butyl-1-cyclohexene-1-carboxylic acid; ×; cis-2-t-butylcyclohexanecarboxylic acid; ▲, trans-2-t-butylcyclohexanecarboxylic acid.

under the above conditions. The stereochemistry of the hydrogenation of the intermediate cyclohexene [4] has been altered however: cis- and trans-[5] are formed from [4] in a 4.5 : 1 ratio.
In rhodium-catalyzed hydrogenations of compounds [1] with smaller size of R_1 (R_1 = Me, Et, iPr; R_2 = H, Me) cyclohexene [2] as well as cyclohexene [4] have been observed as intermediates.[24] The maximum concentration of [4] in the reacting mixture is substantially lower than for R_1 = t-Bu but the total quantity of [4] desorbed from the surface is of the same order of magnitude. Thus, with decreasing size of the alkyl substituent the ease of hydrogenation of [4] in the presence of [1] (governed by adsorption and surface reaction rate of [4] relative to [1]) increases. This is comprehensible. Cyclohexene [2] attains a concentration of 5-6% in the above-mentioned hydrogenations. The maximum concentration is observed near the end of the reaction, consequently the total amount of [2] desorbed is only slightly more. The low reactivity of [2] with respect to [4] will be caused by the increased substitution of the double bond. The very small role of [2] in the hydrogenation of [1] (R_1 = t-Bu) may be taken as an indication that the addition of hydrogen chiefly starts at the carbon atom carrying the t-Bu group.[25]
When the aromatic carboxyl group is flanked by two methyl groups (2,6-dimethylbenzoic acid), the hydrogenation over rhodium is closely related to that of [1] (R_1 = t-Bu). Here, 2,6-dimethyl-1-cyclohexene-1-carboxylic acid desorbs from the surface and appears to be the main source of the c-2,t-6-dimethyl-r-1-cyclohexanecarboxylic acid formed.
Data on the hydrogenation of [1] (R_1 = t-Bu, R_2 = H, Me) over ruthenium, platinum and palladium are given in ref. 1. As to the manifestation of intermediate cyclohexenes, i.e. the maximum concentration attained in the reacting mixture, the order of catalyst metals is Rh > Ru > Pt, Pd. The total quantity of cyclohexene [4] desorbed is over ruthenium about the same as over rhodium but much less over platinum. The stereochemical results (i.e. the cis/trans ratios) obtained for the hydrogenations over palladium indicate that either desorption of alkenes takes place on a large scale (combined with relatively fast readsorption and reaction) or process (i) or (ii) plays an important role. In view of the separate position of palladium among the other transition metals in exchange [18] and hydrogenation processes the last mentioned possibility cannot be excluded.

It may be mentioned that the hydrogenation of 1,2-di-t-butylbenzene over rhodium, studied by van de Graaf, [26] constitutes an excellent example of the appearance of two step next to one step ring saturation. As to this aspect this reaction is closely connected to the hydrogenation of [1] (R_1 = t-Bu).
The two step process is predominating in the hydrogenation[2] of 1,3,5-tri-t-butylbenzene [6] over rhodium, platinum, and palladium. The greater part of the reacting molecules desorbs as cis-1,3,5-tri-t-butylcyclohexene [7] after addition of four hydrogen atoms from the metal surface. This follows from the course of these hydrogenations (ref. 2, Fig. 1-3) as well as from the observation that separate hydrogenations of [6] and [7] yield the same ratio of cis, cis- and cis, trans-1,3,5-tri-t-butylcyclohexane (see Table I).

Table I. Product composition in hydrogenations[a] of 1,3,5-tri-t-butyl benzene and 1,3,5-tri-t-butylcyclohexenes

Substrate	Catalyst	Products in % cis, cis	cis, trans
1,3,5-tri-t-butylbenzene [6]	Rh/C	84	16
1,3,5-tri-t-butylbenzene	Pt/C	93	7
1,3,5-tri-t-butylbenzene	Pd/C	98	2
cis-1,3,5-tri-t-butylcyclohexene [7]	Rh/C	84	16
cis-1,3,5-tri-t-butylcyclohexene	Pt/C	93	7
cis-1,3,5-tri-t-butylcyclohexene	Pd/C	98	2
cis-1,3,5-tri-t-butylcyclohexene	[b]	98	2
trans-1,3,5-tri-t-butylcyclohexene [8]	Pt/C	-	100
trans-1,3,5-tri-t-butylcyclohexene	Pd/C	-	100
trans-1,3,5-tri-t-butylcyclohexene	[b]	-	100

a. In n-heptane at 25° and atmospheric pressure.
b. Reductions with diimide (formed in situ from p-toluenesulfonyl-hydrazine) for 24 hours at 100°.

Some insight in the appearance of [7] in the hydrogenation of [6] over platinum and palladium was gained[2] by measuring the rates of hydrogenation of [6], [7] and some related compounds and by carrying out competition experiments. Deuterations of [6] and [7] otherwise showed that the addition processes are accompanied by complex exchange phenomena in which in this case also the t-Bu groups are involved.[2]
It was interesting to note that in the hydrogenation of [7] over

platinum and palladium some dehydrogenation occurs yielding [6]. This was not observed in the hydrogenation of trans-1,3,5-tri-t-butylcyclohexene [8]. Therefore, it may be concluded that with [6] and [7] addition as well as elimination of hydrogen take place by cis processes.

The hydrogenation of [6] and [7] over ruthenium has been investigated by Hartog and Weterings.[27] Combination with the present work yields the following order of metals as to the appearance of [7] during the hydrogenation of [6]: Rh > Ru > Pt > Pd.

Other examples[24] in which the two step process plays an important role in the catalyc hydrogenation of the aromatic nucleus include the rhodium-catalyzed hydrogenation of phthalic acid, dialkyl phthalates, and 1,4-di-t-butylbenzene [9].

Compound [9] is distinghuished from several 1,4-dialkylbenzenes studied[24,28,29] in yielding a relatively high percentage of cis-1,4-di-t-butylcyclohexane (cis-[10]) when hydrogenated over platinum, rhodium and palladium at 25°. Hydrogenation of 1,4-di-t-butylcyclohexene [11] yields cis- and trans-[10] in similar high ratios.

In particular the stereochemistry of hydrogenation of [9] and [11] over palladium is noteworthy as 1,4-dialkylbenzenes and 1,4-dialkylcyclohexenes generally yield the more stable trans-1,4-dialkylcyclohexane in excess when hydrogenated over palladium.[30,31]

The stereochemical results of the hydrogenation of disubstituted cyclohexenes (i.e. the cis/trans ratio of the cyclohexanes obtained) cannot be rationalised in a simple way. For example the question whether adsorption/desorption equilibria are fast compared to the surface reactions and the problem which reaction step is rate-controlling under a given set of conditions are still in discussion. When accepting the formation of the half-hydrogenated state as the rate- and product-determining step for hydrogenations at atmospheric pressure one has to consider two adsorbed states each connected with two transition states of addition of the first hydrogen atom. As to the geometry of the above states, bond eclipsing around the carbon atoms of the original double bond is preferred; as a consequence the ring is in a boat conformation.[26,31,32]

This model predicts satisfactorily several stereochemical trends observed in the hydrogenation of 1,4- and 2,3-substituted cyclohexenes,[1,26,33] such as the high percentage of cis-isomer obtained in the hydrogenation (Pt, Rh) of 1-t-butyl-4-X-cyclohexenes and, on the other hand, the predominant formation of trans-isomer in the hydrogenation (Rh, Ru, Pd, Pt) of 2-t-butyl-3-X-cyclohexenes. Application of the above approach to the hydrogenation of 1,3- and 2,4-substituted cyclohexenes, however, is less successful.[33]

Liquid-phase hydrogenations at atmospheric pressure in the tem-

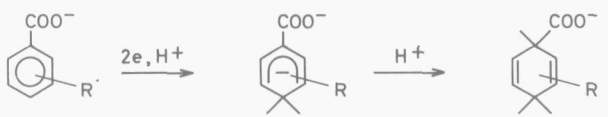
perature range 0-90° show that with increasing temperature the amount of the more stable cyclohexane isomer generally increases. Pronounced effects are observed for example in the hydrogenation of 1-t-butyl-4-X-cyclohexenes over platinum and rhodium. [33] The effect of temperature is much less when working at high pressure (200 atm H_2). This is in accordance with the proposal[16] that under such conditions the rates of adsorption (for the two adsorbed states) are product-controlling.

Double bond migration phenomena on the catalyst surface have been studied by us by comparing the results of hydrogenation of 4-t-butyl-1-hydroxymethylcyclohexene and 1-t-butyl-4-hydroxymethylcyclohexene. In the former substrate the C-O bond is at an allyl position and extensive hydrogenolysis occurs; in the other substrate double bond migration is required to satisfy hydrogenolysis conditions. The order of migration activity obtained from these experiments is Pd > Rh > Pt. Furthermore it is found that increase of temperature increases the amount of migration.

Finally, it may be remarked that 'trans-addition' of hydrogen (mechanism (ii)) could cross several of the above considerations. In search of the existence of this mechanism we have studied the heterogeneous hydrogenation of hexamethyl-Dewar-benzene (hexamethylbicyclo [2.2.0]hexa-2,5-diene). [34] Unfortunately, the information obtained did not suffice for a decisive answer about mechanism (ii). At present we consider this mechanism less probable and not intended for a major role in heterogeneously catalyzed hydrogenations.

2. Reduction and reductive alkylation of benzoic acid and alkylbenzoic acids with lithium in liquid ammonia

The partial reduction of the benzene nucleus with solutions of alkali metals in liquid ammonia in the presence of a suitable proton donor (mostly ethanol) is a well-known procedure. [35,36] Yet, relatively few data are available for the metal-ammonia reductions of benzoic acid and alkylbenzoic acids, [37-40] which generally are formulated as



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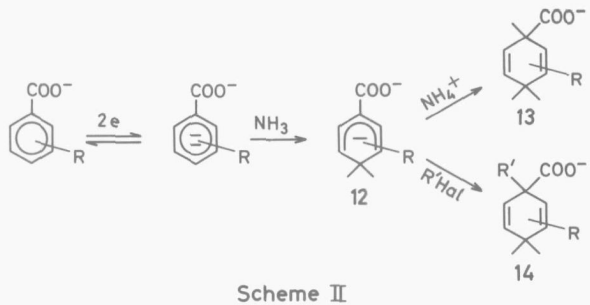
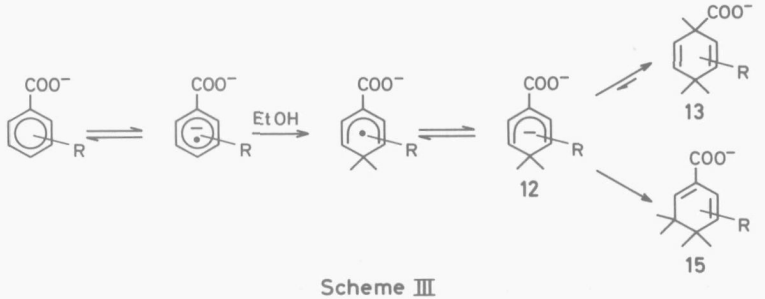
We have studied[8] this reaction and the related reductive alkylation for preparative as well as for mechanistic reasons:
(i) It will be clear that lithium-ammonia reduction followed by catalyc hydrogenation is a two step alternative for the direct hydrogenation of alkylbenzoic acids. Partial hydrogenation of compounds [13] is a potential route to alkyl-substituted 2-cyclohexene-1-carboxylic acids, whereas complete saturation yields alkylcyclohexanecarboxylic acids.
(ii) One may wonder whether a proton donor is a necessity for obtaining species [12] and [13] or whether ammonia itself can protonate the negatively charged aromatic nucleus. Species [12] was considered particularly important in view of the preparation (by alkylation of [12]) of 1-alkyl-substituted 2,5-cyclohexadiene-1-carboxylic acids [14]. Hydrogenation of [14] would afford 1-alkylcyclohexanecarboxylic acids, thus providing an alternative for the Koch synthesis (see I.5.2).
(iii) Experiments with 4- and 3-deuterobenzoic acid have been included to provide information regarding the reversibility of the protonation of the nucleus.
(iv) Ammonia, ammonia-ethanol, and ammonia-water have been compared as the media with special reference to double bond migration phenomena in [13].
The results of numerous lithium-ammonia reductions and reductive alkylations of benzoic acid and alkylbenzoic acids (Tables I and II in ref. 8) have led to the following picture for these reactions. When working in liquid ammonia without added proton donor (see Scheme II) the aromatic acid accepts two electrons and a proton yielding the dianion [12]. In [12] the electron accepting carboxylate group is situated at the most negative position[41] of the cyclohexadienyl anion. We assume that a trianion is required to abstract a proton from ammonia.[42] Experiments with 4-deuterobenzoic acid (Table IV in ref. 8) showed that this proton addition is irreversible.



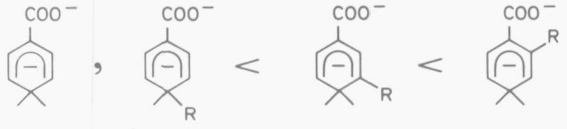
Scheme II

The dianion [12] can be protonated by e.g. ammonium chloride to yield the unconjugated system [13] in a kinetically controlled reaction, as has been discussed[43-45] for other benzenoid substrates. When alkyl halides were added to solutions of [12] in ammonia essentially quantitative alkylation at the 1-position was observed yielding [14]. A convenient method of preparing acids [14] was found to consist of adding lithium to a solution or suspension of the alkylbenzoic acid in ammonia until permanent blue colour and then adding excess of alkyl halide.
Under classical conditions, i.e. in the presence of ethanol, Scheme III applies. Anion [12] is supposed to undergo almost complete protonation to yield [13]. With R = H and R = 3- or 4-alkyl isomerization of [13]into [15] may occur, the extent of which was found to depend on the conditions applied. Longer residence times in the ammonia-ethanol-ethoxide medium as well as higher temperatures promote isomerization of [13] into the conjugated system [15]. The conservation of most of the labeling in a sample of 1,5-cyclohexadiene-1-carboxylic acid obtained from 3-deutero-benzoic acid proved the slowness of the reverse reaction ([15] → [13]).



Scheme III

No isomerization [13]→[15] was observed in the case of R = 2-alkyl. Taking the extent of isomerization - under given conditions - as a measure of the basicity of the dianions involved (in other words of the equilibrium concentration of [13]) the following sequence is obtained.



This sequence has been rationalised[8] on the basis of electronic[46] and steric effects.
When using water as the proton donor, the isomerization [13] → [15] was not observed. Obviously, in the presence of water a much lower concentration of [13] is allowed than in the presence of the less acidic ethanol. Reduction with the lithium-ammonia-water system was found to be the method of choice when 3- and 4-alkylbenzoic acids are to be reduced to the 1,4-dihydro products. Experiments in which ammonium chloride was present during the reduction revealed extensive reduction of the carboxyl group.[8,24] Thus, 4-methylbenzoic acid yielded a mixture of 4-methylbenzaldehyde, 4-methylbenzylalcohol, p-xylene, and 4-methyl-2,5-cyclohexadiene-1-carboxylic acid. Under these circumstances some undissociated carboxyl groups might be involved and attacked.
Some thirty new alkyl-substituted 2,5-cyclohexadiene-1-carboxylic acids were prepared in the course of this study. Some of the acids together with their pK_a^*'s are listed in Table XII. For preparative and other details we refer to ref. 8.
Reduction of aromatic systems with lithium and ethylamine[47] was applied for the synthesis[2] of 1,4-di-t-butylcyclohexene and cis- and trans-1,3,5-tri-t-butylcyclohexene ([7] and [8]). In the lithium-ethylamine reduction of 1,3,5-tri-t-butylbenzene a 2.4:1 mixture of [7] and [8] was obtained which was separated by preparative GLC. As to the mechanism of this reduction a three step course can be envisaged: reduction to a 1,4-cyclohexadiene derivative, isomerization to a conjugated system, and again reduction.
Upon reduction of 2-methylbenzoic acid with lithium and ethylamine, the 'normal' dihydro product, 2-methyl-2,5-cyclohexadiene-1-carboxylic acid, was obtained. Apparently, here the isomerization required for continued reduction does not occur. Reduction of 4-t-butylbenzoic acid in this way also gave mainly dihydro products. In both experiments the conversion of the aromatic acid was far from complete, in spite of the use of a large excess of lithium.

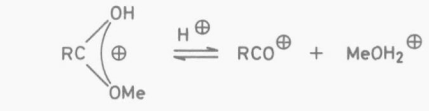
3. Ester hydrolysis using concentrated sulfuric acid[3]

From mixtures of isomeric alkyl-substituted cyclohexanecarboxylic acids, as obtained by hydrogenation of unsaturated precursors, generally only one of the isomers can be obtained in a pure state[1,7] by recrystallization of the mixture of acids or of easily accessible derivatives, e.g. benzylamine salts. Additional isomers can be obtained by converting mixtures of acids (often mother liquors of the above recrystallizations) into mixtures of methyl esters and subjecting these to preparative GLC. Alternatively, mixtures of isomeric methyl

esters may be obtained by catalytic hydrogenation of methyl alkylbenzoates.[1]

For the hydrolysis of samples of methyl esters as isolated by preparative GLC we wished to have at our disposal a simple, rapid and non-epimerizing technique. It was found[3] that a short treatment with concentrated sulfuric acid at room temperature fulfils these requirements[48] and provides a preparatively convenient method of hydrolysis.

Apparently the $A_{AC}1$ mechanism[49] is involved with the equilibria (see Scheme IV) in favour of the protonated acid due to the excess of water.



Scheme IV

Some kinetic results for the hydrolysis of esters in concentrated sulfuric acid are shown in Table II (for additional data see Table I in ref. 3).

Table II. Ester Hydrolysis Rates in 95% Sulfuric Acid at 25°

Ester	First order rate constant ($s^{-1} \times 10^4$)
Methyl trans-4-t-butylcyclohexanecarboxylate	17.0
Methyl cis-4-t-butylcyclohexanecarboxylate	94
Methyl 1,t-4-dimethyl-r-1-cyclohexanecarboxylate	55
Methyl 1,c-4-dimethyl-r-1-cyclohexanecarboxylate	179
Methyl nonanoate	9.2
Methyl 2-n-propylpentanoate	18.2
Methyl benzoate	0.65
Methyl 4-methylbenzoate	2.41
Methyl 3-methylbenzoate	1.51
Methyl 2-methylbenzoate	182
Methyl 3-bromobenzoate	0.032
Methyl 3-chlorobenzoate	0.035
Methyl 4-methoxybenzoate	10.2
Methyl mesitoate	$> 10^3$

Steric effects in the hydrolysis in sulfuric acid can be understood when it is accepted that the transition state of hydrolysis is less space-demanding than the protonated ester; any van der Waals strain in the latter will then increase the rate of hydrolysis. Two pairs of epimeric methyl alkylcyclohexanecarboxylates provide examples of this: the compounds with an axial methoxycarbonyl group are hydrolyzed distinctly faster than their isomers with an equatorial ester group, obviously as a consequence of release of steric strain during the reaction. The reverse is known to be true in hydrolysis in dilute acid[50] and in alkaline hydrolysis.[51, 52] Furthermore it may be noted that methyl trans-4-t-butylcyclohexanecarboxylate is hydrolyzed in sulfuric acid at the same rate as its acyclic analogue methyl 2-n-propylpentanoate.

A more pronounced steric effect is observed for methyl 2-methylbenzoate which compound hydrolyzes 75 times faster than methyl 4-methylbenzoate.

As to electronic effects, a Hammett rho value[53, 54] of - 3.6 is calculated - using rate constants of methyl benzoate and 3-substituted methyl benzoates - showing that $A_{AC}1$ hydrolysis is more sensitive towards substituent influences than the $A_{AC}2$ hydrolysis in more dilute acid.[55] The $A_{AC}1$ splitting may proceed in two ways,[56] in either case additional positive charge has been developed on the carboxyl carbon in the transition state. This explains the high rho value observed. Furthermore, a Yukawa-Tsuno resonance parameter[57] of 0.35 is derived from the reaction rate constant of methyl 4-methoxybenzoate.

Finally, it may be noted that methyl mesitoate, possessing three activating methyl groups, is found to be hydrolyzed very fast in 95 as well as in 90% sulfuric acid, demonstrating that use of 100% sulfuric acid[58, 59] is not necessary.

4. Separation of isomeric cyclohexane derivatives by selective inclusion into thiourea

We have found[4] that trans-4-alkylcyclohexanecarboxylic acids form adducts (inclusion compounds) with thiourea[60] whereas the corresponding cis-isomers generally do not. This fact enabled successful separation of several pairs of epimeric 4-alkylcyclohexanecarboxylic acids. In addition to the acids reported in ref. 4 also 4-t-pentyl-[7], 4-cyclohexyl-[7, 61], and 4-trimethylsilylcyclohexanecarboxylic acid[62] could be separated conveniently in this way into the cis- and the trans-isomer.

According as the dimensions of the alkyl group approach the inner dimensions of the thiourea channel more stable adducts are obtained (probably as a result of overall increase of attractive van der

Waals forces between the guest molecules and the walls of the host). Thus, the solubilities of trans-4-R-cyclohexanecarboxylic acids in a saturated solution of thiourea in methanol at 20° depend on R in the order[4] Et > iPr > t-Bu < t-Pent. The very stable adducts of trans- and cis-1,4-di-t-butylcyclohexane provide other examples of the good accommodation of t-butyl groups in the thiourea channel. X-ray rotation diagrams showed[5] that the repeat periods of the trans-4-alkylcyclohexanecarboxylic acids in the thiourea adducts correspond to twice the length of the molecule, apparently as a consequence of dimerization by hydrogen bonding. Inspection of molecular models of the dimers of e.g. cis- and trans-4-t-butylcyclohexanecarboxylic acid [16] reveals (see Fig. 2) that the equatorial substituents in trans-[16] ensure a linear shape of the dimer (a) whereas the dimensions of dimeric cis-[16] (b) - with the t-butyl groups equatorial and the carboxyl groups axial - do not allow accommodation in the thiourea channel. A non-linear shape is also exhibited by the mixed dimer (c).

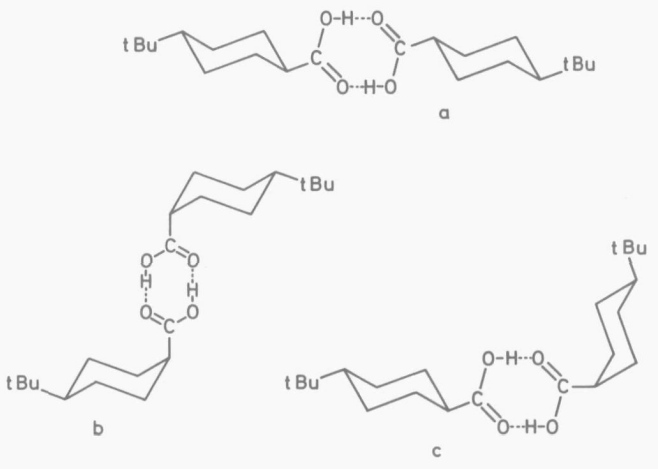


Fig. 2. Dimers of trans- and cis-4-t-butylcyclohexanecarboxylic acid [16].

Some other geometries for a cis-4-alkylcyclohexanecarboxylic acid are to be considered which might allow at first sight inclusion into thiourea.
(i) Inclusion as a monomer with the alkyl group equatorial and the carboxyl group axial. From the view of space demand this should

be allowed, as methyl cis-4-t-butylcyclohexanecarboxylate forms a thiourea adduct.[5] A rather high concentration of ester (in methanol) is required, however, to ensure adduct formation. Increase of concentration of the corresponding acid, cis-[16], is more limited due to lower solubility. In general, compounds with free hydroxyl groups seem not particularly well suited to produce stable thiourea adducts; this may be exemplified by the low tendency of the 4-t-butylcyclohexanols to form adducts.

(ii) Adduction as a dimer with the alkyl group R axial and the carboxyl group equatorial. When R is bulky (t-Bu, t-Pent) such a geometry would seem improbable in view of spatial demands of R and also because the ring conformation is expected to change. For R = Me, on the other hand, the dimer in the above conformation would seem to fit into the thiourea channel. Indeed, cis-4-methylcyclohexanecarboxylic acid was found to yield an adduct when applying a high concentration of acid and a low temperature (0°). Still, the adduct of the trans-isomer was found to be distinctly more stable, enabling purification of the trans-isomer. In this particular case direct crystallization, affording the trans-isomer, is preferred, however.

(iii) Inclusion as a dimer with the rings in a non-chair conformation. Then, at the cost of about 3 kcal/mole to the ring, a linear geometry would be obtained with a length comparable to that of the trans-dimers. So far, no evidence for this possibility has been obtained for cis-4-alkylcyclohexanecarboxylic acids.

Other examples of thiourea separation of isomeric alkyl-substituted cyclohexanecarboxylic acids are the separation of 4-t-butyl-1-methyl-cyclohexanecarboxylic acid[24] (the eae-isomer with the carboxyl group in equatorial position is selectively included), and the selective inclusion of the two isomers with equatorial carboxyl group (the eae- and the eee-isomer) of 4-t-butyl-2-methylcyclohexanecarboxylic acid.[7]

A useful separation in the cyclohexene series is the selective inclusion[33] in thiourea of 4-t-butyl-3-cyclohexene-1-carboxylic acid from mixtures with 3-t-butyl-3-cyclohexene-1-carboxylic acid (as obtained by Diels-Alder addition).

Several esters of cis- and trans-4-t-butylcyclohexanecarboxylic acid have been tested[5] for adduct-forming ability. It was invariably found that the cis-esters display much less tendency to form thiourea adducts than the corresponding trans-esters. This enabled separation of ethyl, t-butyl, and cyclohexyl 4-t-butylcyclohexanecarboxylate in the cis- and trans-isomers, by applying two-step recrystallization procedures. In this connection it may be mentioned that also di-t-butyl 1,4-cyclohexanedicarboxylate could be sepa-

rated[63] by selective inclusion of the trans-isomer into thiourea. The above selectivities would seem to originate from the fact that the cis-isomers have to adopt a (less stable) non-chair conformation to ensure good accommodation in the thiourea host lattice.
Several pairs of 1-t-butyl-4-R-cyclohexanes have been examined for separation through thiourea adducts. It was found that when R = Me the cis-isomer is preferentially included, in accordance with studies of Russian workers,[64] whereas for R=iPr and R=t-Bu thiourea gives some preference to the trans-isomer. The latter also holds for the 1,4-diisopropyl- and the 1,4-dicyclohexylcyclohexanes.
The above shift in preference of thiourea can be understood by examining molecular models of the hydrocarbons, with the dimensions of the thiourea channel in mind. When an axial methyl group is added to t-butylcyclohexane at the 4-position channel-fitting would seem to improve, when introducing other axial 4-alkyl groups in t-butylcyclohexane the cross-section of the molecule is seen to be critical. On the other hand equatorial alkyl groups at the 4-position should be branched to provide a good contact with the thiourea walls.
Length determination of guest molecules[5] by X-ray diffraction studies (cf. II. iii) of thiourea adducts confirmed that cis-4-butyl-1-methylcyclohexane is in a chair conformation in thiourea. Unfortunately, no decisive answer was obtained for the ring conformation of the other cis-1,4-dialkylcyclohexanes.
The differences in adduct-forming ability between isomeric 1,4-dialkylcyclohexanes are less pronounced than for the above-mentioned acids and esters. Consequently repeated recrystallization of the adducts is required to obtain the preferentially adducted isomer in a pure state.
It may be mentioned that also selenourea - adducts of which compound were prepared for the first time in this laboratory[15] - forms inclusion compounds with several 1,4-dialkylcyclohexanes. Though the difference in channel diameter between thiourea and selenourea adducts seems to be small, selenourea was found to be more selective in the choice of its guest compounds. Some examples are given in ref. 15.
Some thiourea experiments with pairs of isomeric 1,3-dialkylcyclohexanes deserve mention. In the case of 1-t-butyl-3-methylcyclohexane both isomers form an adduct with thiourea, the trans-isomer (with the methyl group in axial position) being preferentially adducted. On the other hand neither of the isomers of 1,3-diisopropylcyclohexane yields an adduct. In the case of 1,3-di-t-butylcyclohexane the trans-isomer is found to give an adduct, whereas the cis-isomer does not. Apparently, the non-chair ring conforma-

tion[65,66] of trans-1,3-di-t-butylcyclohexane allows inclusion into the thiourea channel.
Finally, attention may be drawn to the effect of some variation of the ring part of guest compounds. For adducts of six-membered ring systems the rule observed is: the more saturated the ring, the more stable the thiourea adduct. For instance the adducts of cis- and trans-1,4-di-t-butylcyclohexane are more stable than the adduct of 1,4-di-t-butylcyclohexene which in its turn is more stable than the adduct of 1,4-di-t-butylbenzene. These differences in adduct-forming ability are sufficiently great to permit use in preparations.[2]

5. Miscellaneous

5.1 Epimerization techniques

Epimerization (configurational equilibration) at the α-carbon either of the free acid or of the methyl ester has been applied[7] for preparative purposes to many alkyl-substituted cyclohexanecarboxylic acids. Acids can be equilibrated[7] by heating them with concentrated hydrochloric acid-acetic acid (1 : 3 by volume) at about 150°. This technique has been applied to cis-2-alkylcyclohexanecarboxylic acids,[1,7] c-2,c-6-dialkyl-r-1-cyclohexanecarboxylic acids,[7] and c-2,c-4-dialkyl-r-1-cyclohexanecarboxylic acids,[7] which compounds (with axial carboxyl group) all are readily accessible by catalytic hydrogenation of the corresponding benzoic acids. The epimer with equatorial carboxyl group predominates in the equilibrium mixture and can be purified in general easily by recyrstallization.
Configurational equilibration at C_1 of methyl esters is known to proceed by boiling with a solution of sodium methoxide in methanol. We used this method preferentially in cases in which the equilibrium composition required preparative GLC for separation of the epimers. Examples include the preparation[7] of t-3,t-5-diethyl- and t-3,t-5-di-t-butyl-r-1-cyclohexanecarboxylic acid starting from the c,c-isomers, which are readily available by hydrogenation of the aromatic compounds.
Another example of the preparation of a cyclohexane system with an axial methoxycarbonyl group starting from its epimer is the synthesis[7] of some methyl t-2-R-t-5-t-butylcyclohexanecarboxylates [18]. Again, the all-cis acids, providing [17], are accessible by catalytic hydrogenation of the corresponding aromatic acids.

For R=Me and R=Et the eae-isomer [17] is preferred, for R=iPr and R=t-Bu, however, the equilibrium lies in favour of [18] showing substantial variation in the vicinal ea-COOMe-R interaction. For R=iPr, the equilibrium constant amounts to 5.8 ($-\Delta G = 1.04$ kcal/mole); combination with the conformational energy of the methoxycarbonyl group[67] (1.27 kcal/mole) yields $\Delta G = 2.3$ kcal/mole for the ea-COOMe-iPr interaction. For R=t-Bu it is doubtful whether [17] and [18] are in the chair conformation.

5.2 Koch carboxylation

Tertiary carboxylic acids can be prepared by treating alcohols or olefins (or hydrocarbons in the presence of a lower tertiary or secondary alcohol) with carbon monoxide (often generated in situ from formic acid) in a strongly acidic medium.[68-71] We used this method as an alternative to reductive alkylation (I.2) in the synthesis of some 1-alkyl-substituted cyclohexanecarboxylic acids, the acidities of which are discussed in section III. Besides the known acids 1-ethyl- and 1,3-dimethylcyclohexanecarboxylic acid[69] and the decalin-9-carboxylic acids,[72] a number of new acids were prepared in this way.

Starting from 4-t-butyl-1-methylcyclohexane as well as from 4-t-butyl-1-methylcyclohexanol we prepared c-4-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid.[73] Similarly, t-3-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid was obtained from 2-methyl-4-t-butylcyclohexanol. Thus the Koch procedure provides selectively the aee-isomers with the carboxyl group in axial position. The corresponding eae-acids were obtained from mixtures of the two isomers prepared by reductive methylation of t-butylbenzoic acids followed by hydrogenation, and by carboxylation of the Grignard compounds of 4- and 3-t-butyl-1-bromo-1-methylcyclohexane.

As an example of side-chain carboxylation we mention the preparation of 2-methyl-2-(trans-4-t-butylcyclohexyl)propionic acid from 2-(trans-4-t-butylcyclohexyl)-2-propanol. The yield is low, however, due to the formation of many side products.

Complex mixtures of acids were also obtained when subjecting t-butylcyclohexanols to the Koch procedure. As found by Peters[1,74] side reactions are suppressed by applying the Haaf modification[75] with slow stirring of the mixture. t-Butylcyclohexanols were converted in this way[1] into 3 : 1 mixtures of 1-t-butylcyclohexanecarboxylic acid and 2-methyl-2-(1-methylcyclohexyl)propionic acid. The synthetic importance of this technique is stressed by the fact that so far attempts at reductive t-alkylation of benzoic acid were unsuccessful.

5.3 Diels-Alder addition

The Diels-Alder addition[76] has been applied incidentally in the present work for the purpose of introducing a double bond at a given position in a six-membered ring system. For instance 4-t-butyl-3-cyclohexene-1-carboxylic acid can be best prepared[33] by Diels-Alder reaction of 2-t-butylbutadiene and acrylic acid. Another example is the preparation[1] of 2-t-butyl-1-cyclohexene-1-carboxylic acid by 1,4-cycloaddition of butadiene and methyl t-butylacetylenecarboxylate, followed by partial hydrogenation and hydrolysis.

Secondly, the retention of configuration of the reactants in the Diels-Alder reaction can be applied to prepare a given isomer by proper choice of the dienophile. Thus, 1,t-2-dimethyl-r-1-cyclohexanecarboxylic acid was conveniently prepared by Diels-Alder reaction of butadiene and tiglic acid ((E)-2-methyl-2-butenoic acid), followed by hydrogenation.

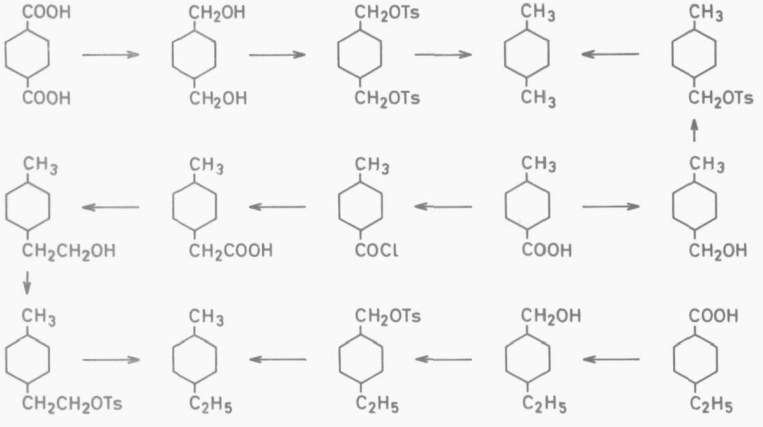
5.4 Cyclohexane derivatives as starting materials in some syntheses

Alkylcyclohexanols (easily accessible by hydrogenation of the corresponding phenols) would seem suitable starting materials for the synthesis of alkylcyclohexanecarboxylic acids through replacement of hydroxyl by bromine followed by a Grignard reaction. However, common procedures for the first reaction fail in that much isomerized product[77] is formed, for instance 4-t-butylcyclohexanol yields a.o. 3-t-butyl-1-bromocyclohexane. An alternate procedure, which has been applied[7] in the present study, involves the preparation of the tosylate which can be converted into the bromide by a solution of calcium bromide in DMF.[78] Another method involves heating of the tosylate with sodium cyanide in N-methylpyrrolidone[79] yielding the cyanide which is hydrolyzed to give the carboxylic acid. For the synthesis of most cyclohexylacetic acids use has been made of the Arndt-Eistert synthesis. A low temperature (0°) is recommended for the preparation of the starting acid chlorides in order to prevent epimerization. As might be expected the rearrangement of the diazoketones involved was found to occur stereospecifically.

II. CONFIGURATIONAL ANALYSIS

We have developed and applied several methods and criteria in order to assign reliably the configuration to the various sets of epimeric acids and other cyclohexane derivatives. Chemical as well as physical correlations have been made. A survey follows.

(i) Chemical proofs of structure. A number of 4-alkylcyclohexanecarboxylic acids and 1,4-dialkylcyclohexanes have been correlated chemically [3-13,24] with the 1,4-cyclohexanedicarboxylic acids, the configuration of which had been established with certainty. [80] As an example we give the chemical proof of structure of the 4-ethyl- and the 4-methylcyclohexanecarboxylic acids (see Scheme V). The reactions shown in the diagram were carried out for the cis- as well as for the trans-compounds. Moreover, some 1,2-disubstituted cyclohexanes have been correlated chemically with the known [81] 1,2-cyclohexanedicarboxylic acids.



Scheme V

The stereochemical results (Table I) of the hydrogenation [2] of cis- and trans-1,3,5-tri-t-butylcyclohexene ([7] and [8]) provide a direct proof of structure for these compounds as well as for both 1,3,5-tri-t-butylcyclohexanes. Compound [7] yields cis,cis- as

well as cis,trans-1,3,5-tri-t-butylcyclohexane upon hydrogenation or reduction with diimide whilst [8] gives exclusively the cis,trans-isomer.
In some cases the course of the hydrogenation of aromatic compounds (e.g. 2-t-butylbenzoic acid[1]) provided strong evidence for the configurations of the cyclohexane derivatives obtained.

(ii) Equilibration. Configurational equilibration (cf. I.5.1) at the α-carbon has been applied[7] to many pairs of epimeric acids and methyl esters. The configuration with the carboxyl or methoxycarbonyl group in equatorial position was assigned to the more stable epimer. This assignment was also found to hold for the 2-alkylcyclohexanecarboxylic acids, showing that reversal of stability, as has been observed for the 2-t-butylcyclohexanols,[82] does not occur here. However, when vicinal interactions can be evaded in the epimer with axial carboxyl or methoxycarbonyl group exceptions to the above rule may occur; we mentioned already that methyl t-2-isopropyl-t-5-t-butyl-r-1-cyclohexanecarboxylate was found to be more stable than its epimer with equatorial methoxycarbonyl group.

(iii) Length determination in thiourea.[5,83] It may be recalled that the inclusion or non-inclusion of a 4-alkylcyclohexanecarboxylic acid in thiourea may be looked upon as a strong indication of trans- or cis-configuration of the isomer in question. With many other pairs of 1,4-disubstituted cyclohexanes both isomers were found to give an adduct with thiourea (though generally of unequal stability). A number of the adducts obtained were analyzed[5] by performing C- and N-determinations and by taking X-ray rotation diagrams. From these diagrams the repeat distance of the guest molecules in the direction of the c axis was calculated. In general this repeat period was found to correspond to the linear dimension of one molecule, showing head-to-tail stacking of the guest molecules. Exceptions to this are observed for most carboxylic acids. Table III gives some results.
When in the adducts both isomers are in the chair conformation, the trans-isomer (I) is expected to possess a longer period than the corresponding cis-isomer (IIa). About equal periods are expected, however, when the cis-isomer adopts a non-chair conformation such as IIb in the thiourea channel.

I IIa IIb

Table III. Repeat periods of thiourea adducts

No.	Guest compound	Period, Å host	guest
19	trans-4-isopropyl-1-methylcyclohexane	12.4	10.4
20	cis-4-isopropyl-1-methylcyclohexane	12.4	9.3
21	trans-4-t-butyl-1-methylcyclohexane	12.5	10.4
22	cis-4-t-butyl-1-methylcyclohexane	12.4	9.3
23	trans-1,4-di-t-butylcyclohexane	12.4	12.4
24	cis-1,4-di-t-butylcyclohexane	12.4	11.3
25	trans-1,4-dicyclohexylcyclohexane	12.4	15.1
26	cis-1,4-dicyclohexylcyclohexane	12.4	15.1
27	methyl trans-4-t-butylcyclohexanecarboxylate	12.3	12.3
28	methyl cis-4-t-butylcyclohexanecarboxylate	12.4	10.7
29	trans-1-acetyl-4-t-butylcyclohexane	12.5	11.1
30	cis-1-acetyl-4-t-butylcyclohexane	12.5	9.8
31	trans-1-bromo-4-t-butylcyclohexane	12.5	10.8
32	cis-1-bromo-4-t-butylcyclohexane	12.5	9.5

With adducts [19]-[22] and [27]-[32] (see Table III) the differences in repeat period are understood on the basis of chair conformations of the guest compounds: the cis-isomers occupy a distinctly shorter section of the thiourea channel than the trans-isomers. In fact, the cis-isomers in adducts [20], [22] and [32] occupy channel lengths which are only slightly greater than that of t-butylcyclohexane (9.0 Å). This is to be expected for a chair conformation with the methyl group ([20] and [22]) and the bromine atom [32] in axial position and thus not contributing significantly to the 'length' of the molecule.

These results demonstrate the potential use of length-determination in thiourea for configurational analysis of pairs of isomeric 1,4-disubstituted cyclohexanes.

With adducts [23]-[26] and some related adducts[5] the question arises whether the ring in the cis-isomers is in a flexible or in a chair conformation in the adducted state. The identical period observed for the adducts [25] and [26] would strongly suggest a non-chair conformation for the central ring of the cis-isomer. The calculated length of cis-1,4-di-t-butylcyclohexane is 11.3 Å in the case of a boat conformation and 10.4 Å for a chair conformation (using 2.0 Å for the van der Waals radius of the methyl group). In view of the length observed in its adduct [24] it is likely that a non-

chair conformation is involved in thiourea. It may be noted that in adduct [23] the guest has adopted the thiourea repetition. Clearly, the analysis of adducts [23]-[26] allows no conclusion regarding the configuration of the guest compounds.

(iv) NMR spectra. Non-equivalence of alkyl groups as revealed by NMR spectroscopy allowed assignment of configuration to a number of cyclohexane derivatives.[2,7] For instance the NMR spectra of c-3,t-5-di-t-butyl-r-1-cyclohexanecarboxylic acid and of the corresponding nitrile show two signals for the protons of the t-butyl groups, thus providing a proof of structure. Another example is r-2, c-4, t-6-tri-t-butylcyclohexanone [2] which compound is distinguished from its two epimers by its NMR spectrum, which shows three signals for the protons of the t-butyl groups.
A general method of analysis [84] is based on the band width and the chemical shift of the signal due to the α-proton in substituted cyclohexane derivatives. We have used this criterion in the configurational analysis of frozen alkyl-substituted cyclohexanecarboxylic acids. Equatorial α-protons (carboxyl group axial) were found to resonate at lower field (δ 2.5-3.0 ppm) than the other ring protons and appeared as relatively narrow bands, whereas the signals due to axial α-protons usually overlapped with the signals of the other ring protons. In this way the position of the carboxyl group could be determined easily.
When the splitting patterns of the α-proton absorption is simplified as in 2,6-dialkyl-substituted cyclohexane derivatives, the NMR spectrum generally allows assignment of structure at once. Examples include c-2,c-4,c-6- and t-2,t-4,t-6-tri-t-butyl-r-1-cyclohexanol. [2]

(v) Mass spectra.[85] It has been found [1] that mass spectrometry is able to distinguish between the cis- and trans-isomers of 3- and 4-t-butylcyclohexanecarboxylic acid. The fragmentation of the cis-isomers appears to be largely governed by the ability of the t-butyl and the carboxyl group to interact. Transfer of a hydrogen atom to the (ionised) carboxyl group followed by loss of C_4H_7 leads to the base peak at m/e 129 in the spectra of cis-3- and cis-4-t-butylcyclohexanecarboxylic acid. Interaction between the t-butyl and the carboxyl group is not possible (unless isomerization occurs) in the case of trans-3- and trans-4-t-butylcyclohexanecarboxylic acid. Here, loss of the t-butyl group from the molecule ion, giving m/e 127, is an important fragmentation. [1]
Several sets of isomeric more highly substituted cyclohexanecarboxylic acids with t-butyl groups at the 3- or 4-position have been found [86] to show similar characteristic mass spectral differ-

ences, thus leaving no doubt about the mutual configuration of the t-butyl and the carboxyl group. In an analogous way mass spectra distinguished between the cis- and trans-isomers of 4-t-pentylcyclohexanecarboxylic acids[1] and 4-t-butylcyclohexaneacetic acids.[86]

(vi) GLC retention times. Relative GLC retention times of sets of isomeric cyclohexane derivatives have been found to be quite helpful for a tentative assignment of configuration. Two retention time (and boiling point) regularities to which no exceptions have been observed are: other things being equal, equatorial COOR > axial COOR[1,7,24,87] and axial Me > equatorial Me.[5,14,88] For instance the retention time order of the methyl 3,5-dimethylcyclohexanecarboxylates is aee > eee > eae.

For a mobile system such as methyl cis-2-methylcyclohexanecarboxylate the relative retention time with respect to its epimer cannot be given a priori: on the other hand the experimental order of these methyl esters cis > trans indicates that the cis-isomer prefers the conformation with the methyl group in axial and the methoxycarbonyl group in equatorial position.

Several rules have been postulated regarding relations between physical properties, such as density, refractive index and boiling point, and the configuration of epimeric cyclohexane derivatives.[89] An accurate historical analysis of the origin and the scope of these rules has been made by Verkade et al.[14]

As to differences in boiling point between epimeric cyclohexane derivatives the data available allow the rule of thumb that for polar substituents the epimer with the polar substituent in euqatorial position (other things being equal) has the higher boiling point.[7,24,90] This result is quite reasonable. Regarding alkyl groups other than methyl (see above) much data on pairs of epimeric dialkylcyclohexanes have been assembled by Russian workers[91] as well as in this laboratory. Here, the boiling point sequence is found to depend sometimes on the way of ring substitution. Thus for the 1,2- and 1,3-diisopropylcyclohexanes[24] the ae-isomer is found to possess a higher boiling point that the ee-isomer whereas the reverse holds for the 1,4-diisopropylcyclohexanes.[5,92] A similar reversal is observed for the di-t-butylcyclohexanes[26,65,93] in which case the situation is of course more complicated due to the role of non-chair ring conformations.

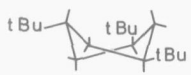
(vii) Density and refractive index. We have advanced the rule[14,94] that with cyclic stereoisomers in which the substituents are bound to identical rings the isomer with the higher density and the higher refractive index is that which has the higher heat content. This

rule can be used with good confidence as has been shown a.o. for a series of alkylcyclohexylamines.[95] Generally the difference in density between epimeric cyclohexane derivatives is more pronounced than the difference in refractive index.

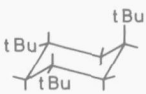
III. CONFORMATIONAL ANALYSIS. pK_a^*-MEASUREMENTS

1. 1,4-Di-t-butylcyclohexane and 1,3,5-tri-t-butylcyclohexane

The isomeric 1,4-di-t-butylcyclohexanes (cis- and trans-[10]) and cis,cis- and cis,trans-1,3,5-tri-t-butylcyclohexane ([33] and [34]) were prepared[9,2] by us since we were interested in the question whether in cis-[10] and in [34] the strain of an axial t-butyl group is so large that a non-chair conformation is predominant.
Cis-[10] has been examined[9] by various tools including infrared and NMR[96] spectroscopy, X-ray and electron diffraction[97] techniques, without obtaining a definite answer to the above question. The data present strong evidence, however, that cis-[10] prefers a non-chair conformation. This is supported by some other properties[9] of cis-[10] viz. melting point, heat of fusion, thiourea inclusion, and the difficult separation from trans-[10]. Therefore the enthalpy difference[9] between cis- and trans-[10] is considered to be a good estimate of the enthalpy difference between the chair and a non-chair conformation of cyclohexane.



34 a



34 b

For compound [34] a non-chair conformation as [34a] as well as a chair conformation [34b] with one axial t-butyl group have to be considered. The NMR spectrum of [34] (60 MHz, -100 to +40°) presents some evidence in favour of [34a]: the t-butyl groups are equivalent, and the ring protons appear as one narrow band, whereas the NMR spectrum of [33] shows the ring protons over a much wider area. This picture is acceptable when the flexible conformation [34a] is preferred. Other support of [34a] stems from the relatively low melting point and heat of fusion of [34] and also from its structural relationship to trans-1,3-di-t-butylcyclohexane which compound is considered to prefer a non-chair form.[65,66]

2. pK_a^*-values of 4- and 3-alkyl-substituted cyclohexanecarboxylic acids

Methods of conformational analysis of cyclohexane derivatives have relied on the absence of any polar or steric effect of 3- and 4-alkyl substituents on the functional group and its environment.[98,99] This was accepted for frozen systems as t-butylcyclohexyl compounds as well as for the conformers of mobile cyclohexane systems. Recently, several departures from this postulate have been reported, deduced from kinetic studies[100-102] and equilibrium measurements.[103,104] We have measured[7] the thermodynamic dissociation constants of forty 3- and 4-alkyl-substituted cyclohexanecarboxylic acids in 50% ethanol-water (Tables I and II in ref. 7) in order to find out to what extent the acidity of an equatorial or axial carboxyl group is influenced by an alkyl group at the 3- or 4-position.
Effects of equatorial 4- and 3-alkyl groups on an equatorial 1-carboxyl group can be gathered from Table IV which table contains examples of such situations. 4-Alkyl groups are found to cause just a slight acid-weakening, whereas 3-alkyl substituents exert more substantial effects, which increase with growing bulk of the alkyl group. These ee-3-alkyl effects are found to be additive.

Table IV. pK_a^*-values of all-equatorial 4- and 3-alkyl- and 3,5-dialkylcyclohexanecarboxylic acids in 50% ethanol-water at 25°

t-4-R	pK_a^*	c-3-R	pK_a^*	c,c-3,5-di-R	pK_a^*
H	6.20				
4-Me	6.20	3-Me	6.23	3,5-di-Me	6.26
4-Et	6.22	3-Et	6.27	3,5-di-Et	6.36
4-iPr	6.22	3-iPr	6.29	3,5-di-iPr	6.38
4-t-Bu	6.22	3-t-Bu	6.30	3,5-di-t-Bu	6.43

Examples in which axial 1-carboxyl groups are influenced by equatorial 4- or 3-alkyl groups are given in Table V. The value of the cis-4-t-alkylcyclohexanecarboxylic acids is believed[7] to be a good estimate of the pK_a^* of the chair conformer of unsubstituted cyclohexanecarboxylic acid with the carboxyl group axial. The data reveal that equatorial 3-t-alkyl groups weaken the acidity of an axial 1-carboxyl group considerably.
Two factors can be envisaged[7] for the origin of the acid-weakening ee- and ae-3-alkyl effects: (i) the hydrophobic 3-alkyl group exerts some hindrance to solvation in the carboxylate anion,[105] (ii) the 3-alkyl substituent brings about a ring geometry which differs from that of the conformers of cyclohexanecarboxylic acid.

Table V. pK_a^*-values of immobile cis-4-alkyl-, trans-3-alkyl-, and trans,trans-3,5-dialkylcyclohexanecarboxylic acids

c-4-R	pK_a^*	t-3-R	pK_a^*	t,t-3,5-di-R	pK_a^*
				3,5-di-Et	6.84
4-t-Bu	6.68	3-t-Bu	6.90	3,5-di-t-Bu	7.06
4-t-Pent	6.69	3-t-Pent	6.93		

As to ring deformation, valence-force calculations[106] and NMR analysis[107] on methylcyclohexane show that the changes in the geometry of the ring part around the 3-position introduced by an equatorial methyl group are negligible. In t-butylcyclohexane[106,108] such effects are more substantial but still small. However, the axial proton at the carbon carrying the t-butyl group is bent somewhat toward the centre of the ring and might cause hindrance to solvation of a γ-syn carboxylate anion.
Ref. 7 contains a few examples in which an equatorial carboxyl group is influenced by an axial 3-alkyl group. The effect seems to depend strongly on the character of the alkyl group but more examples are required to settle this.
When the axial 3-alkyl group is tertiary, as in c-3,t-5-di-t-butyl-r-1-cyclohexanecarboxylic acid,[7] the question arises once more (cf. III.1) whether the system prefers a non-chair or a chair conformation.

3. 2-Alkylcyclohexanecarboxylic acids and model compounds

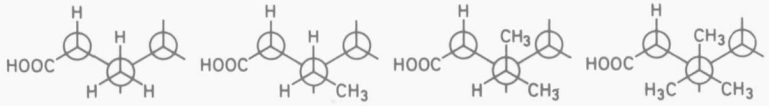
In 2-alkylcyclohexanecarboxylic acids direct steric interaction between alkyl and carboxyl group may occur. An equatorial-equatorial interaction is likely to be involved in trans-2-alkylcyclohexanecarboxylic acids whereas the cis-isomers will exist in general as a conformational equilibrium ae $\rightleftarrows$ ea. The positions of such chair/chair equilibria have been estimated[7] by comparing the acidity of 2-alkylcyclohexanecarboxylic acids with that of suitable frozen 2,4- and 2,5-dialkylcyclohexanecarboxylic acids e.g. 2-alkyl-4(5)-t-butylcyclohexanecarboxylic acids. Altogether pK_a^*-values of some fifty 2-alkyl-substituted cyclohexanecarboxylic acids were determined (Table III in ref. 7) in 50% ethanol-water at 25°. First of all the various model compounds enabled estimation of the four types of vicinal alkyl-carboxyl interactions in terms of ΔpK_a^*-units (allowing for any 3- and 4-alkyl effects). Table VI gives pK_a^*-increments with respect to the pK_a^*-values of the equatorial and axial conformer of cyclohexanecarboxylic acid; values in pa-

rentheses stem from compounds for which also non-chair conformations are to be considered. The increments are in part mean values; see ref. 7 for the separate values.

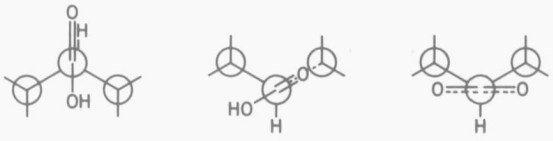
Table VI. pK_a^*-increments resulting from vicinal alkyl-carboxyl interactions

2-R	ΔpK_a^*			
	e-COOH, e-R	e-COOH, a-R	a-COOH, e-R	a-COOH, a-R
Me	0.02	0.19	0.39	-0.02
Et	0.11	0.30	0.40	0.08
iPr	0.19	0.43	0.66	0.16
t-Bu	0.42	(0.66)	0.69	(0.16)

Some of the vertical differences in Table VI can be understood by examining the preferred conformations of the alkyl groups. Thus, Newman projections (see below) of the four ee-combinations show that the third γ methyl group introduced must accept a syn position with respect to the carboxyl group as a result of which the acid strength is reduced appreciably.

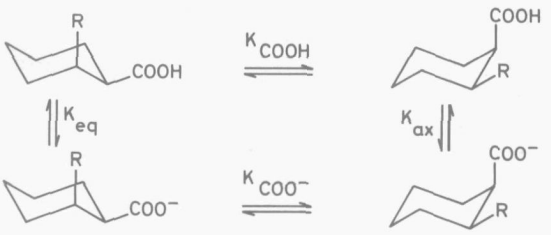


The pK_a^*-increments observed show that a 2-alkyl group weakens the acidity of a 1-carboxyl group in the order aa < ee < ea < ae (position of carboxyl given first). This sequence can be understood when accepting[6,7,109,110] I ($\varphi = 0^\circ$) and II ($\varphi = 120^\circ$) as the preferred conformations of equatorial and axial carboxyl and carboxylate groups, respectively. For the axial carboxylate group also conformation III ($\varphi = 90^\circ$) can be considered.[6] It is recognized then that quite different 2-alkyl-carboxyl interactions are involved which become more serious in the above order of ΔpK_a^*-values.



I II III

The differences in ea- and ae-2-alkyl-carboxyl interactions have a bearing on the chair-chair equilibria of cis-2-R-cyclohexanecarboxylic acids and their anions (see Scheme VI), the positions of which have been estimated[7] for R=Me, Et, and iPr (see Table VII).



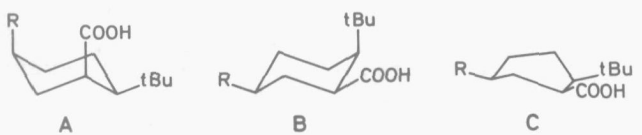
Scheme VI

Table VII. Conformational equilibrium constants of cis-2-R-cyclohexanecarboxylic acids

No.	R	K_{COOH}	$-\Delta G$, kcal/mole	K_{COO^-}	$-\Delta G$, kcal/mole
35	Me	0.30	-0.7	0.06	-1.7
36	Et	0.35	-0.6	0.07	-1.6
37	iPr	4.2	+0.8	0.9	-0.06

The data show that acids [35] and [36] prefer the ea- to the ae-conformation whereas the reverse is true for [37]. In compounds [35] and [36] the alkyl-carboxyl interaction will be more serious in the ae- than in the ea-conformer.[7,109] The change in conformational preference from [36] to [37] is more abrupt than would be expected on the basis of conformational energies[67] and is due to a relative destabilization of the ea-conformer of [37], which is recognized easily.[7]

Non-chair ring conformations are supposed to contribute in some of the 2-alkyl-substituted cyclohexanecarboxylic acids studied. For instance for the c-2-t-butyl-c-5-R-r-1-cyclohexanecarboxylic acids (R=Me, iPr, t-Bu) two chair conformations (A, B) and a non-chair conformation (e.g. C) have to be envisaged.



The experimental pK_a^*-values[6,7] exclude A as the predominant conformation but cannot distinguish between B and C. Evidence for an important role of C in these acids stems from NMR and IR spectra (cf. ref. 7).

4. Trimethylsilylcyclohexanecarboxylic acids

As part of a program on trimethylsilyl-substituted cyclohexane derivatives we have prepared[62] the cis- and trans-isomers of 2-, 3-, and 4-trimethylsilylcyclohexanecarboxylic acid. The pK_a^*-values of these acids are given in Table VIII together with those of the t-butyl- and isopropylcyclohexanecarboxylic acids.

Table VIII. pK_a^*-values of trimethylsilyl-, t-butyl- and isopropylcyclohexanecarboxylic acids in 50% ethanol-water at 25°

Isomer	Predominant conformation	iPr	t-Bu	$SiMe_3$
trans-4	ee	6.22	6.22	6.23
cis-4	ae	6.60	6.68	6.71
cis-3	ee	6.29	6.30	6.38
trans-3	ae	-	6.90	6.81
trans-2	ee	6.37	6.60	6.62
cis-2	ae	7.05	7.36	7.22

The pK_a^* of cis-4-trimethylsilylcyclohexanecarboxylic acid is close to that of cis-4-t-butyl- and cis-4-t-pentylcyclohexanecarboxylic acid, showing that the trimethylsilyl group acts as a holding group for the carboxyl and the carboxylate group. A similar conclusion has been reached previously[111] for the trimethylsilyl group with respect to the hydroxyl and the tosyloxy group, which groups have a less pronounced preference for the equatorial position than the carboxyl group. Yet, the strain introduced by an axial trimethylsilyl group will be smaller than that caused by an axial t-butyl group, as a consequence of the length of the C-Si bonds which amounts to 1.9 Å.[112] Therefore, the conformational energy of the trimethylsilyl group is expected to be somewhere about 4 kcal/mole.

The relatively large acid-weakening effect exerted by an equatorial 3-trimethylsilyl group on an equatorial carboxyl group is noteworthy and calls once more attention to the importance of long-distance hindrance to solvation. The ae-3-alkyl effect is somewhat smaller in the case of a trimethylsilyl group than for a t-butyl group, in-

dicating less deformation of the ring.
An equatorial 2-trimethylsilyl group weakens the acidity of an equatorial 1-carboxyl group to the same extent as a t-butyl group; apparently some factors are canceling out. On the other hand the acidity of an axial carboxyl group is less weakened by an equatorial trimethylsilyl group than by a t-butyl group. In this respect two factors are to be considered for cis-2-trimethylsilylcyclohexanecarboxylic acid: (i) the conformational homogeneity might be questioned, (ii) the rotational orientation of the carboxyl and the carboxylate group in cis-2-trimethylsilylsyclohexanecarboxylic acid might differ from that in the t-butyl analogue, in which compound a reorientation to $\varphi = 0^{\circ}$ is accepted.[6] As to factor (ii) it may be mentioned that 2-trimethylsilyl and 2-t-butyl groups have opposite effects on the acidity of benzoic acid.[62] This has certainly to do with a more pronounced rotation[113] of the carboxyl group out of the plane of the benzene ring in the case of a 2-t-butyl substituent.

5. 1-Alkylcyclohexanecarboxylic acids. Predictive pK_a^*-rules

The pK_a^*-values of several types of 1-alkyl-substituted cyclohexanecarboxylic acids have been determined[24] since we were interested in (i) the effect of both types of geminal carboxyl-alkyl interactions on the acidity of the carboxyl group, and (ii) the conformational equilibria of 1-alkylcyclohexanecarboxylic acids (see below).

As potential model compounds for the chair conformers of 1-R-cyclohexanecarboxylic acids with R = Me, Et, and iPr we have prepared and measured the corresponding isomeric 4-t-butyl-1-R-cyclohexanecarboxylic acids. Table IX gives the results together with pK_a^*-values of some other tertiary cyclohexanecarboxylic acids.
pK_a^*-data of aliphatic tertiary carboxylic acid have been obtained by other workers in other media.[114-117] pK_a^*-values of some aliphatic acids in 50% ethanol-water, obtained in this laboratory, were found to be close to the pK_a^*-values of the cyclohexane analogues with equatorial carboxyl group. Examples include diethylacetic acid with pK_a^* 6.21 (cf. cyclohexanecarboxylic acid pK_a^* 6.20) and triethylacetic acid with pK_a^* 6.75 (cf. acid [44], pK_a^* 6.77).

Table IX. pK_a^*-values of 1-alkyl-substituted cyclohexanecarboxylic acids in 50% ethanol-water at 25°

No.	Compound	Conformation	pK_a^*
38	1-methylcyclohexanecarboxylic acid	ae ⇄ ea	6.67
39	t-4-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid	eae	6.61
40	c-4-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid	aee	6.84
41	c-3-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid	eae	6.70
42	t-3-t-butyl-1-methyl-r-1-cyclohexanecarboxylic acid	aee	7.02
43	1-ethylcyclohexanecarboxylic acid	ae ⇄ ea	6.84
44	t-4-butyl-1-ethyl-r-1-cyclohexanecarboxylic acid	eae	6.77
45	c-4-t-butyl-1-ethyl-r-1-cyclohexanecarboxylic acid	aee	6.92
46	1-isopropylcyclohexanecarboxylic acid	ae ⇄ ea	7.08
47	t-4-t-butyl-1-isopropyl-r-1-cyclohexanecarboxylic acid	eae	7.14
48	c-4-t-butyl-1-isopropyl-r-1-cyclohexanecarboxylic acid	aee	7.26
49	1,t-2-dimethyl-r-1-cyclohexanecarboxylic acid	eae ⇄ aea	6.73
50	1,c-2-dimethyl-r-1-cyclohexanecarboxylic acid	aee ⇄ eaa	6.93
51	cis-decalin-9-carboxylic acid	aea	6.91
52	trans-decalin-9-carboxylic acid	aee	7.40

By comparing the pK_a^*-values of t-butyl-substituted 1-R-cyclohexanecarboxylic acids ([39]-[42], [44], [45], [47], [48]) with those of cis- and trans-4- and 3-t-butylcyclohexanecarboxylic acid pK_a^*-increments are obtained which result from 1-R substitution. These ΔpK_a^*-values are shown in Table X together with values for 1-bromo substitution derived from the pK_a^*-values of the 1-bromo-4-t-butylcyclohexanecarboxylic acids.[6] It may be noted that in compounds [41] and [42] 3-alkyl effects are operating which appear to be of the same order of magnitude as those in trans- and cis-3-t-butylcyclohexanecarboxylic acid.

Table X. pK_a^*-increments for 1-R substitution

Position of		ΔpK_a^*			
COOH	R	Me	Et	iPr	Br
ax	eq	0.16 [40] 0.12 [42]	0.24	0.58	-1.69
eq	ax	0.39 [39] 0.40 [41]	0.56	0.92	-1.47

Table X shows that the effect, in terms of pK_a^*-units, of a substituent in 1-axial position on an 1-equatorial carboxyl group is differ-

ent from that of the same substituent in 1-equatorial position on an 1-axial carboxyl group. This feature can be taken[6] as evidence for a different preferred rotational orientation of equatorial and axial carboxyl and/or carboxylate groups. The more pronounced acid-weakening geminal ea-effect may be due then to a rotational re-orientation of equatorial carboxyl and carboxylate groups upon introduction of an 1-axial substituent.[6]

From the pK_a^*-values of [38]-[40] the conformational equilibrium constant, K_{COOH}, of [38] is calculated to be 0.5, showing the ea-conformer of [38] to be more stable than the ae-conformer. However, adamantane-1-carboxylic acid, with $pK_a^* = 6.56$, might also considered as a model compound for the ea-conformer of [38]. Then K_{COOH} would amount to 0.9. Obviously, the rather small difference in acidity between the two conformers of [38] makes the determination of K_{COOH} less accurate.

The pK_a^*-values of compounds [43]-[45] provide $K_{COOH} = 1.0$ for acid [43]. On the other hand, the conformational equilibrium constant of [46] cannot be calculated from the pK_a^*-values of [46]-[48] because [47] is found to be weaker than [46]. Apparently the 4-t-butyl group in [47] exerts an unexpectedly large acid-weakening effect. Some other model compounds for [46] are in preparation to settle this.

Simon et al.[118] have given rules correlating and predicting pK_a^*-values in 80% methyl cellosolve of cyclohexanecarboxylic acids and related cyclic acids. In these rules, one increment is assigned to 1-methyl substitution or ring junction in the 1-position and one increment to any γ-syn hydrogen or γ-syn methyl group. These rules do not allow for changes in the rotational orientation of the carboxyl and the carboxylate group and we have revised them accordingly to provide for this aspect.[6] Moreover we have ascertained[7] that a γ-syn methyl group requires a distinctly higher increment than the corresponding γ-syn hydrogen.

In predicting pK_a^*-values in 50% ethanol-water either the revised rules[6] can be used or one can look for a related measured system adding known increments for vicinal or geminal interaction or for 3-alkyl effects.[7]

For example, cis-decalin-9-carboxylic acid [51] may be assigned a pK_a^* of 6.89 using the revised rules.[6] Alternatively [51] may be viewed as aee-4-t-butyl-1-methylcyclohexanecarboxylic acid [40] to which an axial 2-ethyl group has been added; this yields 6.84 + 0.08 = 6.92 as the predicted pK_a^*. Both calculated values agree well with the experimental pK_a^*.

The predictive methods can be useful for estimating the position of the conformational equilibrium of mobile acids. Thus on the basis

of the experimental pK_a^* of 1,c-2-dimethyl-r-1-cyclohexanecarboxylic acid [50] and the predicted pK_a^*-values of its two conformers it can be concluded that the eaa-conformer plays an important role in the acid and prevails in the anion.[6]

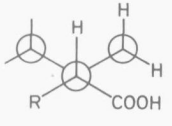
6. Alkyl-substituted cyclohexaneacetic acids

In cyclohexaneacetic acids the six-membered ring and the carboxyl group are separated by a carbon atom and one may wonder whether axial and equatorial CH_2COOH fragments still exhibit a different acidity. We have studied[24] the effect of ring substitution as well as that of α-methyl substitution in these systems. Introduction of one or two α-methyl groups yields $CH(CH_3)COOH$ and $C(CH_3)_2COOH$ groups which will have about the same spatial demands as an isopropyl and a t-butyl group, respectively. pK_a^*-values in 50% ethanol-water at 25° of representative cyclohexaneacetic acids are shown in Table XI.

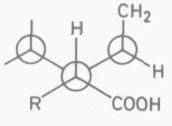
Table XI. pK_a^*-values of alkyl-substituted cyclohexaneacetic acids

No.	Compound	Conformation	pK_a^*
53	cyclohexaneacetic acid	e	6.10
54	trans-4-t-butylcyclohexaneacetic acid	ee	6.12
55	cis-4-t-butylcyclohexaneacetic acid	ae	6.23
56	c-3,c-5-di-t-butyl-r-1-cyclohexaneacetic acid	eee	6.27
57	2-cyclohexylpropionic acid	e	6.28
58	2-(cis-4-t-butylcyclohexyl)propionic acid	ae	6.46
59	2-cyclohexyl-2-methylpropionic acid	e	6.82
60	2-(trans-4-t-butylcyclohexyl)-2-methylpropionic acid	ee	6.81
61	2-(cis-4-t-butylcyclohexyl)-2-methylpropionic acid	"ae"	6.82

The pK_a^*-values of [53], [54] and [56] show that acid-weakening ee-3-t-alkyl effects are operating, on the analogy of the phenomena observed with 3-alkylcyclohexanecarboxylic acids (III.2).
Comparison of acids [54] and [55] shows that an axial carboxymethyl group is about 0.1 pK_a^*-unit weaker than an equatorial one. Projections (see below, R = H) reveal that it is the position of a δ-carbon which makes the difference.



eq



ax

For R = Me (acids [57] and [58] the equatorial/axial difference in acidity is somewhat more pronounced. It is easily seen that here the situations become cyclohexane-like: the environment of the carboxyl group in [57] is comparable to that in c-9, t-10-decalin-r-1-carboxylic acid[7] (pK_a^* 6.28), whereas the situation in [58] resembles that in trans-2-isopropylcyclohexanecarboxylic acid (pK_a^* 6.37). The α,α-dimethylsubstituted cyclohexaneacetic acids ([59]-[61]) are of particular interest in that the cis-isomer [61] is not a weaker acid than compounds [59] and [60] with equatorial substituents. It is improbable that a $C(CH_3)_2COOH$ group could hold a t-butyl group in axial position and we conclude that compound [61] exists largely in a non-chair conformation.

7. 2,5-Cyclohexadiene-1-carboxylic acids

Various alkyl-substituted 2,5-cyclohexadiene-1-carboxylic acids became available by lithium-ammonia reduction and reductive alkylation (I.2). The acidities of these compounds were measured in order to get acquainted with substituent effects in this ring system, the geometry of which is still in discussion. Table XII gives some results.

Table XII. pK_a^*-values of alkyl-substituted 2,5-cyclohexadiene-1-carboxylic acids in 50% ethanol-water at 25°

No.	Compound	pK_a^*
62	2,5-cyclohexadiene-1-carboxylic acid	5.48
63	3-t-butyl-2,5-cyclohexadiene-1-carboxylic acid	5.77
64	3,5-di-t-butyl-2,5-cyclohexadiene-1-carboxylic acid	6.08
65	2-t-butyl-2,5-cyclohexadiene-1-carboxylic acid	5.83
66	1-methyl-2,5-cyclohexadiene-1-carboxylic acid	5.76
67	3-t-butyl-1-methyl-2,5-cyclohexadiene-1-carboxylic acid	6.17
68	3,5-di-t-butyl-1-methyl-2,5-cyclohexadiene-1-carboxylic acid	6.54
69	t-4-t-butyl-1-methyl-2,5-cyclohexadiene-r-1-carboxylic acid	5.80
70	c-4-t-butyl-1-methyl-2,5-cyclohexadiene-r-1-carboxylic acid	6.08
71	1-isopropyl-2,5-cyclohexadiene-1-carboxylic acid	6.03
72	3-t-butyl-1-isopropyl-2,5-cyclohexadiene-1-carboxylic acid	6.41
73	c-4-t-butyl-1-isopropyl-2,5-cyclohexadiene-r-1-carboxylic acid	6.32

The data on compounds [62]-[64] reveal that rather strong acid-weakening 3-alkyl effects are operating in these systems. In fact, the acid-weakening by a 3-t-butyl group is almost as large as that exerted by a 2-t-butyl substituent [65]. Even more pronounced 3-

alkyl effects are observed in 1-alkyl-2,5-cyclohexadiene-1-carboxylic acids (cf. compounds [66]-[68] and [71], [72]). It may be noted that the above 3-alkyl effects are even more substantial than the 3-t-alkyl effects observed for benzoic acids[105] in which compounds electronic effects are contributing. We believe that in the cyclohexadiene system alteration of solvation of the double bond(s) and the carboxylate anion is the main factor.
Recent conclusions regarding the structure of 1,4-cyclohexadiene and its derivatives are rather contradictory. Electron diffraction data have been interpreted in terms of a planar conformation[119] (I) as well as in terms of a boat-like conformation[120] (II). Opposite conclusions have also been drawn from NMR studies.[121,122]

I

II

In this connection the fact that t-4-t-butyl-1-methyl-2,5-cyclohexadiene-r-1-carboxylic acid [69] is about as strong as the parent acid [66] whereas the cis-isomer [70] is distinctly weaker, may be of interest. In case of a planar conformation this difference in acidity can be understood; in [70] the t-butyl and the carboxyl group are at the same side of the ring whereas in planar [69] the influence of the 4-t-butyl group is expected to be small. In case of conformation II the t-butyl group will prefer a b-position. Consequently, the methyl group will be at a b-position and the carboxyl group at an a-position in [69] whereas the reverse is true for [70]. Then the observed pK_a^*-values would imply that in [66] the carboxyl group is predominantly at an a-position and the methyl group at a b-position and moreover that this conformer would be stronger acidic than the inversed one (COOH at b, Me at a). This would seem rather improbable. Also the relatively small differences in NMR spectral data of [69] and [70] are in favour of a planar or nearly planar conformation.
Finally, attention may be drawn to the opposite effect of 2,6-dialkyl-substitution in benzoic acid[123] and the corresponding non-conjugated dihydro and all-equatorial hexahydro acids (see Table XIII). Whereas acid-strengthening occurs in the aromatic series, with a maximal effect in the case of 2,6-di-Me-substitution, gradual acid-weakening is observed in the other two series. The combined data would allow a (rough) estimate of the magnitude of the acid-strengthening inhibition of resonance in the 2,6-dialkylbenzoic acids.

Table XIII. Effects of 2,6-dialkyl-substitution in benzoic acids, 2,5-cyclohexadiene-1-carboxylic acids, and cyclohexanecarboxylic acids

Substitution	pK_a^* in 50% ethanol-water at 25°		
	benzoic acid	2,5-cyclohexadiene-1-carboxylic acid	eee-cyclohexane-carboxylic acid
H	5.48	5.48	6.20
2,6-di-Me	4.78	5.48	6.22
2,6-di-Et	5.00	5.72	6.45
2,6-di-iPr	5.12	6.10	6.68

SAMENVATTING

De onderwerpen van dit proefschrift betreffen bereiding, configuratie en conformatie van niet-aromatische zesringsystemen met alkyl- en carboxyl-substitutie. De resultaten van dit werk zijn voor een belangrijk deel reeds in de vorm van tijdschriftartikelen gepubliceerd.
Aromatische verbindingen vormden in veel gevallen de uitgangsstoffen voor de synthesen. Twee werkwijzen voor de reductie van de aromatische kern, te weten katalytische hydrogenering en lithium-ammoniak reductie, werden nader bestudeerd.
De vloeistof-fase hydrogenering van alkylbenzoëzuren en afgeleide methylesters over palladium-, platina-, rhodium- en ruthenium-katalysatoren werd onderzocht met speciale aandacht voor een optreden van een twee-staps waterstofadditie-proces en de consequenties daarvan voor de productsamenstelling. De hydrogenering van 2-t-butylbenzoëzuur over rhodium vertoonde een zodanig beeld dat het aandeel van de verschillende hydrogeneringsroutes alsmede de relatie tot de uiteindelijke cis/trans-samenstelling gemakkelijk vastgesteld kon worden. Bij de hydrogenering van 1,3,5-tri-t-butylbenzeen over rhodium, platina en palladium bleek het twee-staps-proces, via cis-1,3,5-tri-t-butylcyclohexeen, sterk te overheersen. Voorts werd voor een aantal digesubstitueerde cyclohexenen de stereochemie van hydrogenering bestudeerd.
Gegevens werden verzameld over het mechanisme van de lithium-ammoniak reductie - met of zonder protondonor - van benzoëzuur en alkylbenzoëzuren. In het kader van dit werk werd een geriefelijke synthese gevonden voor 1-alkyl-2,5-cyclohexadieen-1-carbonzuren. Deze reductieve alkylering gevolgd door een hydrogeneringsstap opende een route naar 1-alkylcyclohexanecarbonzuren hetgeen een welkom alternatief betekende voor de eveneens toegepaste Koch-carboxylering.
Mengsels van epimere methylesters van alkyl- en dialkylcyclohexaancarbonzuren werden meestal met behulp van preparatieve GLC gescheiden. Voor de omzetting van methylesters in de corresponderende zuren werd een efficiënte hydrolysetechniek ontwikkeld bestaande uit een behandeling met geconcentreerd zwavelzuur. Deze reactie werd kinetisch onderzocht onder andere bij een serie methylbenzoaten.
Epimere 4-alkylcyclohexaancarbonzuren konden gescheiden worden door selectieve insluiting van het trans-isomeer in thioureum. Ook diverse andere scheidingen van isomere cyclohexaanderivaten

met behulp van thioureumadducten werden gerealiseerd.
Bij een aantal paren 1,4-digesubstitueerde cyclohexanen bleek zowel het cis- als het trans-isomer een thioureumadduct te vormen. Gevonden werd dat de lengte van de isomeren in thiourea (verkregen uit draaikristalopnamen) veelal voldoende verschillend is voor een configuratietoewijzing.
Voor een aantal cyclohexaanderivaten werd een chemisch structuurbewijs geleverd door deze stoffen langs chemische weg te correleren met verbindingen met vaststaande configuratie. Daarnaast verschaften NMR- en massa-spectra enkele betrouwbare configuratiecriteria voor alkyl-gesubstitueerde cyclohexaancarbonzuren. Ook GLC-retentietijden bleken bruikbaar te zijn voor configuratieanalyse.
In diverse van de in het onderzoek betrokken cyclohexaansystemen prefereert de ring waarschijnlijk een flexibele boven een stoelconformatie. Dit geldt bijvoorbeeld voor cis,trans-1,3,5-tri-t-butylcyclohexaan en voor de c-2-t-butyl-c-5-alkyl-r-1-cyclohexaancarbonzuren. Argumenten voor een gewijzigde ringconformatie werden ondermeer verkregen uit NMR- en IR-spectra en bij de zuren ook uit pK_a^*-waarden.
Van een honderdtal alkyl- en dialkylcyclohexaancarbonzuren werd de aciditeit gemeten in 50% ethanol-water bij 25°. pK_a^*-incrementen werden afgeleid voor de beïnvloeding van equatoriale en axiale carboxylgroepen door alkylgroepen op de diverse ringposities. 4-Alkylgroepen verzwakken de aciditeit van een 1-carboxyl groep nauwelijks, 3-alkylsubstituenten doen dit daarentegen substantieel. Bij 2- en 1-alkylgroepen is het zuurverzwakkend effect vrij sterk afhankelijk van de axiale of equatoriale positie van carboxyl- en alkylgroep. Voor een aantal cis-4- en cis-2-alkylcyclohexaancarbonzuren werd uit pK_a^*-waarden de ligging van het conformatie-evenwicht berekend.
Aan de hand van de pK_a^*-waarden van de trimethylsilylcyclohexaancarbonzuren werden de effecten van de t-butylgroep en de grotere maar minder compacte trimethylsilylgroep vergeleken.
Ook van een aantal in de ring en op de α-plaats gesubstitueerde cyclohexaanazijnzuren werd de pK_a^* bepaald. Het met cis-1,4-di-t-butylcyclohexaan in essentie homomorfe 2-(cis-4-t-butylcyclohexyl)-2-methylpropionzuur prefereert vermoedelijk een flexibele conformatie.
Uit de pK_a^*-waarden van alkyl-gesubstitueerde 2,5-cyclohexadieen-1-carbonzuren komt naar voren dat hierbij 3-alkylsubstituenten een relatief groot zuurverzwakkend effect uitoefenen. De effecten van 4-alkylgroepen leveren een bijdrage tot de lopende discussie over de geometrie van het 1,4-cyclohexadieensysteem.

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STELLINGEN

I

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II

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III

Het is de vraag of de lithium-ammoniak reduktie van trimethylsilylbenzeen zo selectief plaatsvindt als Harvey doet voorkomen.
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IV

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V

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IX

De experimentele gegevens van Jardine en McQuillin op het gebied van de homogene en heterogene hydrogenering van 3-oxo-$\Delta^{4,5}$-steroiden vormen een onvoldoende basis voor de door deze auteurs getrokken conclusies.
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X

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XI

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XII

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XIII

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XIV

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XVI

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