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Clathrate Formation from 3-(2′,2′-Dihalovinyl)-2,2-dimethylcyclopropanecarboxylic Acid and Aromatic Compounds: Preparation, Structure, and Application in Separation of Stereoisomers

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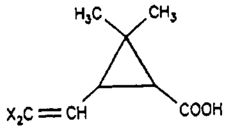
Clathrate formation was discovered and investigated in a series of stereoisomers of 3-(2′,2′-dihalovinyl)-2,2-dimethylcyclopropanecarboxylic acid, 1 (X = Cl, Br). It was found that the equimolar mixture of (1*R*)-cis and (1*S*)-cis acids gives rise to crystalline inclusion complexes with simple aromatic compounds such as benzene, fluorobenzene, thiophene, pyrrole, furan, and 2-methylfuran, always in the stoichiometric ratio 1:1:1 with respect to the participating components. No other stereoisomeric mixture of any single enantiomer of the acid 1 forms inclusion complexes. The crystal structure of the inclusion complex obtained from the racemic cis acid 1 (X = Cl) and benzene was determined and compared with that of the neat racemic cis acid. Applicability of the novel inclusion complexes for separation of geometrical (cis vs trans) as well as optical ((1*R*)-cis or (1*S*)-cis vs (1*RS*)-cis) isomers has been demonstrated.

Some esters of 3-(2′,2′-dihalovinyl)-2,2-dimethylcyclopropanecarboxylic acid, 1 (X = Cl or Br), first synthesized by Farkaš and Šorm,[1] belong among the most potent and at present most widely employed synthetic pyrethroid insecticides. The stereochemistry of the cyclopropane acid moiety strongly, and sometimes dramatically, affects their insecticidal potency. In most instances esters of the acid in the cis configuration are more active than those with trans configuration; moreover, the esters of the acid with the absolute configuration 1*R* are much more active than those with the 1*S* configuration.[2] Development of procedures leading to the desirable pure acid isomers is of considerable interest. In spite of impressive progress attained in stereo- and enantioselective synthesis of the parent acid,[3] separation processes allowing isolation of a given isomer (or isomeric pair) from an isomeric mixture continue to be an indispensible part of most practical syntheses. Fractional distillation[4] and/or fractional crystallization,[1] although tedious, are probably the sole methods hitherto available for such separation purposes.



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Now we have found that the problem of separation of geometric and also optical isomers of the acid 1 (X = Cl, Br) can be simplified by means of molecular complexes[5] that arise selectively from a single pair of the parent acid and an appropriate aromatic compound. The new molecular complexes, which we discovered serendipitously,[7] arise by dissolving an isomeric mixture of the acid 1 in limited amounts of the aromatic compound. Upon cooling, a crystalline molecular complex forms. It consists of the cis isomers of the acid 1 with absolute configurations 1*R* and 1*S* and the aromatic compound, always in the stoichiometric ratio 1:1:1. Analogous complexes of the corresponding racemic trans acid 1 are much less stable (and at the same time much more soluble), becoming desolvated during isolation. No single isomer ((1*R*)-cis, (1*R*)-trans, (1*S*)-cis, (1*S*)-trans) was found to form inclusion complexes when starting with either individual or mixed isomers.

Table I. Crystal Data for the Racemic *cis*-3-(2′,2′-Dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic Acid and Its 2:1 Benzene Inclusion Compound

	$C_8H_{10}O_2Cl_2$	$C_8H_{10}O_2Cl_2{\cdot}0.5(C_6H_6)$
T (°C)	−32	−87
space group	$P\bar{1}$	$P\bar{1}$
a	5.982 (4) Å	5.984 (3) Å
b	8.030 (4) Å	9.390 (4) Å
c	11.160 (3) Å	11.071 (1) Å
α	97.30 (2)°	78.60 (2)°
β	88.17 (4)°	87.05 (2)°
γ	65.74 (4)°	72.79 (3)°
ρ_{calc}	1.438	1.415
V	482.7 (9) Å^3	582.5 (7) Å^3
Z	2	2

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(5) Capability of three- and four-membered ring compounds to serve as inclusion hosts for various uncharged organic molecules has been recently demonstrated by Weber et al. (ref 6a). During the preparation of the manuscript, a diastereoisomeric separation of flumethrin, a well-known synthetic pyrethroid, by formation of inclusion complex with 2,6-dimethylnaphthalene has been reported (ref 6b), providing another example of practical application.

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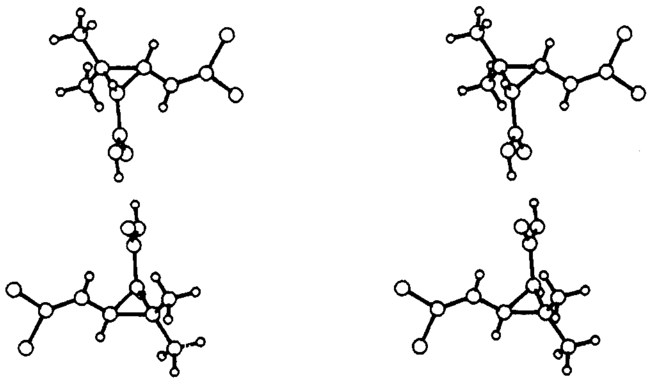

Figure 1. A stereoview of the unsolvated acid.

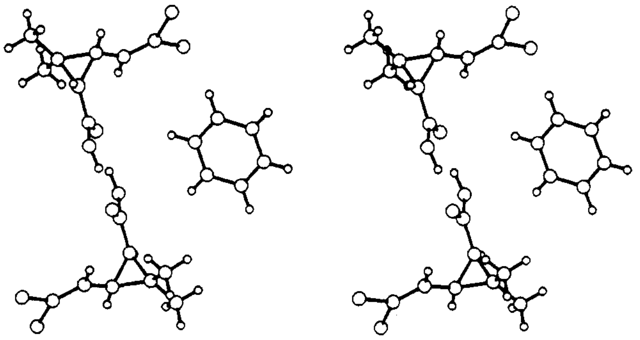

Figure 2. A stereoview of the benzene inclusion compound.

Formation of inclusion compounds is thus limited to the racemic cis acid ((1*R*)- and (1*S*)-cis isomers in the ratio 1:1).

We have found that molecular complex formation is most common for simple unsubstituted aromatic compounds, typically benzene, thiophene, pyrrole, and furan. Pronounced complex-forming ability for substituted aromatics was observed only for fluorobenzene and, to some extent, for 2-methylfuran. Toluene and chloro- and bromobenzene form metastable complexes, if any. Reluctance of the more bulky substituted aromatics to undergo molecular complex formation may be attributable to intermolecular steric factors.

The molecular complexes obtained are crystalline compounds melting with decomposition and gradual loss of the volatile aromatic component. The overall composition of the complexes was determined unambiguously by ^{1}H NMR spectroscopy, exhibiting signals of the cis acid 1 (X = Cl or Br) and of the corresponding solvent of crystallization in the integrated ratio 2:1. Thermal decomposition (80–100 °C, 1 Torr, 4 h) of the complex yields quantitatively the corresponding racemic cis acid 1.

X-ray analyses of the complex arising from the pure racemic cis acid 1 (X = Cl) with benzene and of the neat racemic cis acid (obtained by a crystallization from hexane) were carried out.

These two structures were solved and refined, Table I (details of the analyses will be reported elsewhere). The acid moieties in both structures are almost identical, forming centrosymmetric dimers in each (Figures 1 and 2, respectively). The only statistically significant intramolecular difference is a small change in the cyclopropyl–vinyl torsion angle.

A comparison of the two structures shows that incorporation of the benzene "guest" molecules requires only an increase in the unit cell volume, primarily through a lengthening of the *b* axis, accompanied by a change in α. To accommodate the benzene in the lattice, acid layers are displaced 3.4 Å in the neat acid [011] direction. Other important intermolecular contacts and motifs are retained upon incorporation of benzene. A visual stereocomparison of the two structures makes the similarities clear.

Since the fundamental structural unit is a centrosymmetric racemic acid dimer, a single enantiomer cannot accommodate solvent in the same manner. The reason that the corresponding trans racemate forms a less stable complex is not clear.

The marked selectivity we have now established in the formation of the inclusion complexes from the racemic cis acid 1 (X = Cl, Br) offers interesting possibilities for separation of various stereoisomeric mixtures of the acid 1. The most obvious application concerns separation of the racemic cis from the racemic trans acid 1 (X = Cl or Br). Upon treatment of a mixture of the racemic cis and trans acids 1 with the appropriate aromatic solvent the inclusion complex of the racemic cis acid is the only one that precipitates. When the starting mixture contains about 20% of the trans isomer, the cis complex is obtained almost quantitatively (98% of theoretical), containing merely traces (~1%) of the trans isomer.[8] Thus, formation of crystal solvates results in purification of the cis geometrical isomer from the trans isomer.

Importantly, inclusion complex formation may be utilized also for separation of a single enantiomer (in particular (1*R*)-cis or (1*S*)-cis) from the corresponding racemic cis acid 1. When, for example, an isomeric mixture of the cis acid 1 (X = Cl, or Br) containing some excess of one enantiomer ((1*R*)-cis over (1*S*)-cis or vice versa) is treated with an appropriate aromatic solvent, the inclusion complex containing exactly equal proportions of 1*R* and 1*S* isomers precipitates, rendering an increase in the excess of one enantiomer in the mother liquor. Enantiomeric enrichment from 30–40% ee to 81–87% ee[9] may thus be attained in a single step. The racemic acid obtained may then be subjected to a standard optical resolution such as via diastereomer salt separation. Inclusion complex formation may thus become part of a cyclic process for separation of optical antipodes of *cis*-3-(2′,2′-dihalovinyl)-2,2-dimethylcyclopropanecarboxylic acids, 1 (X = Cl or Br), whereby racemic crystals are redissolved to form a racemic solution which is further resolved by diastereomeric salt separation.

In conclusion, we have found that the acid 1 forms inclusion complexes with simple aromatic compounds such as benzene or thiophene with exceptional selectivity. In particular, only the racemic cis acid 1 participates in clathrate formation, with no clathrates being formed either from the corresponding racemic trans isomer or from any individual enantiomer, irrespective of configuration. A novel efficient procedure for separation of the geometrical as well as optical isomers of the acid 1 has been developed utilizing these clathrates.

Experimental Section

Starting Materials. Racemic cis and trans acids 1 (X = Cl and Br) were prepared and optically resolved into antipodes by reported procedures.[10]

Preparation of Inclusion Complexes from Aromatic Solvents and Pure Racemic Cis Acid 1 (X = Cl and Br). General Procedure. One gram of the racemic cis acid 1 (X = Cl or Br) was dissolved under reflux in 2 mL of the appropriate aromatic solvent (acid 1 (X = Br) requires 4 mL of benzene) and

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[8] The cis/trans ratio was determined by GLC after converting the acids to methyl esters by diazomethane treatment.

[9] The percent ee is based on our value α_D = +33.70° (*c* = 1.2, CHCl$_3$) for (1*R*)-*cis*-3-(2′,2′-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, which is higher than reported (−31° (*c* = 1, CHCl$_3$)) for the *S* isomer (ref 10).

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Table II. Yields (%) of 2:1 Inclusion Complexes of the Racemic Cis Acid 1 (X = Cl or Br) with Aromatic Solvents

	X			X	
aromate	Cl	Br	aromate	Cl	Br
benzene	92	94	furan[a]	83	89
fluorobenzene	92	91	2-methylfuran	49	69
thiophene	93	91	pyrrole	82	85

[a] Dissolved at 80 °C under pressure.

cooled to 0 °C in an ice bath (solutions in benzene were cooled to 8–10 °C). The crystals that deposited were filtered and washed with a small amount of the cool solvent. Yields and amounts of solvents used are given in Table II.

Separation of the Racemic Cis Acid 1 (X = Cl) from the Corresponding Cis–Trans Isomeric Mixture Using an Inclusion Complex with Thiophene. A 9.93-g portion of the racemic cis–trans mixture of the acid 1 (X = Cl) containing ca. 20% of the trans isomer was dissolved under reflux in thiophene (50 mL). Cooling in an ice bath afforded a crystalline inclusion complex, which upon desolvation (100 °C, 4 h, 1 Torr) yielded 7.89 g of the racemic cis acid (98% of theoretical based on the content of the cis isomer in the original isomeric mixture). The isolated cis acid contained less than 1% of the trans isomer. Replacement of thiophene by other appropriate aromatic compounds leads to similar results.

Separation of the Racemic Cis Acid 1 (X = Cl) from the Corresponding Optically Active (1*S*)-Cis Isomer Using an Inclusion Complex with Benzene. A 36.3-g portion of the laevorotatory cis acid 1 (X = Cl), $\alpha_D = -9.8°$ ($c = 1.21$, $CHCl_3$), i.e. 29% ee, was dissolved under reflux in benzene (44 mL). The crystalline complex which deposited upon cooling (ca. 10 °C) was filtered, washed with a small amount of the cool solvent, and thermally desolvated (80 °C, 24 h, 10 Torr). This yielded 21.6 g of the racemic cis acid $\alpha_D = 0.0°$ ($c = 1.20$, $CHCl_3$). Evaporation of the mother liquor yielded 13.1 g of the optically enriched (1*S*)-cis acid, $\alpha_D = -27.22°$ ($c = 1.20$, $CHCl_3$), which corresponds to ca. 81% ee.

Separation of the Racemic Cis Acid 1 (X = Cl) from the Corresponding Optically Active (1*S*)-Cis Isomer Using an Inclusion Complex with Thiophene. A procedure analogous to that described above using 18.0 g of the cis acid 1 (X = Cl), $\alpha_D = -12.4°$ ($c = 1.20$, $CHCl_3$), i.e. 37% ee, and thiophene (18 mL) afforded 10.18 g of the racemic cis acid and 7.30 g of the enriched (1*S*)-cis isomer, $\alpha_D = -29.17°$ ($c = 1.20$, $CHCl_3$), i.e. 87% ee.

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Calculated Properties of the 22 Carbon/Nitrogen Cubanoids

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Some properties of the 22 possible carbon/nitrogen cubanoids (i.e., $(CH)_{8-n}N_n$ $0 \le n \le 8$) have been calculated and are presented here. By use of the AM1 and PM3 semiempirical models, all the C/N cubanoids are shown to correspond to stationary points on the appropriate energy hypersurfaces. These stationary points are demonstrated to be local stable points via vibrational frequency calculations. The AM1 and PM3 models yield significantly different ΔH_fs, and this disparity increases as the amount of nitrogen in the cubanoid increases. The AM1 and PM3 ΔH_fs are compared with MNDO values and, in a few high-symmetry cases, with RHF/6-31G*// results. The potential of the C/N cubanoids as energetic materials is examined by prediction of two detonation properties of the condensed-phase materials. In order to make these predictions, condensed phase mass densities (ρ_0) are calculated with Stine's method. Then, by use of the ρ_0 values and the calculated ΔH_fs, Chapman–Jouguet detonation pressures and velocities are determined. The calculations indicate that any of the C/N cubanoids that contain four nitrogens or more would be high-performance energetic materials. One highly symmetric nitrated cubanoid structure (T_d symmetry $C_4(NO_2)_4N_4$) is also examined using the same approach.

I. Introduction and Background

In this paper, a theoretical study is reported of the 22 cubanoid structures with chemical formulas $(CH)_{8-n}N_n$ with $0 \le n \le 8$. The limiting structures (i.e., $(CH)_8$ and N_8) are true cubes (i.e., O_h point group). Replacement of CH groups by nitrogen in the $(CH)_8$ structure breaks the O_h symmetry and results in structures with reduced symmetry (see Tables I and II) and similarly for N_8 cubane. Note that the CH group and nitrogen atom are isoelectronic and therefore the C/N cubanoids form an isoelectronic set of structures.

The C/N cubanoids are interesting for a number of reasons. For example, the pure carbon form $(CH)_8$ has been synthesized and studied extensively by Eaton and his co-workers.[2] In spite of the high strain energy (ca. 166 kcal/mol) present in carbon cubane, it is quite stable.[3] Carbon cubane slowly decomposes when heated to 200 °C.[4] The high thermal stability of this very strained structure is thought to result from the symmetry forbiddeness of the reactions that can take it to smaller/less strained structures.[5] Because the C/N cubanoids are isoelectronic with $(CH)_8$, it is possible these structures will show analogous stability. Secondly, ab-initio theoretical results for N_8 indicate it is a stable entity in which large amounts of energy can be stored.[6] If it could be synthesized, it is likely that N_8 would be the most powerful chemical explosive in existence.

In the light of these comments, the molecular stability and potential of the C/N cubanoids as energetic materials are examined here. In particular, we examine the question of how the energetic properties of the cubanoid are en-

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