cis-Cyclononene Conformational Families and a Crystallographic Example of a Skew-Chair−Boat Type-2 Conformation

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Cyclononanes from the 7 low-energy conformational archetypal families (twist-boat−chair, twist-chair−boat, twist-chair−chair, twist-chair−twist-chair, skew-chair−boat, skew-chair−chair, and skew-boat−boat) were transformed into 12 of 13 MM3 stochastically generated *cis*-cyclononenes. This was done by systematically converting single bond synclinal endocyclic torsion angles, one-at-a-time, into double-bond synperiplanar analogues, followed by geometry optimization [e.g. density functional theory B3LYP/6-31G(d)]. Torsion angles adjacent to the new double bond maintained their signs, while their magnitudes usually changed considerably to accommodate the new neighboring synperiplanar torsion angles. The six remaining torsion angles all maintained their signs and approximate magnitudes compared to corresponding values in the seven saturated parent structures. As a result, the same "twist"/"skew" conformational descriptors previously used for the saturated conformers can now also be applied to the corresponding unsaturated analogues. Three conformational families have multiple members (subtypes) in which the double bond is located at different positions on the same ring conformation. The solid-state structures of (±)-1-phenyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (**22**) and (1*RS*,3*SR*)-1-phenyl-3-methyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (**23**) were determined by single-crystal X-ray diffraction analysis. The asymmetric unit of the P$\bar{1}$ unit cell for **22** contains two symmetry-unrelated molecules, both of which exhibit a skew-chair−boat (SCBtype-2) conformation identical to that found for crystalline **23**. This subtype has yet to be found in the Cambridge Crystallographic DataBase. Crystal lattice packing considerations alone cannot explain the observation of the SCBtype-2 conformation since ^{1}H NMR spectroscopy shows the same conformational bias when the crystals are dissolved in CDCl$_3$.

Introduction

Medium rings share a common trait in that, unlike cyclohexane, they are strained in all of their conformations. Considering the heat of combustion/methylene group, cyclononane is the most strained member of the medium-ring cycloalkane family, (CH$_2$)$_n$, where n = 8−12.[1] The main contributors to strain in the medium rings arise from bond angle, torsion angle, and nonbonded effects (especially transannular nonbonded interactions). Dale[2] has stated that, on the basis of thermochemical strain, cyclononane can be considered the most typical medium-sized ring. He goes on to say that "it can be considered to be the smallest macrocyclic alkane inasmuch as torsion angles larger than 120° start to play a role."[2] In addition, he notes that "the greater mobility of the ring permits conformational conversions to take place in more localized step processes rather than as synchronous changes of the whole ring".[2] We have recently reviewed the stereochemistry of nine-membered rings containing one strong synperiplanar (ca. 0°) endocyclic torsional constraint.[3] This structural restriction may arise from a variety of sources: e.g. cis double bond, benzannelated ring, fused-oxiranyl/-aziridinyl rings, *cis*-lactam/lactone, etc.

In a very early work, Hendrickson[4] depicted six achiral and four chiral cyclononane conformations. He showed that the plane-symmetrical models were all higher in energy than the three chiral ones. Only two of the four C_2-symmetry conformers were provided with a descriptor: the "D_3" conformer [the most stable model, and later defined as a "twist-boat−chair" (TBC, **1**)[5]] and the "twist-chair−chair" (TCC, **2**) (the second most stable model). The next most stable C_2 model was subsequently affixed

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[†] Department of Chemistry.

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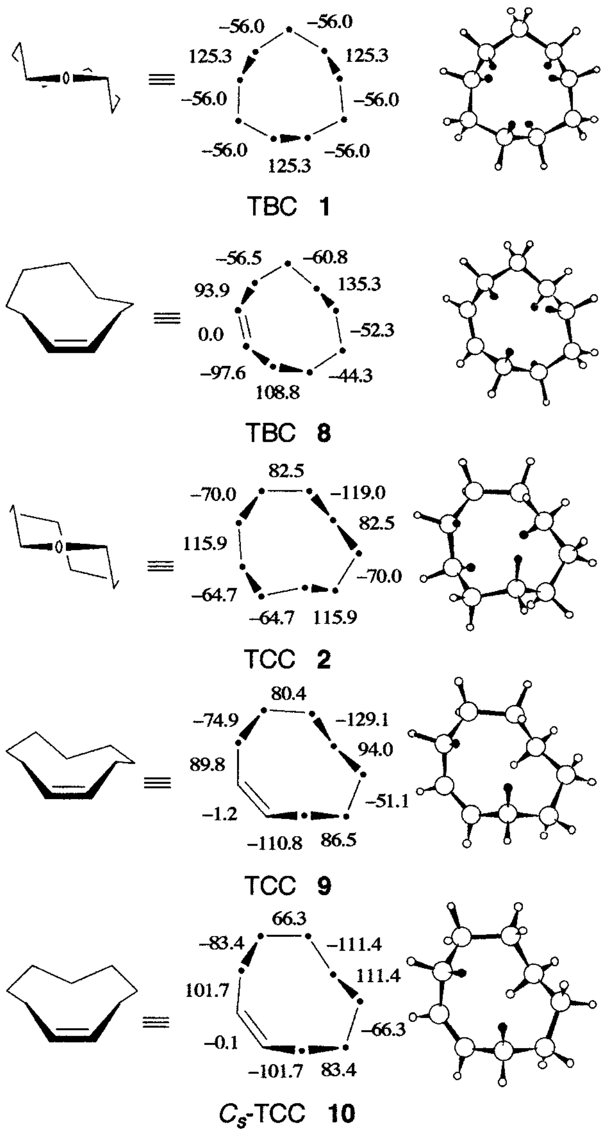

FIGURE 1. Torsion angles, iconic 2D projections, and ball and stick representations of density functional theory B3LYP/6-31G(d) 3D models for twist-boat–chair (TBC) cyclononane (**1**) versus TBC *cis*-cyclononene (**8**) and twist-chair–chair (TCC) cyclononane (**2**) versus *cis*-cyclononene TCC (**9**) and C_s-TCC (**10**).

a “twist-chair–boat” (TCB, **3**) descriptor by Anet and Krane.[5] Models **1**–**3**, and all others in Figures 1–5 (with the exception of MM3[6,7] calculated models **5** and **6**), are illustrated as 2D iconic projections[8a,b] of actual B3LYP/6-31G* density functional theory[9,10] (DFT) 3D molecular models. They are also shown as ball and stick[11] structures depicting transannular interactions between black

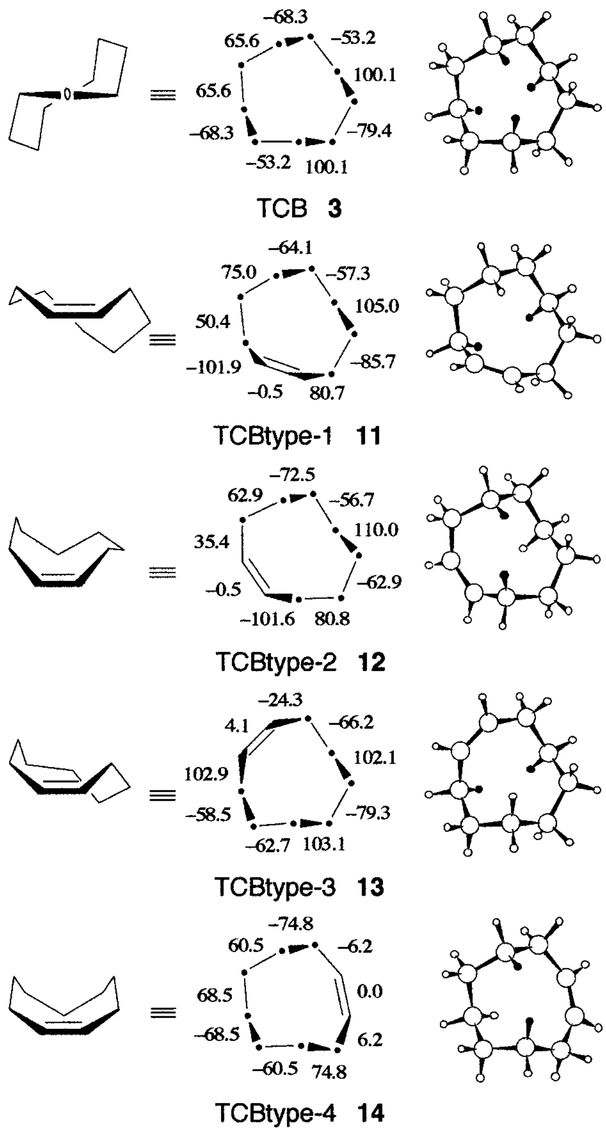

FIGURE 2. Torsion angles, iconic 2D projections, and ball and stick representations of density functional theory B3LYP/6-31G(d) 3D models for twist-chair–boat (TCB) cyclononane (**3**) versus TCBtypes 1–4 *cis*-cyclononene (**11**–**14**).

colored endo-oriented protons. These three chiral conformations are the thermodynamically important ones for cyclononane,[5,12,13] and one of their interconversion modes involves bringing a torsion angle to zero (a so-called “kayaking”[14] movement). Thus, Hendrickson’s achiral cyclononane models more closely resemble transition states rather than ground-state conformational entities.

Dale made very significant and pioneering contributions to the field of medium-ring conformations and their interconversion modes.[15] Using manual calculations performed on the basis of molecular models, he reported[15] a new cyclononane conformation [now noted[16] as the “skew-

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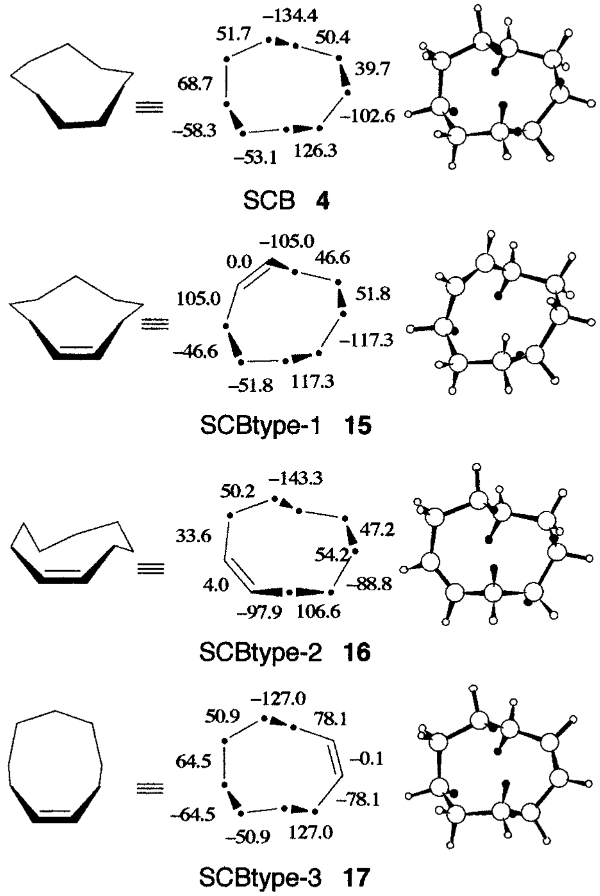

FIGURE 3. Torsion angles, iconic 2D projections, and ball and stick representations of density functional theory B3LYP/6-31G(d) 3D models for skew-chair–boat (SCB) cyclononane (**4**) versus SCBtypes 1–3 *cis*-cyclononene (**15**–**17**).

chair–boat" (SCB, **4**; see Figure 3) and exhibiting C_1 symmetry]. He also developed conformational descriptors on the basis of the number of bonds between "corner" ring atoms, which were defined as those having identical signed synclinal (gauche, ca. 60°) endocyclic torsion angles on either side {e.g. [333] = TBC **1**, [144] = TCC **2**, and [225] = TCB **3**}. However, these descriptors are not unique in some cases. Disubstitution of "corner" ring atoms have a stereochemical advantage in that neither ligated group points toward the interior of the ring.

Two additional cyclononane conformations of potential importance in conformational interconversion pathways were found by stochastic conformational search algorithms and were reported by Lipton and Still,[17] while Raber[16] and co-workers independently found these two, plus one more. The first conformation has been described by Raber[16] and co-workers as a "twist-chair–twist-chair" (TCTC, **5**, depicted as an MM3 calculated model in Figure 4) and exhibits C_1 symmetry. The second conformation was called a "skew-chair–chair" (SCC, **6**, also depicted as an MM3 model in Figure 4) and shows C_2 symmetry, while the third was noted as a "skew-boat–boat" (SBB, **7**; see Figure 5) also having C_2 symmetry. Anet[18] has criticized the TCTC **5** and SCC **6** cyclononane conformations mentioned by the Still[17] and Raber[16] groups by stating that both conformations are really very similar to TCC. The TCTC conformation was said to be an unsymmetrical variant of the TCC conformation where some torsional angles have increased slightly and others decreased slightly. The SCC conformation was stated to be essentially a TCC type that is less open and more elongated along the C_2 axis.[18] He noted that while these two conformations are local minima using the MM2[19] force field (or the MM3 force field, as shown by Saunders[20]), they were not found with some other molecular mechanics force fields. When they were found, their interconversion barriers were calculated to be extremely low in energy.

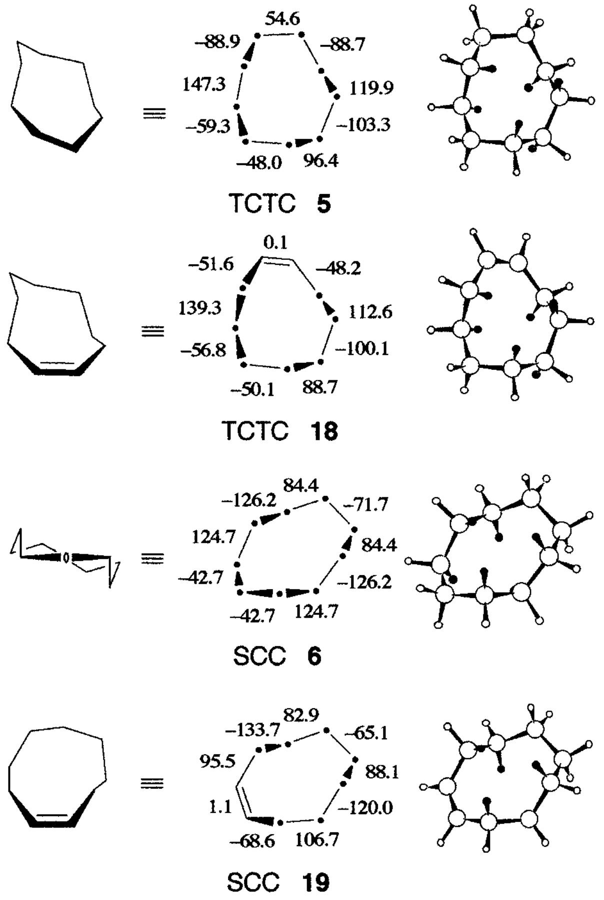

FIGURE 4. Torsion angles, iconic 2D projections, and ball and stick representations of MM3 3D models for twist-chair–twist-chair (TCTC) cyclononane (**5**) and skew-chair–chair (SCC) cyclononane (**6**) versus density functional theory B3LYP/6-31G(d) 3D models for TCTC *cis*-cyclononene (**18**) and SCC *cis*-cyclononene (**19**).

In one of the earliest studies on *cis*-cyclononene conformations, Favini and co-workers performed simple molecular mechanics calculations on four C_s-symmetry conformations. One of them had C_2 symmetry, and one exhibited C_1 symmetry.[21a,b] The four achiral ones were

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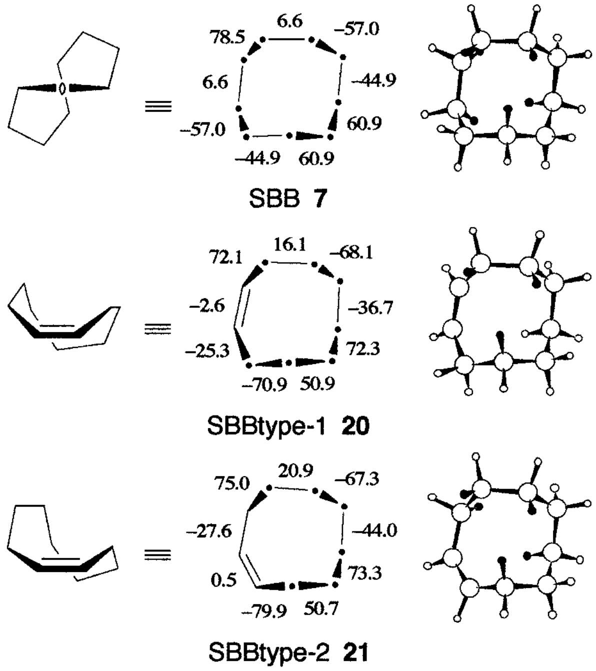

FIGURE 5. Torsion angles, iconic 2D projections, and ball and stick representations of density functional theory B3LYP/6-31G(d) 3D models for skew-boat−boat (SBB) cyclononane (**7**) versus SBBtypes 1 and 2 *cis*-cyclononene (**20**, **21**).

defined as "boat−boat", "boat−chair", "chair−chair", and "chair−boat" (whose torsion angles are similar to **17**), while the C_2-symmetry chiral analogue was called a "twist-chair−chair" (torsion angles unrelated to the cyclononane TCC). In this limited series, the asymmetric conformation (denoted as "form A") was the minimum energy structure followed by the "boat−boat" achiral conformation.[21b]

Furusaki et al.[22] performed an MM2 molecular mechanics investigation of *cis*-cyclononene ring conformations as part of an X-ray crystallographic study of isolaurallene and neolaurallene marine natural products. Eight chiral and two achiral C_s-symmetry *cis*-cyclononene conformations were discussed and have been assigned two-letter conformational descriptors. The relative energies reported by Furusaki et al.[22] are listed in Table 1. The same four achiral descriptors previously used by Favini et al.[21a,b] were affixed to structures in the Furusaki et al.[22] set, despite the fact that only one of them (chair−boat **17**) was found to be identical to any of the four older ones. The other achiral conformation was described as a "boat−chair" (**15**). Two of the chiral conformations showed "pseudomirror" symmetry and thus were given "achiral"-like descriptors: "chair−chair" (**9**) and "boat−boat" (**20**). The pseudoreflection plane bisects the ring so that torsion angle signs in half of the ring are all inverted relative to corresponding signs in the other half, but as opposed to an authentic "σ-plane" with true enantiotopic sets, magnitudes of pseudoenantiotopically related torsion angles are not equal. The remaining six chiral structures were referred to as "AS1" (**11**), "AS2" (**8**), "AS3" (**16**), "AS4" (**12**), "AS5" (**18**), and "AS7" (**13**), where AS = "asymmetric". The "asymmetry" descriptor was based upon their observation that not *all* torsion angle signs in half of the ring are inverted relative to those of corresponding torsion angles in the other half. The authors noted that their "AS1" (**11**) conformation was already studied by Favini et al.[21b] and had the lowest energy in the series.

Using a very effective stochastic search method[23] and the MM3 force field, Saunders and Jiménez-Vázques undertook conformational searches of 6- to 11-membered ring lactones, as well as *cis*- and *trans*-cycloalkenes.[24] They found 28 *cis*- and *trans*-cyclononene conformers whose relative energies were within an energy window of 40.5 kcal from the global minimum.[24] In this group, there are 13 *cis*-cyclononene (10 chiral and 3 achiral) and 3 *trans*-cyclononene conformations whose relative energies were no more than 7.5 kcal above the global minimum.[24] Three of these *cis*-cyclononene conformations were new (chiral **19**, **21**, and achiral **14**), and 10 were found previously by Furusaki et al.[22] The relative energies of these cyclononene conformers were reported in a table without assigning conformational descriptors. The relative energies of the MM3 geometry optimized 13 *cis*-cyclononene conformers calculated by Saunders and Jiménez-Vázques[24] are also given in Table 1 of this work. A pictorial representation of the MM3 lowest-energy *cis*-cyclononene shows it to correspond to the "AS1" (**11**) conformer of Furusaki et al.[22] (also their MM2 lowest energy structure).

Noe and co-workers[25] also made a conformational study of *cis*-cyclononenes using molecular mechanics (grid search technique and MM3) and ab initio (RHF/6-311G*) computational methods, as well as dynamic NMR spectroscopy. Eight *cis*-cyclononene conformations were reported, and once again, all were without assignment of conformational descriptors. However, pictorial representations (four of which also had torsion angle values) show seven of them to correspond to those reported by Furusaki et al.[22] (MM2) and later by Saunders and Jiménez-Vázques (MM3). The lowest MM3 relative strain energy and −189.3 and 25 °C ab initio relative free energy *cis*-cyclononene conformer in their study corresponds to the same "global minimum energy" structure **11** calculated by Saunders and Jiménez-Vázques[24] (given an "AS1" descriptor by Furusaki et al.[22]). The eighth structure (**10**, labeled by them as "1f") was new and will be shown in this work to be a C_s-symmetry putative transition state for enantiomerization of **9** rather than a bona fide stable conformation for *cis*-cyclononene. The relative free energies at −189.3 °C of the ab initio (RHF/6-311G*) calculated structures given by Noe and co-workers[25] are listed in Table 1. A dynamic NMR study of *cis*-cyclononene was made, and the ^{13}C NMR spectrum at −189.3 °C was interpreted in terms of two conformations. These were a C_1-symmetry major conformer (population 66%) and a minor species, both in dynamic equilibrium. The minor species had either inherent C_s symmetry or was the C_s-symmetry time average of two C_1-symmetry enantiomers interconverting via a low-energy barrier.[25] The authors

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TABLE 1. DFT B3LYP/6-31G* Calculated Relative Energies (kcal) of Geometry-Optimized *cis*-Cyclononene 8–21 Conformations versus Literature Values for RHF/6-311G*, MM3, and MM2 Molecular Modeling Methods

B3LYP/6-31G*	RHF/6-311G* (or 6-31G*)[a]	MM3[b]	MM2[c]
0.00 TCBtype-1 **11**	0.00 (0.00) TCBtype-1	0.000 TCBtype-1	0.00 TCBtype-1
0.67 TBC **8**	0.77 (0.57) TBC	0.021 TCC	0.14 TCC
1.27 TCC **9**	1.00 (1.05) TCC	0.261 TCBtype-2	0.55 TBC
1.35 SCBtype-1 **15**	[1.25 C_s-TCC][d]	0.669 SCBtype-1	0.57 TCBtype-2
[1.47 C_s-TCC][e] **10**	1.36 (1.29) SCBtype-1	0.722 TBC	1.05 SCBtype-1
1.65 TCBtype-2 **12**	1.65 (1.67) TCBtype-2	[0.764 C_s-TCC][e]	2.34 TCBtype-3
2.28 TCBtype-3 **13**	(2.33) TCBtype-3	2.096 TCBtype-3	3.42 SCBtype-2
4.15 SCBtype-2 **16**	(4.43) SCBtype-2	3.894 SCBtype-2	4.07 SCBtype-3
4.55 SCBtype-3 **17**	(5.02) SCBtype-3	5.296 SCBtype-3	5.33 SBBtype-1
5.74 TCBtype-4 **14**	(6.27) SCC	6.126 SBBtype-1	6.58 TCTC
5.95 SCC **19**	(6.59) TCBtype-4	6.177 SCC	
6.36 SBBtype-2 **21**	(6.93) SBBtype-1	6.184 SBBtype-2	
7.14 TCTC **18**	(7.68) TCTC	6.714 TCBtype-4	
7.32 SBBtype-1 **20**	(7.84) SBBtype-2	7.388 TCTC	

[a] RHF/6-311G* relative free energy data calculated at −189.3 °C were taken from ref 25. RHF/6-31G* relative energies (this work) for comparison are given in parentheses. [b] Data taken from ref 24 with the exception of that for C_s-TCC (**10**), whose geometry-optimized structure was calculated (this work) using an input structure having torsion angles of "1f" from Noe and co-workers.[25] [c] Data taken from ref 22. [d] Value reported in ref 25 for structure "1f" by Noe and co-workers placed in brackets. [e] Data placed in brackets since fundamental normal vibrational frequency calculations of structure **10** (this work) afford one negative (imaginary) frequency.

proposed C_1-symmetry **11** and "pseudomirror" C_1-symmetry **9** for the respective major and minor species noted at low temperature. They concluded that these *cis*-cyclononene conformations did not resemble Anet and Krane's[5] experimentally relevant conformations of cyclononane.[25] Earlier, Anet and Krane,[5] using molecular mechanics calculations and dynamic ^{13}C NMR spectroscopy, had estimated a dynamic equilibrium for cyclononane at −173 °C. It consisted of ~95% D_3 symmetry (333 or TBC **1**) and ~5% C_1 symmetry (225 or TCB **3**). The room temperature equilibrium was stated to consist of roughly 50% TCB (**3**), 40% TBC (**1**), and 10% C_1 symmetry (144 or TCC **2**).[5] Our work will show that *cis*-cyclononene conformers **11** and **9** are related to the same respective TCB and TCC conformational families of cyclononane **1** and **2**.

Unfortunately, there is no logical connection between the Furusaki et al.[22] two-letter symmetry-based *cis*-cyclononene descriptors and the "twist/skew"-type descriptors (TCB, TBC, TCC, TCTC, SCB, SCC, and SBB) previously used for the saturated parent structures. This paper describes the organization of the 13 lowest MM3 energy *cis*-cyclononenes listed by Saunders and Jiménez-Vázques[24] into the same seven low-energy conformational archetypal families already used for cyclononanes. Three of these families contain multiple members or subtypes. As a result of this new organization, the "twist/skew"-type cyclononane descriptors can now be applied to the corresponding seven *cis*-cyclononene families.

A search of the Cambridge Crystallographic DataBase (CCDB) was undertaken as part of our studies on benzannelated medium-size rings related to the octagonal ring nonnarcotic analgesic drug nefopam hydrochloride[26] and its nine-membered ring analogue homonefopam hydrogenfumarate.[27] The CCDB provides crystallographic examples of 10 of the 13 *cis*-cyclononene conformations. Recently, two structurally related homonefopam-like derivatives have been found whose conformationally biased solution-state and X-ray crystallographically determined solid-state structures coincide with one of the *cis*-cyclononene conformations missing in the CCDB. Their stereochemistry is also discussed herein.

Results and Discussion

Input structures were constructed having torsion angles based on the seven cyclononane conformations noted by Raber[16] and co-workers, and their geometry was first optimized using the MacMimic 3.0[7] MM3-92 molecular mechanics program. These structures then underwent ab initio geometry optimization using either RHF/6-31G* basis set[28] or DFT B3LYP/6-31G* basis set[9,10] electronic structure methods. In accord with Anet's[18] criticism of the TCTC and SCC cyclononane conformations, both RHF/6-31G* basis set and DFT B3LYP/6-31G* basis set methods also show that these two saturated conformations are not energy minima under the conditions of the electronic structure calculation. Geometry optimization of these two conformations, by either technique, led to the TCC model. Models of the two lowest cyclononane conformations (TBC and TCB) are almost the same in calculated energies, and they exchange roles as the "global minimum" in the series, according to the particular modeling method that is utilized. From RHF/6-31G* basis set studies, the relative energy ordering of the saturated conformations was found to be similar to that determined by molecular mechanics. This order is the following (kcal): TCB **1**, 0.00; TBC **3**, 0.08; TCC **2**, 1.16; TCTC **5**, unstable; SCB **4**, 3.68; SCC **6**, unstable; SBB **7**, 11.46. The energies for these models in B3LYP/6-31G* basis set studies were calculated to be the following (kcal): TBC **1**, 0.00; TCB **3**, 0.08; TCC **2**, 1.38; TCTC **5**, unstable; SCB **4**, 3.39; SCC **6**, unstable; SBB **7**, 10.51. Despite the instability of MM2 or MM3 calculated input structures for TCTC and SCC cyclononane using RHF or B3LYP geometry optimization, TCTC[29,30] and

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TABLE 2. Torsion Angles in Cyclononane 1−7 (Italics) and *cis*-Cyclononene 8−21 DFT or MM3 Calculated Models versus X-ray Crystallographically Determined Values for (1*R*)-22 and (1*R*,3*S*)-23[a]

	torsion angle								
conformation	1	2	3	4	5	6	7	8	9
TBC **1**	*−56.0*	*−56.0*	*125.3*	*−56.0*	*−56.0*	*125.3*	*−56.0*	*−56.0*	*125.3*
TBC **8**	0.0	−97.6	108.8	−44.3	−52.3	135.3	−60.8	−56.5	93.9
TCC **2**	*−64.7*	*−64.7*	*115.9*	*−70.0*	*82.5*	*−119.0*	*82.5*	*−70.0*	*115.9*
TCC **9**	−1.2	−110.8	86.5	−51.1	94.0	−129.1	80.4	−74.9	89.8
[C_s-TCC][b] **10**	−0.1	−101.7	83.4	−66.3	111.4	−111.4	66.3	−83.4	101.7
TCB **3**	*−68.3*	*−53.2*	*100.1*	*−79.4*	*100.1*	*−53.2*	*−68.3*	*65.6*	*65.6*
TCB type-1 **11**	−101.9	−4.6	80.7	−85.7	105.0	−57.3	−64.1	75.0	50.4
TCB type-2 **12**	−0.5	−101.6	80.8	−62.9	110.0	−56.7	−72.5	62.9	35.4
TCB type-3 **13**	−58.5	−62.7	103.1	−79.3	102.1	−66.2	−24.3	4.1	102.9
TCB type-4 **14**	−74.8	−6.2	0.0	6.2	74.8	−60.5	−68.5	68.5	60.5
SCB **4**	*51.7*	*68.7*	*−58.3*	*−53.1*	*126.3*	*−102.6*	*39.7*	*50.4*	*−134.4*
SCB type-1 **15**	−0.0	105.0	−46.6	−51.8	117.3	−117.3	51.8	46.6	−105.0
SCB type-2 **16**	50.2	33.6	4.0	−97.9	106.6	−88.8	47.2	54.2	−143.3
SCB type-3 **17**	50.9	64.5	−64.5	−50.9	127.0	−78.1	−0.1	78.1	−127.0
TCTC **5**	*−103.3*	*119.9*	*−88.7*	*54.6*	*−88.9*	*147.3*	*−59.3*	*−48.0*	*96.4*
TCTC **18**	−100.1	112.6	−48.2	0.1	−51.6	139.3	−56.8	−50.1	88.7
SCC **6**	*−42.7*	*−42.7*	*124.7*	*−126.2*	*84.4*	*−71.7*	*84.4*	*−126.2*	*124.7*
SCC **19**	−68.6	1.1	95.5	−133.7	82.9	−62.1	88.1	−120.0	106.7
SBB **7**	*−44.9*	*−57.0*	*6.6*	*78.5*	*6.6*	*−57.0*	*−44.9*	*60.9*	*60.9*
SBB type-1 **20**	−36.7	−68.1	16.1	72.1	−2.6	−25.3	−70.9	50.9	72.3
SBB type-2 **21**	−44.0	−67.3	20.9	75.0	−27.6	0.5	−79.9	50.7	73.3
cryst **22** (no. 1)	62.8(4)	39.2(4)	−6.1(5)	−84.4(4)	119.4(4)	−101.2(4)	42.3(5)	47.2(4)	−157.5(3)
cryst **22** (no. 2)	62.4(4)	40.5(4)	−7.4(5)	−84.1(4)	119.3(4)	−101.5(4)	43.2(5)	46.6(4)	−157.3(3)
cryst **23**	59.1(2)	43.8(3)	−6.2(3)	−86.4(3)	115.9(2)	−100.2(2)	46.6(3)	43.3(2)	−154.1(2)

[a] With the exception of SCC and TCTC cyclononane, all geometry-optimized models were calculated using the density functional theory B3LYP functional with a 6-31G* basis set. Due to the transformation of SCC and TCTC cyclononane input structures into TCC during DFT and RHF geometry optimizations, the MM3-92-calculated torsion angles for these two cyclononane models are given. [b] Both the MM3 and B3LYP geometry optimization calculations of C_s-TCC (**10**) afford one negative (imaginary) fundamental normal vibrational frequency.

SCC[31,32] ring-substituted analogues clearly do exist in the CCDB.

***cis*-Cyclononene Conformational Families.** A *cis*-cyclononene structure was constructed using the "AS1" torsion angles described by Furusaki et al.[22] and then subjected to MM3 geometry optimization. This was then used as the input structure for the stochastic conformational search program of Saunders[23a] in MacMimic 3.0[7] MM3-92 to generate 1000 structures. Thirteen (10 chiral and 3 achiral) of these were unique and below an arbitrarily set limit of 7.5 kcal in calculated energy (the next *cis*-cyclononene in the list has a very high relative energy of 29.811 kcal). To investigate conformational similarities between cyclononane and *cis*-cyclononene, each of the seven cyclononane conformations was used as a starting point to generate a *cis*-olefinic analogue. One of the cyclononane synclinal bonds was replaced by a double bond and then subjected to semiempirical AM1 energy minimization to provide input structures for final DFT[9] B3LYP/6-31G* geometry optimization. The process was then repeated starting with another synclinal bond and was terminated when all were explored. Using this technique, 12 (10 chiral and 2 achiral) unique *cis*-cyclononene conformations were found within an arbitrary window whose height was ca. 8 kcal energy above the global minimum. The relative energies of these B3LYP/6-31G* models are listed in Table 1. Bond torsion angles adjacent to the new double bond maintained their signs, while their magnitudes usually changed considerably to accommodate the neighboring new synperiplanar torsion angles. The 6 remaining torsion angles in each of the 12 *cis*-cyclononene conformations all maintained their signs and approximate magnitudes compared to corresponding values in the saturated parent structure (see Table 2). Four cyclononane conformations afforded only one *cis*-cyclononene conformation as a result of the systematic conversion, one-at-a-time, of all the synclinal bonds within the saturated parent. The same "twist/skew"-type conformational descriptors as affixed to the parent could then be readily assigned to the respective cyclononenes. However, three saturated conformations each gave rise to a "family" of unsaturated analogues in which the cis-double bond was located at different positions on a ring having the same conformation. In this case, the same "twist/skew" conformational descriptor was affixed to each member of the family. They were differentiated from one another by denoting them as "type-1", "type-2", etc. (where in the case of the TCB and SCB families, "type-1" was the lowest calculated energy family member and "type-3" was the highest one).

To determine which one of 13 MM3 stochastic search *cis*-cyclononene conformers was not part of the set of 12 generated by the synclinal single bond to synperiplanar double bond conversion method, each of the 12 conformations was subjected to MM3 energy minimization. "Twist/skew" conformational descriptors could now be assigned to all the *cis*-cyclononenes in the Saunders and Jiménez-Vázques[24] list (and these are now affixed to their literature reported values in Table 1) with the exception of a 6.714 kcal relative energy conformer exhibiting C_s symmetry (**14**). Molecular graphics inspection of this conformational model showed it to closely resemble TCB, **3**, and

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(32) Tochtermann, W.; Luttmann, K.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Tetrahedron Lett.* **1987**, *28*, 2521.

thus it was assigned a TCBtype-4 descriptor since its relative energy was higher than those of the three other unsaturated members of this family (**11**−**13**). Molecular graphics representations of the 13 *cis*-cyclononene conformers (**8**−**21**) in Figures 1−5 are oriented in the same manner as their corresponding saturated parents (**1**−**7**).

The seven cyclononane conformations are all chiral, and five of them have at least one C_2 axis. Since the number of ring atoms is odd, these axes must pass through a ring atom on one side (and between its isoclinal geminal protons) and through the midpoint of a C−C bond on the other. For the resulting cyclononenes to maintain their C_2 symmetry, the endocyclic torsion angles containing these "specially positioned" single bonds have to be capable of changing to synperiplanar values. To maintain the medium-ring conformation, endocyclic torsion angles that are the best candidates for single bond to double bond conversion are synclinal in magnitude. However, in four of the five cases, the specially positioned C_2-bisected single bonds in cyclononanes had either large orthogonal (ca. 90°) or anticlinal (ca. 120°) torsion angles (which made them extremely poor candidates for single bond to double bond conversion). In the fifth case (SCC), the synclinal torsion angle for the specially positioned C−C bond was ca. 30° larger than a 40° alternative that then yielded the double bond. Therefore, C_2-symmetry cyclononane to *cis*-cyclononene conversion resulted in a desymmetrization affording C_1-symmetry analogues.

The cyclononene TBC and TCC analogues of cyclononane (**1** and **2**) are depicted as the respective structures **8** and **9**; see Figure 1. The seven sp^3-hybridized ring atoms in each of these rings superimpose[7] nicely on corresponding atoms in TBC and TCC cyclononane with root-mean-squared (rms) positional differences of only 0.138, and 0.165 Å, respectively. Furusaki et al.[22] used the "AS2" descriptor for **8** and the "chair−chair" (CC) descriptor for **9**. A graphical comparison of TBC and TCC cyclononanes (**1** and **2**) with their respective unsaturated analogues (**8** and **9**) shows an important general constructive feature of single to double bond conversion: usually at least one H···H transannular interaction is removed when a ring carbon is changed from sp^3 to sp^2 hybridization.

While C_2-symmetry TCC (**2**) exhibits homotopic sets of torsion angles (all torsion angle signs and magnitudes in half of the ring are identical to those of corresponding angles in the other half), its olefinic analogue, C_1-symmetry TCC (**9**), has a plane of pseudomirror symmetry. Noe and co-workers[25] have described a C_s-symmetry structure (**10**) in terms of torsion angles, as well as MM3 and RHF/6-311G* relative energies. A geometry optimization of this conformation was recalculated with MM3 and then by B3LYP/6-31G*. Inspection of the set of B3LYP/6-31G*-calculated torsion angles in Table 2 shows **10** to have a close structural relationship with TCC cyclononane **2** and cyclononene **9**. The seven sp^3-hybridized ring atoms in **10** superimpose on corresponding atoms in **2** and **9** with rms positional differences of 0.267 and 0.174 Å, respectively. A "C_s-TCC" descriptor can thus be assigned to **10**. Although the C_s-symmetry input geometry was stable in MM3 and B3LYP/6-31G* calculations, both cases afforded one negative (imaginary) fundamental normal vibrational frequency. Therefore, while **10** cannot be a bona fide conformation, it does closely resemble a low-energy putative transition state for the enantiomerization of **9**, and thus might have relevance to the *cis*-cyclononene low-temperature NMR studies reported by Noe[25] and co-workers. On the basis of relative energies and symmetry, conformations now known as TCBtype-1 (**11**) and TCC (**9**) were suggested by the authors to be candidates for the respective *cis*-cyclononene major and minor species at −189.3 °C. Since it is noted that Anet and Krane[5] report a room-temperature equilibrium involving cyclononane TCB (**3**), TBC (**1**), and TCC (**2**) conformations, it does seem that there is a connection between experimentally relevant conformations for both the saturated and cis-unsaturated nine-membered rings.

In the set of 13 bona fide cyclononene conformations listed in Table 1 (**8**, **9**, **11**−**21**), the MM2, MM3, RHF/6-31G*, or B3LYP/6-31G* global minimum conformation was the same [the first member of a series of four diastereomeric cyclononenes derived from the saturated twist-chair−boat (TCB, **3**) conformation]; see Figure 2. The members of this TCB family are designated as TCBtypes 1−4 (**11**−**14**) and have been arranged in terms of increasing calculated energies; i.e., the above-noted global minimum was given the TCBtype-1 descriptor. The saturated TCB conformation depicted in **3** has three synclinal magnitude homotopic sets of torsion angles: −53°; 66°; −68°. The "type-1" cyclononene has a synperiplanar torsion angle replacing the smallest synclinal angle in the saturated molecule. The synperiplanar torsion angle in the "type-2" species replaces the largest value synclinal angle, while that in the "type-3" species is in place of the middle value angle. Inspection of TCB **3** shows black colored protons that suffer transannular H···H interactions. One of these interactions has been removed in each one of the corresponding unsaturated TCB structures. The seven sp^3-hybridized ring atoms in each of these rings superimpose very well on corresponding atoms in TCB cyclononane with rms positional differences of only 0.095, 0.151, 0.049, and 0.052 Å, respectively. Comparison of the torsion angles in the earlier study of Furusaki et al.[22] show that their "AS1", "AS4", and "AS7" described conformations are equivalent to TCBtypes 1−3 (**11**−**13**), respectively. Table 2 shows that the olefinic bond of C_s-symmetry 6.714 kcal Saunders and Jiménez-Vázques[24] *cis*-cyclononene (**14**) corresponds to an anticlinal 100° bond in the TCB cyclononane (**3**) model. Conversion of this single bond to a cis double bond did not produce an MM2 geometry optimized structure in the TCB family. Thus, TCBtype-4 (**14**) could only be found via the stochastic search method.

Only one of the cyclononanes, the C_1-symmetry skew-chair−boat SCB (**4**), exhibits a plane of pseudoreflection symmetry (there actually are two pseudoplanes in this model). Due to the odd number of ring atoms, each plane goes through a ring atom on one side and bisects a C−C bond on the other. When either of the two specially positioned single bonds becomes a double bond, the resulting plane is now transformed into a bona fide σ-plane. SCB cyclononane (**4**) contains six different synclinal torsion angles, but only three of them can be converted, one-at-a-time, to synperiplanar values while keeping the SCB conformation invariant. These three diastereomeric structures constitute an additional cyclononene multimember conformational family (SCB structures **15**−**17**); see Figure 3. Conversion of any of the other SCB cyclononane synclinal angles affords a change in the conformational family. The double bond in the lowest energy member in the SCB family, designated SCBtype-1 **15** (C_s symmetry), arises from the second smallest synclinal angle in the series of six. Conversion of the second largest angle gives the second highest energy member, SCBtype-2 **16**. Finally, conversion of the smallest value synclinal angle into a synperiplanar one forms the last and highest energy member of the family, SCBtype-3 **17** (C_s symmetry). The SCBtype-1 (**15**) and SCBtype-3 models (**17**) are two of the three achiral examples among the 13 *cis*-cyclononene conformations. In all three SCB subtypes, some of the transannular H···H interactions are removed when SCB cyclononane single bonds are converted into double bonds. The seven sp^3-hybridized ring atoms in each of these rings superimpose very well on corresponding atoms in **4** with rms positional differences of only 0.138, 0.154, and 0.097 Å, respectively. Both Favini et al.[21a] and Furusaki et al.[22] used a "chair−boat" descriptor for SCBtype-3 **17**.

While the TCTC and C_2-symmetry SCC cyclononane MM2 input structures (**5** and **6**) are unstable in RHF and B3LYP geometry optimizations, their corresponding cyclononene analogue models (**18** and **19**; see Figure 4) can be readily calculated by these same methods. The seven sp^3-hybridized ring atoms in each of these rings superimpose very well on corresponding atoms in **5** and **6** with rms positional differences of only 0.115, and 0.079 Å, respectively. Furusaki et al.[22] assigned the "AS5" descriptor to TCTC **18**. In the 13 cyclononene conformations in this study, it is unique that the double bond in TCTC **18** does not remove a transannular interaction present in the saturated analogue (**5**).

The skew-boat−boat (SBB) is the third unsaturated conformational family with multiple members; see Figure 5. Noe and co-workers[25] reported the RHF/6-311G*-calculated relative free energies at −189.3 °C for six *cis*-cyclononene structures, but those for the SBB family were not included. For comparison, RHF/6-31G* relative energies are listed in Table 1 for these 6, as well as for the remaining conformations in the set of 13 under discussion. Of the 13 calculated *cis*-cyclononene conformational models, the two SBB members exhibit high relative energies [although their internal ordering within the SBB family is dependent on the particular computational electronic structure modeling method (RHF or DFT) used]. SBB cyclononenes **20** and **21** are respectively 6.93 and 7.84 kcal higher than TCBtype-1 (**8**) by RHF/6-31G*, while the order is reversed when calculated by the B3LYP/6-31G* method (respectively 7.32 and 6.36 kcal higher than **8**). As a result, the "type-1" descriptor cannot be unequivocally assigned to the "lowest" calculated energy model in the family, and thus the "types 1−2" descriptors were arbitrary assigned. The seven sp^3-hybridized ring atoms in each of these rings superimpose nicely on corresponding atoms in C_2-symmetry SBB cyclononane **7** with rms positional differences of only 0.141 and 0.079 Å, respectively. Furusaki et al.[22] used a "boat−boat" (BB) descriptor for SBBtype-2 **21**.

Conformational descriptors help provide a useful reference frame for stereochemical investigations. The existence of multiple conformations prompts a discussion of their relative energies. Energy ranking of some of the *cis*-cyclononene conformations is dependent upon the particular molecular modeling method used for their calculation (see Table 1). However, perusal of the results in this table shows a number of general trends irrespective of the particular calculation method used. The energy window of the 13 conformations is between 6.5 and 8.0 kcal from the global minimum, and the TCBtype-1 **11** conformation is the global minimum by DFT, RHF, and molecular mechanics methods. In addition, the TCC **9** and TBC **8** conformations are within a range of ca. 1.3 kcal from the global minimum by all methods, and the SCBtype-1 **15**, TCBtype-2 **12**, and TCBtype-3 **13** conformations are within the range of 0.2−2.4 kcal from the global minimum. Finally, the highest energy conformations in the series are SBBtype-1 **20**, SBBtype-2 **21**, and TCTC **18**. Therefore, in general, the *cis*-cyclononene twist-chair−boat (types 1−3), twist-chair−chair, and twist-boat−chair conformations are estimated to be relatively low in energy, skew-chair−boat and skew-chair−chair are intermediate in energy, and skew-boat−boat and twist-chair-twist-chair conformations are high in energy.

May "twist/skew" conformational descriptors be assigned to nine-membered rings more complicated than the parent *cis*-cyclononene? The answer is very positive. A search of the CCDB was undertaken for nine-membered rings containing one synperiplanar torsion constraint, and "twist/skew" conformational descriptors were then applied to the molecules answering the structural query. With this having been accomplished, it follows that one would inquire into the conformational distribution of these molecules. However, care must be taken since packing considerations, interactions/constraints by substituents, and/or ring heteroatoms can all play important roles in influencing which conformation is present in the crystalline state. Also, the well-known phenomena of "conformational polymorphism" or "conformational pseudopolymorphism" (e.g. anhydrates versus hydrates) strongly suggests that unraveling crystalline-state conformational preference is sometimes a very complicated undertaking. Furthermore, synperiplanar torsion angles not only arise from *cis*-olefins but also from diverse structural entities such as oxiranes, aziridines, lactams, benzannelated rings, etc. Nevertheless, *with the proviso that there is a statistically significant number of examples*, it is reasonable to expect that those *cis*-cyclononene lower energy conformational archetypes, among the 13 noted above, will also be prevalent in the set of CCDB entries. If based on proper statistical sampling, this expectation should be sound despite the high probability that database molecular structures are considerably more intricate than the relatively simple skeleton of the parent molecule. With the hope that the ca. 140 CCDB examples represent a statistically meaningful quantity, one finds that about three-quarters of them fall into only 5 of the 13 conformational types: TBC (23%);[33] TCC (19%);[34] TCBtype-1 (18%);[35] SCBtype-1

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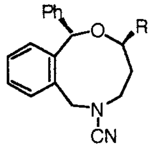
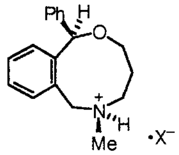
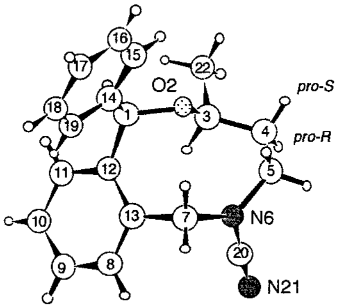
(12%)[36] (a representative CCDB example is cited for each conformational type). The remaining conformations are present in lower amounts: SCC (9%);[37] TCBtype-2 (6%);[38] SCBtype-3 (5%);[39] TCBtype-3 (3%);[26] TCTC (3%);[40] SBBtype-1 (ca. <1%).[41] Furthermore, while C_s-symmetry TCC (**10**) is not a conformational possibility for simple *cis*-cyclononene (at least according to the MM3 and B3LYP vibrational frequency calculations), it too can be found in the CCDB, given the appropriate substituents and ring heteroatoms.[42]



22 R = H
23 R = Me



24 X⁻ = Cl⁻ or bifumarate



23

SCBtype-2 Conformation in the Solid State. To the best of our knowledge, there are no examples of the SCBtype-2 conformation for *cis*-cyclononene-type analogues to be found in the CCDB. Using single-crystal X-ray diffraction analysis and NMR spectroscopy, we now report that the nine-membered rings of the "homonefopam"-type (±)-1-phenyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (**22**) and its (1*RS*,3*SR*)-3-methyl analogue (**23**) are folded into SCBtype-2 conformations in both the crystalline and solution ($CDCl_3$) states.[43] Two symmetry-unrelated molecules of **22** have been found in the asymmetric unit of the crystal. They both exhibit the same conformation as seen by the extremely small 0.017 Å rms difference for superimposition of corresponding CN, C_{ipso}, and the non-hydrogen nine-membered ring atoms. Superimposition of these same atoms in **23** on corresponding ones in molecules 1 and 2 of **22** affords small rms differences of only 0.047 and 0.044 Å, respectively.

Other analogues of this ring system afford different conformations; e.g. the (1*RS*,6*RS*)-1-phenyl-6-methyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine (**24**) moiety in both the hydrogen fumarate salt (crystalline solid state) and in the hydrochloride salt (CD_2Cl_2 solution) exists in what is now called the "TCBtype-3" conformation.[27] Two related crystalline state structures with 2,5-benzoxazonine ring skeletons and a substituted benzothieno analogue are known. These fold into what can now be described as "SCBtype-3",[39] "TCBtype-2",[39] and "TCBtype-3"[44] conformations.

Atom numbering for stereochemical and NMR discussion is shown in the X-ray crystallographically determined ball and stick structure **23**. The crystallographically determined endocyclic torsion angles 1−9 listed for (1*R*)-**22** (molecules 1 and 2) and (1*R*,3*S*)-**23** are in very good agreement with those measured in the B3LYP/6-31G* model of SCBtype-2 *cis*-cyclononene (**16**); see comparison in Table 2. Superimposition of the nine-membered ring atoms in crystalline **22** (molecules 1 and 2) and **23** upon corresponding atoms in the relevant B3LYP model affords small RMS positional differences of only 0.055, 0.053, and 0.035 Å, respectively. Thus, B3LYP/6-31G* models of **22** and **23** provide accurate geometries for the three crystalline structures. Two cyclononene SCBtype-2 transannular H···H interactions [a very close 2.06 Å H(2endo)···H(7endo) and a slightly longer 2.56 Å H(3endo)···H(6endo) distance in B3LYP model **16**] are eliminated in **22** and **23** by replacement of methylene carbons with nonprotonated atoms, i.e. oxygen and sp^2-hybridized nitrogen. The 2.89(2) Å O(2)···C(7) and 2.87(4) Å C(3)···N(6) transannular distances in crystalline **22** and **23** are slightly shorter (but not statistically different) than corresponding 2.93(2) and 2.97(4) Å values in B3LYP models of **22** and **23**. On the other hand, both the crystallographically and B3LYP determined distances are considerably shorter than the corresponding 3.24 and 3.15 Å values in the B3LYP model of carbocyclic **16**, which suffers from transannular H···H interactions as noted above. Another rationalization for the shorter transannular distances in **22** and **23** involves a possible interaction between O(2) and the N(6) positive end of the strong dipole in N(6)−C(20)≡N(21). This is seen by a 2.98(2) Å O···N distance in crystalline **22** and **23** [3.05(1) Å in B3LYP models **22** and **23**] versus a correspondingly larger 3.58 Å C(2)···C(6) distance in B3LYP model **16**. In all three crystallographically determined structures, the cyano group lies in the plane defined by atoms C(5)−N(6)−C(7) [≤0.1 Å distance of C(20) to the plane]. The phenyl group is approximately orthogonal to the C(1)−H(1) bond in **22** (molecules 1 and 2) and **23** [92, 87, and 76° H(1)−C(1)−C(14)−C(15) dihedral angles, respectively]. Since the phenyl ring is ligated to a Dale-type "corner"[2] atom, neither the phenyl nor the neighboring benzhydrylic proton point toward the ring interior. According to Anet's[45] general definition for the assignment

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TABLE 3. Aliphatic ^1H and ^{13}C NMR Spectral Parameters for (±)-1-Phenyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (22) and (1*RS*,3*SR*)-1-Phenyl-3-methyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (23)[a]

	δ[b]			J_{HH}[d]	
	22	**23**[c]		**22**	**23**
H(1)	5.69	5.69	3ax−CH_3		6.0
H(3ax)	3.45	3.53	3ax−3eq	−10.1	
H(3eq)	3.89		3ax−4proR	4.6	4.2
H(4proR)[e]	1.86	1.83	3ax−4proS	11.3	10.5
H(4proS)[e]	1.98	1.63	3eq−4proR	2.2	
H(5ax)	3.36_7	3.27_8	3eq−4proS	5.9	
H(5eq)	3.48_1	3.28_4	4proR−4proS	−14.6	−14.5
H(7endo)	4.35	4.23	4proR−5ax	11.2	12.9(1)
H(7exo)	4.20	4.08	4proR−5eq	5.4	3.4(1)
CH_3		1.21	4proS−5ax	4.1	4.0
C(1)	83.33	81.01 (79.39)	4proS−5eq	2.9	3.2
C(3)	63.97	69.08 (68.45)	5ax−5eq	−14.6	−14.6
C(4)	27.62	35.45 (34.93)	7endo−7exo	−13.4	−13.3
C(5)	51.42	50.60 (49.88)			
C(7)	55.78	55.54 (55.88)			
CH_3		18.69 (17.37)			
CN	117.83	117.92 (117.56)			

[a] ^1H and ^{13}C ($CDCl_3$) 500.1 and 125.76 MHz, respectively. [b] ppm from tetramethylsilane. [c] Solid-state CPMAS ^{13}C δ values are given in parentheses. [d] Hz; esd = 0.01 Hz or that of last digit given in parentheses. ^1H δ and J_{HH} values in the C(3)−C(5) fragment were iteratively[46] determined by spectral simmulation. [e] Isoclinal diastereotopic methylene proton in the (1*R*)-enantiomer of **22** or in the (1*R*,3*S*)-enantiomer of **23**.

of axial and equatorial descriptors to substituents of rings of any size, the phenyl can be given an equatorial descriptor "only in the most general sense" since it is almost isoclinal. On the other hand, the 3-methyl group in **23** is definitely equatorial by the same definition and resides in a sterically nondemanding environment.

SCBtype-2 Conformation in $CDCl_3$ Solution. The aliphatic ^1H and ^{13}C NMR ($CDCl_3$) spectral parameters of **22** and **23** are listed in Table 3. Due to the second-order nature of the geminal proton pair at C(5), ^1H NMR spectral parameters in the C(3)−C(5) fragment were iteratively determined by spectral simulation calculations.[46] Antiperiplanar-type (ca. 180°) large 11.2, 11.2 Hz (for **22**) and 10.5, 12.9 Hz (for **23**) $^3J_{HH}$ coupling constants were measured for sets of vicinal protons in the respective C(3)−C(4) and C(4)−C(5) bonds. These large magnitude values testify to a low degree of weighted time-averaging and, hence, to a conformational bias for **22** and **23** when dissolved in $CDCl_3$ solution. The observation that each of these large coupling constants involves a different C(4) geminal proton limits the number of relatively low-energy conformational candidates to two (SCBtype-2 and TCBtype-1). NOE intensity enhancements are consistent with only the SCBtype-2 geometry as the preferred conformation: a 1.4% NOE for δ 5.69 H(1) upon {δ 3.45, H(3ax) for **22**} and a 1.3% NOE for δ 3.45 H(3ax) upon {δ 5.69 H(1) for **22**}. This is in accord with a 2.62 Å H(1)···H(3ax) distance in crystalline **22**. Furthermore, a 1.8% NOE for δ 4.35 H(7endo) upon {δ 3.36 H(5ax) for **22**} is commensurate with a 2.26 Å H(5ax)···H(7endo) distance in crystalline **22**. In addition, a 0.9% NOE for δ 3.53 H(3ax) upon {δ 5.69 H(1) for **23**} befits a 2.69 Å H(1)···H(3ax) distance in crystalline **23**. Both H(1) and H(3ax) [and similarly, both H(5ax) and H(7endo)] are located on the same side of the ring in SCBtype-2 crystalline **22** and **23** while they are to be found on opposite sides of the ring in the TCBtype-1 model. The antiperiplanar and synclinal magnitude vicinal coupling constants in the C(3)−C(5) fragment are also consistent with all the corresponding dihedral angles in the three crystal structures. While protons ligated to SCBtype-2 C(3) and C(5) can readily be assigned axial and equatorial descriptors using Anet's[45] general definition, those on the "corner" C(4) are isoclinal and have to be affixed *pro-R* and *pro-S* descriptors according to the particular enantiomer in question.

The solid-state aliphatic ^{13}C NMR chemical shifts measured for SCBtype-2 crystalline **23** (see Table 3) are very similar to corresponding values in the $CDCl_3$ spectrum. A comparison of the two lists of seven values affords an rms difference of only 0.91 ppm. This close agreement is in accord with the ^1H NMR studies showing that the SCBtype-2 stereochemistry of crystalline **23** is maintained in solution.

Conclusion

Thirteen *cis*-cyclononene conformational models have been characterized in terms of the seven families known for cyclononane. As a result, the same "twist"/"skew" conformational descriptors previously used for the saturated conformers can now also be applied to the corresponding unsaturated analogues. Three conformational families have multiple members where the double bond is to be found at different positions on the same ring conformation. In the skew-chair−boat family, the SCBtype-2 conformational subtype exemplified by crystalline **22** and **23** has yet to be found in the Cambridge Crystallographic Data Base. The reason for this particular conformational choice remains unclear at this time, although it might involve attractive O···N electrostatic forces and removal of unfavorable H···H transannular interactions as noted above. The observation of two symmetry-unrelated SCBtype-2 molecules in the asymmetric unit of **22** and an SCBtype-2 structure for the

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(1*RS*,3*SR*)-C(3)-equatorial methyl analogue **23** strongly suggests that lattice packing considerations alone cannot explain the observation of this conformation in these crystals. This is further strengthened by the ^{1}H NMR spectroscopic observation of the same SCBtype-2 conformational bias when these crystalline compounds are dissolved in $CDCl_3$.

Experimental Section

(±)-1-Phenyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (**22**), mp 121−122 °C, was prepared according to the method of Bremner and Thirasasana (lit.[47] mp 121−122 °C). Using the same technique and the corresponding (±)-4-aminobutan-2-ol (Acros Chemical Co.) as starting material, (1*RS*,3*SR*)-1-phenyl-3-methyl-1,3,4,5,6,7-hexahydro-2,6-benzoxazonine-6-carbonitrile (**23**) was obtained as a mixture of (1*RS*,3*RS*)- and (1*RS*,3*SR*)-diastereomers in a 7:2 ratio, respectively. The diastereomers were separated on a silica gel column eluted with a 0 → 3% gradient of MeOH in $CHCl_3$ to yield the (1*RS*,3*SR*)-diastereomer (**23**) as the first fraction, mp 176−177 °C.

Molecular Modeling and Graphics. Density functional theory B3LYP/6-31G(d) geometry optimized models **1**−**4** and **7**−**23** were produced with the Gaussian-98W revision A-7 program,[10] and all (with the exception of **10**) were found to have only positive values for vibrational frequencies. The MacSpartan Plus 1.2.1[28] program was used to perform ab initio restricted Hartree−Fock (RHF) geometry optimizations using a 6-31G* basis set. MM3 calculations and superimposition of molecular structures were performed with the MacMimic 3.0 program.[7] Ball and stick type noniconic molecular graphics were drawn with the Ball&Stick 3.8 program.[11] 2D-iconic projections of the molecular models and X-ray crystallographic 3D-structures were generated using a combination of the CSChem3D Pro 5.0 and CSChemDraw Ultra 5.0 programs.[8a,b]

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectroscopy were recorded at 500.13 and 125.76 MHz, respectively, at ambient temperature on a Bruker DMX-500 NMR spectrometer. Samples were measured in $CDCl_3$ using the deuterium solvent as an internal lock and tetramethylsilane (TMS) as the internal spectral reference. DEPT (90 and 135° pulse angles) were used to ascertain the hydrogen multiplicity of the ^{13}C signals. HMQC 2D-NMR spectroscopy was used to correlate the ^{13}C and ^{1}H chemical shifts. NOE experiments were performed using the NOE-difference technique. Solid-state CPMAS ^{13}C NMR spectra were measured with a Bruker solid-state accessory using the SELTICS pulseprogram, a 5.0 kHz spin rate, and a 30 s relaxation delay. ^{1}H spectral simulation was performed using the Gnmr 4.1 program.[46]

Crystallography. Crystallographic measurements were made on a Enraf-Nonius CAD-4 automatic diffractometer with graphite-monochromated Cu Kα (λ = 1.541 78 Å) radiation. Data crystals were mounted on glass fibers and fixed on a goniometer head on the X-ray diffractometer. The CAD4PC programs[48] were used for centering, indexing, and data collection. The unit cell dimensions were obtained by a least-squares fit of 14 carefully centered reflections in the range of $10.0° \leq \theta \leq 20.0°$. Data were collected at 293(2) K using the $\omega/2\theta$ scan technique. Scans were made with a scan speed of 4° min^{-1} and a background time/scan time ratio of 0.25. Space group determination was based upon systematic absences, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. During data collection, the intensities of two standard reflections were monitored every 100 reflections. No significant decay was observed. Since the maximum and minimum transmission factors were both 1 for either crystal, an empirical absorption correction was not made.

The structures were solved by the application of direct methods and refined by full-matrix least squares on F^2 using the SHELX97 program.[49] Atomic scattering factors stored in the SHELX97 program were those of ref 50. Hydrogens were all placed at calculated positions and refined as riding atoms on their respective attached atom, while non-hydrogen atoms were refined anisotropically.

X-ray Crystallography of 22. Crystallization was performed by vapor diffusion of *n*-hexane into an ethyl acetate solution of **22**. A clear, colorless plate crystal of $C_{18}H_{18}N_2O$ having approximate dimensions 0.35 × 0.20 × 0.15 mm was chosen. Data were collected to a maximum θ value of 65.23° (94.3% completeness to θ). Cell constants corresponded to a triclinic system $P\bar{1}$ cell with dimensions at 293(2) K of a = 8.9104(10) Å, b = 10.4110(12) Å, c = 16.199(2) Å, α = 90.640(4)°, β = 90.640(4)°, γ = 91.266(5)°, and V = 1483.5(3) Å^3. For Z = 4 and fw = 278.34, the calculated density is 1.246 g cm^{-3} and is in accord with two symmetry-unrelated molecules in the asymmetric unit.

An isotropic extinction coefficient was included in the refinement[51] to account for secondary extinction effects;[52] its value was 0.0078(13) μm. At convergence, the final discrepancy indices on F were $R(F) = 0.0772$, $R_w(F^2) = 0.2148$, and GOF = 1.09 for the 3355 reflections with $I_{net} = 2\sigma(I_{net})$ and 380 parameters refined with 0 restraints and 0 constraints.

X-ray Crystallography of 23. Crystallization was performed by vapor diffusion of acetone and then ether into an absolute ethanolic solution of **23**. A clear, colorless needle crystal of $C_{19}H_{20}N_2O$ having approximate dimensions 0.30 × 0.07 × 0.07 mm was chosen. Data were collected to a maximum θ value of 64.85° (99.8% completeness to θ). Cell constants corresponded to a monoclinic system $P2_1/a$ cell with dimensions at 293(2) K of a = 8.666(5) Å, b = 17.2867(4) Å, c = 10.5471(7) Å, β = 96.97(2)°, and V = 1568.4(9) Å^3. For Z = 4 and fw = 292.37, the calculated density is 1.238 g cm^{-3}.

An isotropic extinction coefficient was included in the refinement[51] to account for secondary extinction effects;[52] its value was 0.0010(4) μm. At convergence, the final discrepancy indices on F were $R(F) = 0.0486$, $R_w(F^2) = 0.1111$, and GOF = 1.009 for the 1758 reflections with $I_{net} = 2\sigma(I_{net})$ and 200 parameters refined with 0 restraints and 0 constraints.

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Supporting Information Available: Tables S1−S31, listing crystallographic details, fractional coordinates for non-hydrogen and hydrogen atoms, interatomic bond distances and bond angles, torsion angles, and anisotropic thermal parameters of **22** and **23** and total energy and Cartesian coordinates for density functional theory B3LYP/6-31G(d) geometry optimized models of **1**−**4** and **7**−**23** and for MM3 geometry optimized models of **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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