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Molecular mechanics (MM3) study of the conformations of ethyl esters of diastereoisomeric 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids

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Abstract Molecular mechanics calculation (MM3 force field) were used to study the conformations of diastereoisomeric pairs of ethyl esters of 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids in order to test an assumption from ^1H NMR spectra about their preferred conformations. On the basis of the most probable preferred conformation in each case, an assignment of the relative configurations of these newly synthesized compounds was made in the earlier study. The present computed most favorable conformations are in accord with the earlier qualitative considerations in all cases, thus validating the assignment of the configurations of the diastereoisomers made previously.

Keywords Ethyl esters of 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids · Conformational analysis · Assignment of configuration · Molecular mechanics (MM3)

Introduction

As a part of a project aimed at the synthesis of new chloro-containing compounds, Gaudemar-Bardone and co-workers developed a very simple and efficient one-step method for the synthesis of highly functionalized tetrasubstituted ethanes by Michael addition of organometallic reagents [1] and various monofunctional nucleophiles, such as alcohols, thiols, dimethylphosphite, diphenylphosphine oxide, aniline (some of them are shown in Fig. 1), [1] as well as bifunctional nucleophiles – diols

and their derivatives, glycolic acid, methyl glycolate, mercaptoethanol, 1,2-athanedithiol. [2] The large range of applicability of the method was thus illustrated by the synthesis, in good to excellent yields, of a variety of about 30 new 3-substituted ethyl esters of 4,4,4-trichloro-2-cyano-butanoic acid. The product compounds have two asymmetric centers, so that the formation of two diastereoisomers was possible. In most cases only one isomer was detected (^1H NMR) in the crude reaction product, while in others (e.g. compounds **2** and **4**), the formation of small amounts of the second isomer was observed. For the cases considered in our study, compounds **1–4**, the ^1H NMR data show a small vicinal methine proton coupling constant ($^3J_{2,3}=1.5\text{--}3.5$ Hz) for the preponderant, or the only, diastereoisomer obtained, while a higher value of $^3J_{2,3}$ was estimated for the minor diastereoisomer (6.5–7.3 Hz). [1] The configurations of the diastereoisomers of **1–4** were assigned accordingly on the basis of the vicinal methine proton coupling constants and the assumption for preference of conformations **I** in both isomers. The authors considered it necessary to obtain additional data from an independent source. They thus cautiously designated the isomers as **A** and **B**, [1] or **M** (major) and **m** (minor). [2] The purpose of the present molecular mechanics study is to verify the validity of the assumption for a preference for conformations **I**. [1] If the computed molecular mechanics data confirm a preference for conformation **I** of the diastereoisomers **1–4**, then we can be more confident in the assignment of their configurations previously made. [1]

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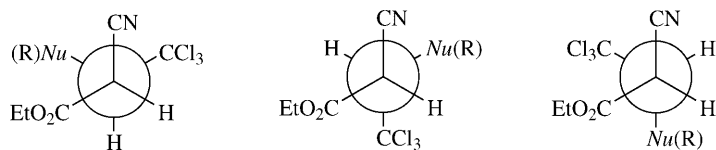
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Computational details

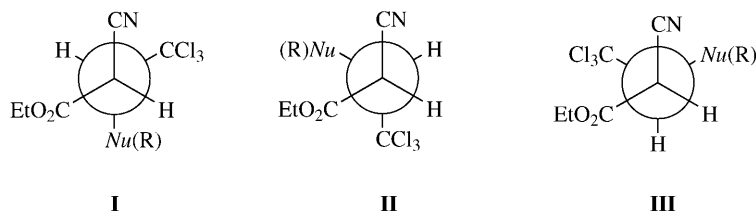
The computational conformational analysis of the diastereoisomers of **1–4** was carried out utilizing the MM3 force field [3, 4, 5, 6] with the Goldstein–Allinger parameters for cyano compounds, [7] and some torsional parameters, related to structural units containing a cyano group, reoptimized recently by one of us. [8] For the

Fig. 1 Designation of conformations in the diastereoisomers of ethyl esters of 3-substituted-4,4,4-trichloro-2-cyano-butanoic acids

Isomer A



Isomer B



I

II

III

R = Ph (**1**) Nu = OCH₃ (**2**), OCH₂CCH (**3**), SC₂H₅ (**4**)

purpose of the present study we found it necessary to readjust one additional torsional parameter, 4-1-1-6 [MM3 atom types: 1=C_{sp3}, 4=C_{sp}, 6=O (C-O-H, C-O-C)]. The torsional force field parameters V_i ($i=1,2,3$) for this dihedral were designated as preliminary values in the force field parameter file of MM3(92). [6] A slightly smaller negative value $V_2=-0.2$ kcal mol⁻¹ (original value $V_2=-0.4$) reproduces the equal participation in equilibrium of the synclinal and the antiperiplanar conformations of 2-cyanoethanol, determined from infrared spectra of the vapor better. [9] An effective dielectric constant of 2.0 was used in the estimation of the electrostatic interactions. The conformational space search algorithm CONFLEX [10] was used to find low-energy conformations. For brevity, the designations g^+ , g^- and t will be used for the dihedrals more distant from the rotation about the C(2)-C(3) bond: C-O-CH₂-CH₃ (**1-4**), C(3)-O-CH₂-CCH (**3**), and C(3)-S-CH₂-CH₃ (**4**).

Results

Computed optimized conformational geometry and relative energies data, as well as the populations of the main conformations (Fig. 1, conformations **I**, **II**, and **III**) of the diastereoisomers of **1-4** are summarized in Table 1.

Three local minima of conformation **I**, **1A.I.1**, have the lowest energy computed with MM3 (Table 1) and a population of about 40%. Another three conformations **1A.I.2** contribute also to the 60% preference for conformation **I**, in accord with the assumption made in [1]. This conformation has an antiperiplanar pair CCl₃/COOEt, as well as a skew disposition of the trichloromethyl group with respect to the cyano group. The same mutual spatial arrangement of the three functional groups characterizes the preferred conformations of the other isomers **A** (**2A-4A**), as well as all diastereoisomers **1B-4B**. The relative energy of the lowest energy local minimum of conformation **II** is only 0.3 kcal

mol⁻¹. The computed dipole moment of **I** is about 1.0 D higher than that of **II**; thus this conformation will be stabilized additionally by the polarization of the solvent molecules in close proximity of the solute. Unfavorable steric interactions in **1A.I** and **1A.II** are diminished by opening the angle C(2)-C(3)-CCl₃ up to 116.0°. The same angle also has the largest deformations in the preferred conformations of **1B**, as well as in all diastereoisomers of **2-4**. The trichloromethyl group exerts the most severe nonbonded repulsion.

Only differences in the total molecular mechanics potential energy have a physical meaning; thus, the analysis of the contributions of individual energy terms may only be considered in relation to the balance between them. Computed energy differences of similar magnitude could result from different balances between steric energy components. The torsional potential is among the most problematic for parameterization and inaccuracies in the adjustment of torsional force field parameters can add up and produce in some cases results of doubtful value. The computed conformational energy data of isomers **1A-4A** present a situation with a decisive role of this energy term. An advantageous torsional energy contribution of 1.9 kcal mol⁻¹ in **1A.I** is almost counterbalanced in **1A.II** by favorable angle bending deformation (1.2 kcal mol⁻¹) and van der Waals interactions (0.6 kcal mol⁻¹). Conformations **1A.I** and **1A.II** have practically the same contributions from electrostatic interactions.

The replacement of the phenyl group (**1A**) by a methoxy group (**2A**) results in a conformational distribution strongly biased towards only one **2A.I** conformation. This conformation has the same value of the dihedral C(3)-C(2)-C=O found for the global minimum conformation of **1A**. Conformations **I** also have the lowest energies for the **A** isomers of **3** and **4**. Here again an opening of angle C(2)-C(3)-CCl₃ to about 115.0° was obtained. The lesser steric demands of the methoxy group compared to the phenyl group yielded a different balance of interactions between conformations **I** and **II** of **2A**

Table 1 MM3 computed data of low-energy conformations of ethyl esters of 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids (**1–4**) [units: angles (degrees), relative energies (ΔE , kcal mol⁻¹)]

Conformation R=Ph (1)	<i>n</i> ^a	NC–C–C–CCl ₃	C3–C2–C=O	C–O–CH ₂ –CH ₃	C2–C3–C ^{ar} –C ^{ar}	ΔE^b
Isomer A						
1A.I.1	0.60	78.2	–4.4	t, g [–] , g ⁺	70.2	0.0; 0.0; 0.2
1A.I.2		71.6	107.7	t, g [–] , g ⁺	66.6	0.3; 0.5; 0.9
1A.I.3		60.0	–114.9	g ⁺ , t, g [–]	60.0	1.8; 2.1; 2.4
		62.1	–166.6	g ⁺ , t, g [–]	56.2	2.0; 2.0; 2.5
1A.II.1	0.40	166.5	–34.8	t, g ⁺ , g [–]	50.1	0.3; 0.3; 0.4
1A.II.2		173.8	128.5	t, g ⁺ , g [–]	52.8	0.5; 0.7; 1.0
1A.III.1	0.0	–86.2	99.5	t	59.1	2.7
Isomer B						
1B.I.1	1.0	71.5	–37.5	g ⁺ , t, g [–]	129.7	0.0; 0.4; 0.5
1B.I.2		75.5	133.0	g [–] , t, g ⁺	130.0	0.1; 0.2; 0.6
1B.II.1	0.0	156.2	–25.3	g ⁺	87.3	3.5
1B.III.1	0.0	–40.7	6.1	t	127.9	3.2
<i>Nu</i> =OCH ₃ (2)						
Isomer A						
2A.I.1	0.71	91.4	–2.9	t, g [–] , g ⁺	–78.8	0.0; 0.1; 0.2
2A.I.2		78.1	97.9	t, g ⁺ , g [–]	–114.5	2.2; 2.4; 2.5
		102.3	148.3	t, g [–] , g ⁺	–82.9	2.2; 2.4; 2.5
2A.I.3		87.2	–128.5	t, g ⁺ , g [–]	–80.0	2.6; 2.6; 2.9
2A.II.1	0.29	156.8	–26.7	g ⁺ , t, g [–]	–111.8	0.7; 0.7; 0.9
2A.II.2		167.9	133.4	t, g ⁺ , g [–]	–112.9	1.3; 1.5; 1.7
2A.III.1	0.0	–81.5	87.8	t	–90.8	3.2
Isomer B						
2B.I.1	0.65	75.7	–34.6	t, g ⁺ , g [–]	124.9	0.0; 0.0; 0.1
2B.I.2		77.3	123.0	t, g ⁺ , g [–]	121.7	0.3; 0.5; 0.6
2B.II.1	0.32	151.8	–22.4	g ⁺ , t, g [–]	79.5	0.3; 0.4; 0.5
		165.4	123.0	t, g [–] , g ⁺	99.5	0.9; 1.0; 1.2
2B.III.1	0.03	–43.7	11.7	g [–] , t, g ⁺	92.0	1.9; 2.1; 2.2
		–74.8	77.4	t, g ⁺ , g [–]	82.2	1.9; 2.2; 2.5
<i>Nu</i> =OCH ₂ CCH (3)						
Isomer A						
3A.I.1	0.78	91.9	0.1	t, g [–] , g ⁺	–81.9	g [–]
		89.4	–0.4	t, g [–] , g ⁺	–78.9	t
3A.I.2		103.6	150.3	t, g [–] , g ⁺	–84.4	g [–]
		98.9	154.5	t, g [–] , g ⁺	–81.8	t
Conformation						
3A.I.3		87.3	–127.2	g ⁺ , t, g [–]	–71.9	g [–]
3A.II.1	0.22	147.6	–22.9	g ⁺ , t, g [–]	–100.9	g [–]
		151.9	–25.9	g ⁺ , t, g [–]	–123.6	g ⁺
		125.2	–18.8	t, g [–]	–96.2	t
3A.II.2		162.1	137.4	t, g ⁺ , g [–]	–103.2	g [–]
		160.1	138.7	t, g ⁺ , g [–]	–125.1	g ⁺
		159.4	134.2	g [–]	–111.6	t
3A.III.1	0.0	–79.8	84.0	t	–85.9	g [–]
Isomer B						
3B.I.1	0.57	73.9	–38.1	g ⁺ , t, g [–]	123.3	t
		54.6	–32.2	t, g ⁺ , g [–]	104.2	g ⁺
		82.5	–27.0	t, g ⁺ , g [–]	140.1	g [–]
3B.I.2		76.6	125.4	t, g ⁺ , g [–]	122.4	t
		64.1	123.4	t, g ⁺ , g [–]	102.9	g ⁺
		84.3	128.6	g [–] , t, g ⁺	144.1	g [–]

Table 1 (continued)

Conformation R=Ph (1)	n^a	NC-C-C-CCl ₃	C3-C2-C=O	C-O-CH ₂ -CH ₃	C2-C3-C _{ar} -C _{ar}	ΔE^b	
3B.II.1	0.42	150.7	-24.7	g ⁺ , t, g ⁻	80.8	g ⁺	0.1; 0.2; 0.3
		151.6	-22.8	g ⁺ , t, g ⁻	78.7	t	0.8; 0.9; 1.0
		155.4	-24.1	t, g ⁺ , g ⁻	124.7	g ⁻	1.7; 1.7; 1.8
3B.II.2		156.5	120.6	t, g ⁻ , g ⁺	87.8	g ⁺	0.8; 0.8; 1.1
		166.3	124.3	t, g ⁻ , g ⁺	101.0	t	1.0; 1.1; 1.5
		173.0	115.7	t, g ⁺ , g ⁻	133.5	g ⁻	1.9; 2.1; 2.2
3B.III.1	0.01	-47.1	20.4	g ⁻ , t, g ⁺	94.7	t	2.4; 2.5; 2.7
Isomer A		<i>Nu</i> =SC ₂ H ₅ (4)		C2-C3-S-CH ₂	C3-S-CH ₂ -CH ₃		
4A.I.1	0.73	78.2	-4.0	t, g ⁻ , g ⁺	-123.6	t	0.0; 0.1; 0.2
		90.5	6.2	g ⁻ , t, g ⁺	-71.6	t	0.5; 0.5; 0.7
		83.6	2.6	t, g ⁻ , g ⁺	-105.0	g ⁻	1.0; 1.0; 1.2
		78.6	-5.2	t, g ⁻ , g ⁺	-137.5	g ⁺	1.3; 1.3; 1.4
		91.6	3.4	g ⁻ , t, g ⁺	-80.2	g ⁺	2.0; 2.1; 2.3
4A.I.2		74.6	-110.0	t, g ⁺ , g ⁻	-101.0	t	2.2; 2.2; 2.4
		76.5	-102.6	t, g ⁺ , g ⁻	-97.2	g ⁻	2.4; 2.4; 2.5
		74.7	-97.9	t; g ⁻	-125.8	g ⁺	2.6; 2.8
4A.I.3		76.1	94.1	t, g ⁻ , g ⁺	-109.6	t	1.2; 1.5; 1.5
		74.7	71.6	t, g ⁺ , g ⁻	-97.0	g ⁻	1.6; 1.8; 1.9
Conformation	n^a	NC-C-C-CCl ₃	C3-C2-C=O	C-O-CH ₂ -CH ₃	C2-C3-S-CH ₂	C3-S-CH ₂ -CH ₃	ΔE^b
4A.II.1	0.26	75.5	87.7	t, g ⁺ , g ⁻	-127.0	g ⁺	1.7; 2.0; 2.0
		83.4	126.0	t, g ⁺ , g ⁻	-123.8	t	1.4; 1.6; 1.7
		167.2	-34.6	t, g ⁺ , g ⁻	-107.8	t	0.8; 0.8; 0.9
		165.2	-34.4	t, g ⁺ , g ⁻	-100.5	g ⁻	1.1; 1.2; 1.3
		165.7	-34.5	t, g ⁺ , g ⁻	-124.8	g ⁺	1.3; 1.4; 1.5
4A.II.2		174.5	129.3	t, g ⁺ , g ⁻	-110.4	t	1.1; 1.3; 1.6
		173.2	130.0	t, g ⁺ , g ⁻	-102.0	g ⁻	1.4; 1.6; 1.9
		172.9	130.2	t, g ⁺ , g ⁻	-126.3	g ⁺	1.6; 1.8; 2.1
4A.III.1	0.01	-78.9	86.9	t, g ⁺	-84.6	t	2.6; 3.0
Isomer B							
4B.I.1	0.89	64.1	-34.3	g ⁺ , t, g ⁻	122.9	t	0.0; 0.1; 0.2
		61.6	-41.5	g ⁺ , t, g ⁻	109.5	g ⁺	1.0; 1.1; 1.3
		66.0	-38.5	g ⁺ , t, g ⁻	135.5	g ⁻	1.1; 1.2; 1.4
		62.0	-33.0	g ⁺ , t, g ⁻	-56.6	t	2.0; 2.2; 2.3
		4B.I.2		68.5	130.3	t, g ⁻ , g ⁺	123.6
62.8	123.7			t, g ⁺ , g ⁻	107.2	g ⁺	1.4; 1.6; 2.2
68.8	122.2			t, g ⁺ , g ⁻	135.8	g ⁻	1.6; 1.7; 2.5
64.7	132.4			g ⁻ , t, g ⁺	-58.0	t	2.4; 2.4; 2.6
4B.II.1	0.10			167.1	-32.1	g ⁺ , t, g ⁻	107.4
		165.4	-31.5	g ⁺ , t, g ⁻	98.3	g ⁺	2.0; 2.0; 2.2
		167.6	-33.1	g ⁺ , t, g ⁻	126.2	g ⁻	2.3; 2.3; 2.5
4B.II.2		174.9	116.9	t, g ⁻ , g ⁺	106.7	t	1.7; 2.0; 2.0
		174.4	117.2	t, g ⁻ , g ⁺	98.5	g ⁺	2.1; 2.4; 2.4
		175.7	116.7	t, g ⁺ , g ⁻	125.3	g ⁻	2.4; 2.7; 2.7
4B.III.1	0.01	-49.3	19.0	g ⁻ , t, g ⁺	85.4	t	2.6; 2.6; 2.8
		-49.2	19.0	g ⁻ , t	85.8	g ⁺	2.8; 2.9

^a Computed populations (at 300 K) of main conformations **I**, **II** and **III**

^b Steric energies (kcal mol⁻¹) of the lowest energy conformations obtained with MM3: **1** (A: 21.04; B: 20.04), **2** (A: 24.49; B: 25.83), **3** (A: 24.93; B: 26.11), **4** (A: 26.08; B: 26.27)

and **1A**. The angle bending energy contribution in this case does not have any significance, while a more favorable torsional energy contribution 1.7 kcal mol⁻¹ in **I** opposes the advantageous nonbonded interactions, van der Waals and electrostatic, in conformation **II**. The dipole moment of conformation **2A.I.1** is 2.1 D larger than that of **2A.II.1**.

The relative importance of the steric compared with the electrostatic interactions slightly decreases when the methyl group in **2A** (-OCH₃) is replaced with a propargyl group in **3A** (-OCH₂C≡CH). The electrostatic interactions in conformation **II** of **3A** are the sole factor balancing the favorable torsional energy component of **I**.

The computed conformational data of the thio ether derivative further confirm the preference of conformation **I** in the series of isomers **A**. With respect to the balance of intramolecular interactions in conformations **I** and **II**, the isomer **4A** presents a situation intermediate between **1A** and **2A**. The van der Waals energy contributions are exactly the same in the two conformations, while more favorable electrostatic interactions, 0.6 kcal mol⁻¹, and angle bending, 0.3 kcal mol⁻¹, balance the preference of conformation **I** by the torsional potential.

MM3 determines a preference for conformation **I** of the isomers **1B–4B**, thus validating the assignment of the relative configurations of the diastereoisomers **A** and **B** in [1]. Here again the preferred conformation **I** has the pair COOEt/CCl₃ in an antiperiplanar mutual disposition. The antiperiplanar C(2)–H/C(3)–H methine hydrogens separate the two pairs of group interactions across bond C(2)–C(3), COOEt/*Nu*(R) and CN/CCl₃, respectively. Thus, the conformations **I** of diastereoisomers **B** possess the favorable features of conformations **I** (antiperiplanar COOEt/CCl₃) and **II** (antiperiplanar C(2)–H/C(3)–H) of isomers **A**. Angle bending energy contributions favor conformation **I** of **1B–4B** in all cases, while all other components add up to further enhance the population of **I** in **1B** and **4B**, or to counterbalance this term in **2B** and **3B**. Our reoptimized value of the torsional parameter V_2 for the dihedral 4–1–1–6 does not have any influence on the computed populations of **2A** and **3A** (this dihedral is in the synclinal arrangement in the two conformations **I** and **II**).

Conclusions

We have examined an earlier assumption for the preferred conformations of diastereoisomeric pairs of ethyl

esters of 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids with molecular mechanics (MM3). [1] Our computed conformational data support the assignment of the configurations of the diastereoisomers based on this assumption. The lack of information about closely related compounds with known configurations prevented us following the more reliable approach of stereochemical assignment by chemical transformations that proceed with retention of the configurations of the asymmetric centers. [1, 2] The combined utilization of spectral [1] and the present computed data provided reliable information about the relative configurations of the compounds studied.

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