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Medium-sized rings: conformational preferences in cyclooctanone driven by transannular repulsive interactions

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The conformational properties of medium-sized rings are of relevance to understand their intramolecular interactions and reactivity. Here we have characterised the conformational landscape of the eight-membered ketone cyclooctanone by broadband rotational spectroscopy in combination with quantum-chemistry calculations. Three conformers, two boat-chair and one twisted boat chair configurations, have been identified and their spectroscopic parameters determined. Cyclooctanone predominantly exists in the global minimum boat-chair conformation, whose bond lengths and angles have been determined for the first time. The relative abundance of the global minimun with respect to the second conformer in the energy ordering, a twisted boat-chair, is 40:1 in all carrier gases used in the supersonic expansion. The conformational preferences of cyclooctanone are driven by minimization of repulsive non-bonded transannular interactions.

Introduction

Characterisation of the conformations and structural features of cyclic alkanes and their derivatives has attracted a great deal of attention over the years, as a testing ground for theories on chemical bond, intramolecular forces and reactivity. Molecular conformation is determined by the balance of intramolecular forces, which in cycloalkanes include angular strain, torsional strain and non-bonded transannular interactions. The structural properties of small rings have been extensively studied.[1–6] Large amplitude motions such as ring-puckering and pseudorotation have been thoroughly characterised in four- and five-membered rings, including cycloalkanes, cycloalkanones and their substituted heterocyles.[7–14] These investigations showed that angular strain is dominant, and provided information on how replacement of a methylene group by a heteroatom or a carbonyl group in the ring affects conformation and the balance of intramolecular interactions. Six-membered cycloalkanes and their derivatives were found to prefer a chair conformation with very low levels of ring strain,[6,15–19] while seven-membered rings suffer some ring strain and undergo pseudorotation.[20,21]

Fewer structural investigations have been reported on medium-sized eight- to twelve-membered cycloalkanes and their derivatives, including cycloalkanones. Conformational analysis of these larger cycles is more complicated as flexibility increases with ring size. Torsional strain and non-bonded transannular interactions are expected to be more important in determining ring conformation.[22] Several studies of medium-sized rings were conducted using X-ray crystallography,[23,24] NMR spectroscopy[25–28] and electron diffraction,[17,20] mostly during the 70s and 80s. These techniques provide very valuable structural information, but they have limitations to characterise multi-conformational systems. An alternative is the use of microwave spectroscopy, which due to its high resolution has the advantage of being able to distinguish without ambiguity between different conformations simultaneously present in the sample.

In this work we report the investigation of the eight-membered ketone cyclooctanone using broadband rotational spectroscopy[29] in combination with quantum-chemistry calculations. Cyclooctanone is used as a precursor in the synthesis of more complex cyclic compounds, such as amber-[30] and violet-smelling odorants[31], and 14-membered cyclic lactones[32], and it is a structural motif present in natural compounds belonging to the terpenoid and lignin classes.[33–35] The conformational landscape of cyclooctanone has been the subject of some computational studies[36–38], which predict several conformers within 10 kJ/mol. Previous experimental NMR data and vibrational and rotational spectroscopic studies[39] were consistent with the presence of one conformation of cyclooctanone in a boat-chair configuration. However, the rotational study was conducted at low resolution, and the rotational constants were estimated to large uncertainties, of up to 100 MHz.

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Electronic Supplementary Information (ESI) available: predicted spectroscopic parameters at different levels of theory, measured frequencies, experimental spectroscopic parameters of the isotopic species and substitution coordinates. See DOI: 10.1039/x0xx00000x

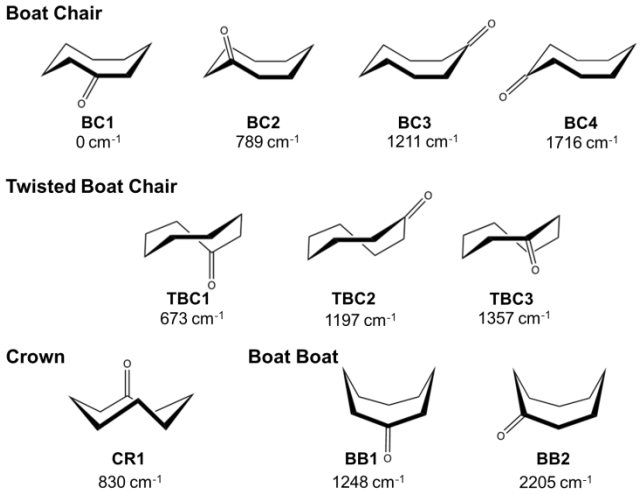

Figure 1. Conformers of cyclooctanone predicted at MP2/6-311++G(d,p)+ZPC level of theory.

Our conformational analysis of cyclooctanone aimed to establish whether one or more conformations coexist, and to get an insight on the intramolecular forces dictating conformational preferences. Are they different from those playing a key role in smaller rings? We have identified three conformers of cyclooctanone showing boat-chair and twisted boat-chair configurations. The structure of the lowest-energy boat-chair conformation has been determined and compared with those reported for cyclooctane and smaller cycloalkanones. The driving force for the preferred conformations of cyclooctanone is to minimise non-bonded repulsive interactions across the ring; the conformational energy ordering is inversely proportional to the extent of these interactions.

Results and Discussion

Conformational landscape of cyclooctanone

Our investigation of the conformational landscape of cyclooctanone, carried out at different levels of theory and using a larger basis set than previous investigations (see details in the Experimental Section), yielded 10 distinct conformers within 50 kJ/mol, which are grouped in four classes according to the configuration of the ring (see Fig. 1): boat-chair (BC), twisted boat-chair (TBC), crown (CR), and boat-boat (BB). This set of conformers and their energy ordering are different from those reported in earlier theoretical studies. The global minimum is predicted to be the same, the boat chair conformation BC1 in our nomenclature (Fig. 1). However, the second conformer in energy is predicted as a twisted boat chair conformer (TBC1), followed by a boat chair conformer (BC2) and a distorted crown conformer (CR1). At all the levels of theory used in this work the boat-chair conformers previously labelled 2[36] or CB-2[38] converged to the twisted boat-chair conformer TBC1, and the formerly reported crown conformation converged to the distorted crown CR1. Our computational results yielded an additional boat-boat conformation BB2, which is the highest in energy. Rotational constants, dipole moments and relative energies of all predicted conformers are collected in Table 1 and Tables S1-S2, and their Cartesian coordinates from MP2/3-611++G(d,p) are included in Tables S3-S12.

Rotational Spectrum

The broadband rotational spectrum of cyclooctanone was collected in the 2-8 GHz region (Fig. 2). It is very intense and on first inspection it does not seem to contain a lot of transitions. The most intense lines were quickly identified as *a*- and *c*-type $J+1 \leftarrow J$ transitions corresponding to the BC1 conformation of cyclooctanone (Fig. 1), predicted to be the global minimum, and observed in a previous microwave study.[39] A total of 69 transitions (collected in Table S13) were fit to the Watson Hamiltonian in the A reduction and III^{l} representation[40] using Pickett's SPFIT/SPCAT programs[41]. They yielded the rotational and centrifugal distortion constants of Table 2, which improve the former estimated values by several orders of magnitude.

Table 1. *Ab initio*[a] spectroscopic parameters for conformers of cyclooctanone.

Parameter	BC1	TBC1	BC2	CR1	BC3	TBC2	BB1	TBC3	BC4	BB2
A[b] (MHz)	1912	1991	2032	1919	1915	2114	1946	2007	2264	2175
B (MHz)	1692	1641	1648	1731	1679	1538	1627	1695	1450	1515
C (MHz)	1175	1100	1124	1128	1233	1118	1243	1118	1017	1126
μ_a (D)	-2.0	2.4	2.4	0.6	1.2	2.0	-2.2	1.9	-3.1	2.9
μ_b (D)	-0.1	0.2	-0.5	-0.6	0.0	-0.5	-0.3	-1.0	0.0	-0.8
μ_c (D)	2.1	-1.7	-1.6	2.1	2.5	2.1	2.1	-1.7	-0.8	-0.9
ΔE_{MP2}[c] (cm^{-1})	0	737	724	878	1196	1198	1261	1286	1684	2151
ΔE_{MP2}+ZPC[d] (cm^{-1})	0	673	789	830	1212	1198	1248	1357	1716	2205
ΔG^{347}[e] (cm^{-1})	0	494	753	716	1074	1115	1101	1341	1606	2132

[a] MP2/6-311++G(d,p); [b] A, B, C are the rotational constants; μ_a, μ_b and μ_c are the electric dipole moment components with signs corresponding to the structures provided in the ESI; [c] Relative electronic energies; [d] Relative electronic energies including the zero-point correction; [e] Gibbs free energies at 347 K.

Since the rotational transitions of BC1 were very intense,

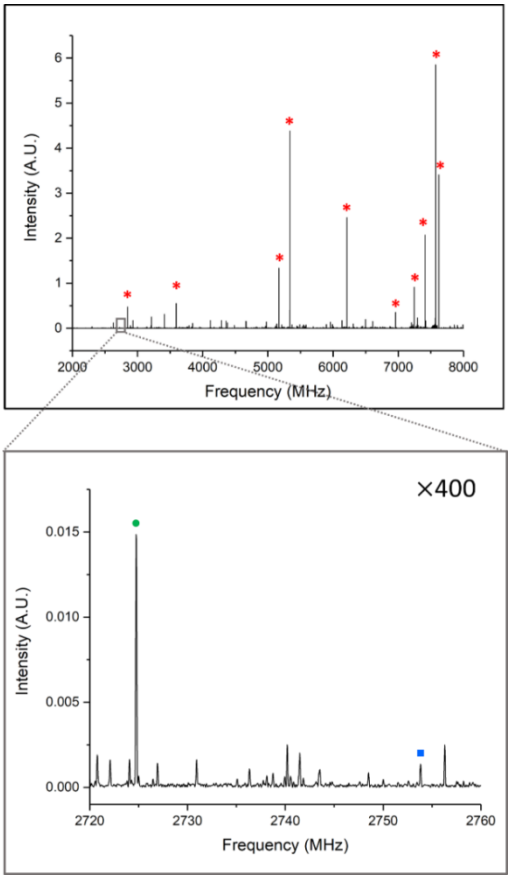

Figure 2. 2-8 GHz spectrum of cyclooctanone in neon. The red stars indicate the rotational transitions of conformer BC1. The enlarged region 2720-2760 MHz shows the 1_{01}←0_{00} rotational transition of TBC1 (green circle) and BC2 (blue square).

Table 2. Experimental spectroscopic parameters of the three observed conformers of cyclooctanone.

Parameter	BC1[f]	TBC1	BC2
A[a] (MHz)	1909.57246(33)[g]	1984.4524(10)	2026.75087(52)
B (MHz)	1683.01292(32)	1632.66619(89)	1638.36289(48)
C (MHz)	1162.36489(30)	1092.10687(92)	1115.46660(42)
κ[b]	0.4	0.2	0.1
Δ_J (kHz)	0.3269(95)	1.246(61)	0.110(28)
Δ_{JK} (kHz)	-0.6958(45)	-3.820(38)	-
Δ_K (kHz)	0.5212(51)	2.908(28)	-
δ_J (kHz)	0.01984(77)	-0.0563(76)	
δ_K (kHz)	0.7584(57)	3.926(50)	-
a/*b*/*c*[c]	y/y/y	y/n/y	y/n/y
σ[d] (kHz)	4.0	5.7	2.0
N[e]	69	37	13

[a] A, B and C are the rotational constants. Δ_J, Δ_{JK}, Δ_K, δ_J and δ_K are the centrifugal distortion constants; [b] Ray's asymmetry parameter; [c] *a*, *b* and *c* are the type of transitions observed; [d] σ is the rms deviation of the fit; [e] N is the number of the fitted transitions; [f] Rotational constants of BC1 from ref. [39] are A = 1910(5) MHz, B = 1680(30) MHz, and C = 1100(100) MHz [g] Standard error in parentheses in units of the last digit.

transitions arising from its ^{13}C and ^{18}O isotopologues in natural abundance (*ca.* 1.1% and 0.2%, respectively), were searched for and observed at the expected frequency shifts from the parent species. The measured transitions (Tables S14-S22) were fit to the same Hamiltonian[40] as the parent species and the determined rotational constants are shown in Table S23.

Once transitions from BC1 cyclooctanone were removed from the spectrum, further inspection led to the assignment of two other conformers of cyclooctanone, and determination of their rotational constants following the same procedure as outlined above (see Table 2, and Tables S24 and S25 for the fits of measured transitions). From the comparison between experimental and theoretical rotational constants, these conformers were identified as TBC1 and BC2. The transitions corresponding to the next conformer in the energy ordering, CR1, could not be observed in the spectrum, probably because it is not sufficiently populated in our supersonic expansion.

All three methods, MP2, B3LYP-D3BJ and M062X with the 6-311++G(d,p) basis set, predict the rotational constants of the three observed conformers reasonably well. MP2 is the best performing method with an average percentage difference of 0.54%, followed by B3LYP-D3BJ with 0.62% and M062X with 0.74% (the percentage difference is calculated as $A_{calc}-A_{exp})/A_{exp}\times 100\%$). MP2 consistently overestimates the B and C constants, while B3LYP-D3BJ underestimates them. The theoretical A rotational constant of conformer TBC1 shows the largest deviation from the experimental value, 1.7% using M062X.

The relative abundances of the observed conformers have been calculated considering that conformational abundance is directly proportional to the intensity of its transitions and inversely proportional to the square of the corresponding dipole moment component. Since all of the assigned conformers have *a*-type spectrum, we estimated conformational relative abundances by comparing common *a*-type transitions. The results (carrying estimated uncertainties of 20%) show that BC1 is significantly more abundant than TBC1 and BC2. Using Ne as a carrier gas, relative conformational abundances are BC1:TBC1:BC2 = 525:12:1. In addition to Ne, we have collected the spectrum of cyclooctanone seeded in He and in Ar, which produce different degrees of conformational relaxation. He is the least effective relaxant among the three noble gases, whilst Ar is the most effective and sometimes leads to the observation of just the lowest-energy conformation.[42] In He, the relative conformational abundances change to BC1:TBC1:BC2 = 210:6:1. In Ar, BC2 could not be detected as the S/N ratio was lower than in the spectra with He and Ne, and the relative abundances of the other two conformers are BC1:TBC1 = 40:1.

In all carrier gases conformer BC1 is about 40 times more abundant than conformer TBC1, the second most abundant conformer. This shows that conformer BC1 is the global minimum and that there is a very strong preference of cyclooctanone to adopt this boat-chair configuration. The change in the relative conformational abundances of BC2:BC1 when changing carrier gas indicates that BC2 relaxes in our supersonic jet. The paths for interconversion are very

Table 3. Experimental bond lengths (Å), angles and dihedral angles (degrees) of BC1 cyclooctanone (r_s and r_0 structures), theoretical MP2 structural parameters, and structural parameters of cyclooctane.

	Cyclooctanone			Cyclooctane
	r_s[a]	r_0[b]	MP2	Electron Diffraction[d]
$r(C_2\text{-}C_1)$	1.527(5)	1.539(6)	1.536	–
$r(C_3\text{-}C_2)$	1.538(13)	1.544(6)	1.545	–
$r(C_4\text{-}C_3)$	1.519(6)	1.540(6)	1.535	–
$r(C_5\text{-}C_4)$	1.557(4)	1.541(6)	1.540	–
$r(C_6\text{-}C_5)$	1.515(16)	1.520(9)[c]	1.522	–
$r(O_7\text{-}C_6)$	1.206(19)	1.215(9)	1.223	–
$r(C_9\text{-}C_6)$	1.535(7)	1.520(9)	1.519	–
$r(C_9\text{-}C_8)$	1.523(4)	1.535(6)	1.533	–
$r(C_8\text{-}C_1)$	1.526(4)	1.533(6)	1.531	–
Avg. r(C-C)	1.530(7)	1.534(7)	–	1.540(1)
$\angle(C_3\text{-}C_2\text{-}C_1)$	115.5(6)	115.2(3)	114.8	117.0(20)
$\angle(C_4\text{-}C_3\text{-}C_2)$	115.5(6)	114.8(2)	114.5	116.1(18)
$\angle(C_5\text{-}C_4\text{-}C_3)$	116.1(3)	115.7(2)	115.7	120.2(10)
$\angle(C_6\text{-}C_5\text{-}C_4)$	111.0(6)	111.8(4)[c]	111.7	116.1(18)
$\angle(O_7\text{-}C_6\text{-}C_5)$	121.0(4)	120.4(5)[c]	120.1	–
$\angle(C_9\text{-}C_6\text{-}C_5)$	117.8(13)	118.8(6)[c]	118.3	117.0(20)
$\angle(C_9\text{-}C_6\text{-}O_7)$	121.1(10)	120.7(8)	121.6	–
$\angle(C_8\text{-}C_9\text{-}C_6)$	115.7(3)	115.6(3)	115.2	116.0(15)
$\angle(C_9\text{-}C_8\text{-}C_1)$	114.8(3)	114.5(4)	114.1	116.1
$\angle(C_8\text{-}C_1\text{-}C_2)$	116.1(1)	116.0(2)	115.7	116.0(15)
$\tau(C_4C_3C_2C_1)$	104.7(9)	105.1(2)	105.8	98.4(35)
$\tau(C_9C_8C_1C_2)$	-56.7(3)	-57.4(5)	-58.6	-68.3
$\tau(C_8C_1C_2C_3)$	-54.4(3)	-53.6(5)	-53.0	-42.0
$\tau(C_8C_9C_6O_7)$	-140.3(7)	-139.7(4)	-138.2	–
$\tau(C_6C_9C_8C_1)$	66.8(10)	67.4(10)	67.6	68.3

[a] The substitution structure has been determined from the atomic coordinates including Costain's error, and with signs taken from from *ab initio* calculations; [b] Effective structure; non fitted parameters were fixed to the MP2/6-311++G(d,p) value; [c] Derived from the determined r_0 structure, not fitted directly; [d] ED[48].

complicated involving a large number of coordinate changes, and including pseudorotation and inversion motions. However, their calculation is out of the scope of this paper. Previously reported barriers for pseudorotation and ring inversion of cyclooctanone were calculated from vibrational and structural data as having upper bounds of 33 kJ/mol and 36 kJ/mol, respectively,[39] and from NMR measurements as 26 kJ/mol and 31 kJ/mol, respectively.[43] These barriers are too high to allow for conformational relaxation in a supersonic jet considering the typical limit of 13 kJ/mol ascribed to multipath molecular systems.[42,44] However, a complete exploration of the potential energy surface may reveal other lower-energy paths for conformational interconversion.

Structural Determination of Cyclooctanone BC1

The observation of the ^{13}C and ^{18}O monosubstituted isotopic species of conformer BC1 permitted to calculate the coordinates of these heavy atoms in the principal inertial axes system using Kraitchman's equations[45,46] (Table S26), and to determine the substitution structure r_s. The effective structure r_0 was determined from a least-square fit of all the experimental moments of inertia,[47] where the structural parameters of the hydrogen atoms were fixed to the MP2/6-311++G(d,p) theoretical values. The bond lengths, bond angles and dihedral angles of the BC1 conformer for both r_s and r_0 structures are collected in Table 3 (see Fig. 3 for atom numbering).

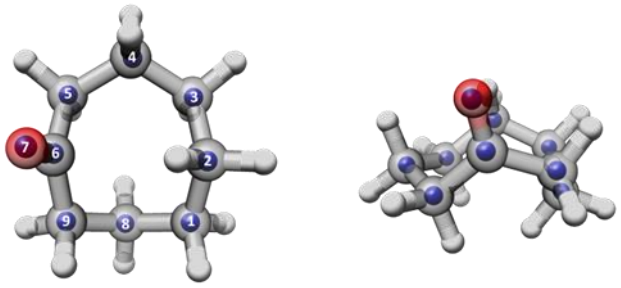

Figure 3. Comparison of the r_s structure of conformer BC1 (purple spheres) with *ab initio* MP2 structure (grey framework).

The resulting structural parameters from both calculations agree well with each other. There is a relatively large discrepancy in the $r(C_4–C_3)$ bond length that is likely due to the large uncertainty of the c substitution coordinate of C_3, very close to zero. The internuclear distances $r(C_6–C_5)$ and $r(C_9–C_6)$ involving the carbonyl carbon C_6 are quite different from each other, which can be ascribed to the uncertainty in the c coordinate of C_6. Bond angles and dihedral angles from substitution and effective structures are within 1°. The ∠(C–C–C) angles, not including the ∠(C–CO–C) angle, have all very similar values of *ca.* 115°, except for $\angle(C_6–C_5–C_4)$ which is about 4° more acute. The lower value of $\angle(C_6–C_5–C_4)$ is consistent across r_s and r_0 structures and it is also predicted by quantum mechanical calculations. Both r_0 and r_s structures are in very good agreement with the theoretical ones. An overlay of the experimental substitution r_s and ab initio MP2 coordinates (Fig. 3) shows their excellent match.

We have compared the structure of cyclooctanone with that of cyclooctane, previously studied by electron diffraction[48], to determine the effect of inserting a carbonyl group in the ring. Structural studies of cyclooctane in the liquid and gas phases indicate that it exists predominantly in a boat-chair conformation.[27,48] Cyclooctanone maintains a strong preference for being in a boat-chair conformation, thus indicating that the overall conformational preference of an eight-membered ring is not affected by substituting a methylene by a carbonyl group. The electron diffraction study of cyclooctane only provided an average sp^3-sp^3 C–C bond length of 1.540(1) Å. Bond lengths for cyclooctanone are slightly shorter, with average values of 1.530(7) Å and 1.534(7) Å for the r_s and r_0 structures, respectively. The values of the bond angles of cyclooctane and cyclooctanone are the same within experimental uncertainties, except for the angles $\angle(C_6–C_5–C_4)$ and $\angle(C_5–C_4–C_3)$, which are about 4° more acute in

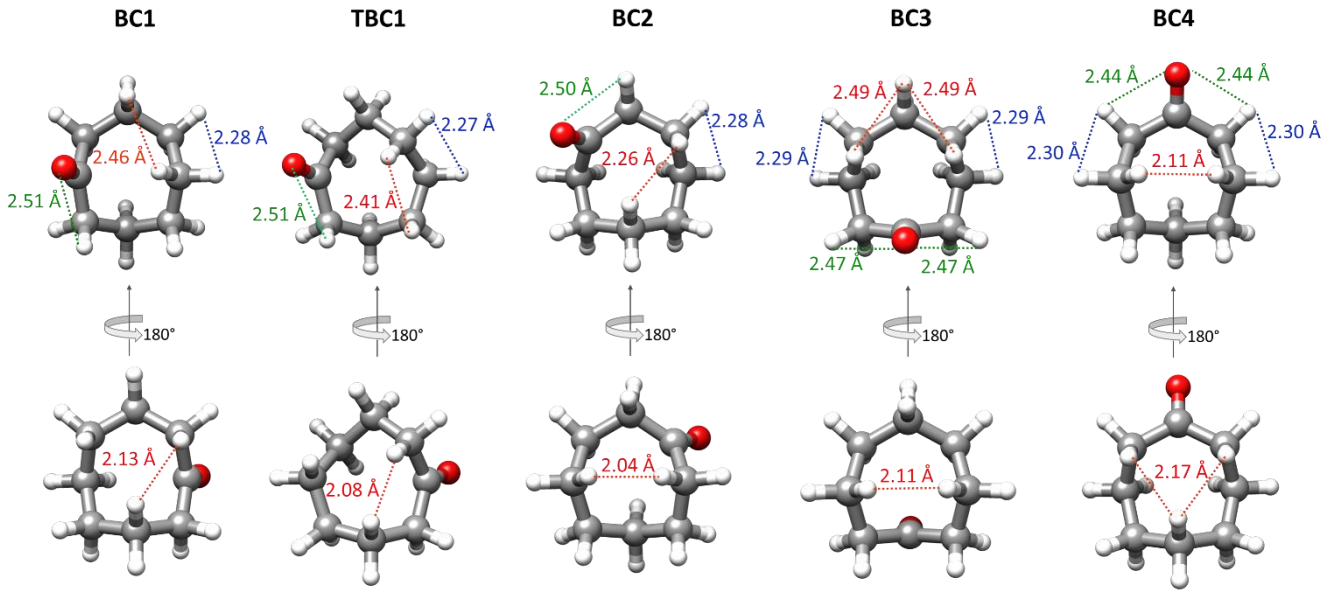

Figure 4. Intramolecular distances for the observed boat-chair and twisted boat-chair conformers **BC1**, **TBC1** and **BC2**, and the higher-energy boat-chair conformers **BC3** and **BC4** at MP2/6-311++G(d,p) level.

cyclooctanone, probably to accommodate the carbonyl group in the ring. The largest changes occur on the dihedral angles, where there are differences of up to 10°, which collectively result in the boat part of the ring being less "puckered" in cyclooctanone than in cyclooctane. This behaviour on including a carbonyl group in the ring has been observed for smaller cycles .[49]

The structure of cyclooctanone can be compared with those of related cyclic ketones previously reported by microwave spectroscopy and electron diffraction.[14,17,20] The average value of 1.534(7) Å for the sp^3-sp^3 C–C internuclear distance of cyclooctanone is similar to those reported for cycloheptanone, cyclohexanone and cyclopentanone (Table 4). The sp^2-sp^3 C–C internuclear distance shows a greater variation, with similar values for cyclooctanone and cycloheptanone, a shorter distance in cyclohexanone and a longer one in cyclopentanone. The sp^2-sp^3 C–C internuclear distances for cyclooctanone and cycloheptanone are closer to that determined for acetone, 1.517(3) Å,[50] probably a reflection of the reduced ring strain in the larger cyclic ketones. The C–O internuclear distances are very similar for all cyclic ketones studied so far, with the exception of cyclohexanone, that exhibits a slightly larger distance. They are also similar to the value determined for acetone 1.210(4) Å. The bond angles show clear trends as the size of the ring increases. In going from cyclopentanone to cyclooctanone, the ∠(C–CO–C) angle becomes more obtuse and closer to the typical sp^2-hybridized angle of 120°. The ∠(C–CO–C) angle of the six-, seven- and eight-membered cyclic ketones are, within uncertainties, essentially the same as that of acetone, of 116.0(15)°. Cyclopentanone presents a considerably more acute angle of 108.6(2)°, reflecting its larger ring strain. Changes in the ∠(C–C–C) angles are dictated by structural requirements due to ring size. The average ∠(C–C–C) angle in cyclooctanone, calculated without including ∠(C_6–C_5–C_4) (see above) and ∠(C–CO–C), is 115.3(3)°, very similar to the average value of 115.5(5)° for cycloheptanone. Cyclohexanone has an average angle of 111.1(2)°, closer to the tetrahedral angle of 109.5°, and cyclopentanone of 103.8(2)°. Dihedral angles cannot be directly compared.

Table 4. Comparison of bond lengths (Å) and bond angles (°) of cyclopentanone,[a] cyclohexanone,[b] cycloheptanone[c] and cyclooctanone.[d]

Parameter	Cyclo-pentanone	Cyclo-hexanone	Cyclo-heptanone	Cyclo-octanone
r(C–C) sp^2-sp^3	1.531(4)	1.503(4)	1.517	1.520(9)
r(C-C) sp^3-sp^3	1.542(3)	1.542(2)	1.536(2)	1.534(7)
r(C=O)	1.213(4)	1.229(3)	1.219(12)	1.215(9)
∠(C–CO–C)	108.6(2)	115.3(3)	117.3(18)	118.8(6)*
Avg ∠(C–C–C)	-	110.8(2)	-	114.8

[a] ED+MW[14]; [b] ED+MW[17]; [c] ED[20]; [d] This work, r_0.

Intramolecular Interactions

There is a huge difference in abundance between conformer BC1 and the other observed conformations of cyclooctanone, which can be rationalised in terms of the various intramolecular interactions at play (see Fig. 4). All observed conformers show attractive C–H···O interactions between the oxygen in the carbonyl group and neighbouring hydrogen atoms, eclipsed configurations of hydrogen atoms that produce steric strain, and repulsive interactions CH···HC across the ring. BC1, TBC1 and BC2 display very similar C–H···O interactions (green). The HCCH eclipsed conformations (blue) are also essentially the same for all three conformers. The main difference lies on the CH···HC repulsive interactions

(red), which are stronger in TBC1 and BC2 than in BC1 because the H atoms are located at shorter distances. The differences in these interactions are larger between TBC1 and BC2 than between BC1 and TBC1, which can be taken as an indication that, for the same position of the carbonyl group in the ring, boat-chair configurations are more energetically favoured than twisted boat chain configurations.

If we compare the theoretical structures for all boat-chair conformations (Fig. 4) it can be seen that BC3 and BC4, although benefiting from having two C–H···O interactions, also have two HCCH eclipsed interactions, and a higher number of short CH···HC interactions across the ring than BC1 and BC2 and therefore they lie at higher energies. The shorter CH···HC interactions for BC4 explain its higher relative energy with respect to BC3.

Conclusions

Three conformers of cyclooctanone, two boat chair and one twisted boat chair configurations, have been identified from the analysis of its high resolution rotational spectrum in a supersonic jet, and their spectroscopic parameters have been determined to high accuracy. The experimental data obtained using different carrier gases demonstrates the strong preference of cyclooctanone to adopt the boat chair BC1 conformation, which is about 40 times more abundant than the next conformation in the energy ordering, the twisted boat TBC1 conformation. The least abundant conformer is a second boat-chair conformation. Our experimental results validate the conformations and energy ordering predicted by our computational calculations, and are consistent with theoretical Gibbs free energies.

The experimental structure of the most abundant conformation of cyclooctanone has been determined, which, to our knowledge, is the first structure of an eight-membered ring determined by rotational spectroscopy. The insertion of a carbonyl group in place of a methylene group does not change the conformational preferences with respect to the eight-membered cycloalkane, but it introduces changes in the bond and dihedral angles that make cyclooctanone a "flatter" molecule than cyclooctane.

Three main types of non-bonded interactions are at play in cyclooctanone, namely attractive C–H···O interactions, eclipsed configurations of hydrogen atoms that cause steric strain, and repulsive CH···HC interactions across the ring. Our data shows that the strong preference of cyclooctanone to be in the boat chair configuration BC1 is due to a reduction of the repulsive interactions for this configuration of the cycle. The energy ordering of cyclooctanone conformers is determined by the strength of the repulsive interactions and the number of eclipsed configurations around the ring.

The conformational and structural analysis presented in this work reveals the intramolecular forces responsible for conformational preferences, and shows the importance of repulsive interactions, which are likely to play a relevant role in other medium-sized cycles. Our results highlight the unique application of rotational spectroscopy in combination with quantum-chemistry calculations to obtain accurate information on the behaviour of complex multiconformational systems. Further studies on the pseudorotation and inversion pathways of cyclooctanone will help understand conformational interconversion and internal dynamics. Structural investigations of larger cyclic ketones will yield information on the balance of intramolecular forces in more flexible and complex rings and help elucidate possible trends as the size of the ring increases. These results can be compared with those from recent rotational studies of large ring crown ethers[51–53], where attractive C–H···O and repulsive O···O interactions dictate conformational preferences, to understand the changes induced by replacing $–CH_2$ groups by oxygen atoms. Accurate information on the interactions of larger cyclic ketones is of use for the design and control of reactions involving medium-sized cycles.[54,55]

Experimental Section

The rotational spectrum of cyclooctanone was recorded using the CP-FTMW spectrometer at King's College London, which operates in the 2-8 GHz frequency range.[56,57] Optimal signals were obtained by placing cyclooctanone (98%, m.p. 313 K) in a bespoke heated nozzle at 347 K. Gas-phase cyclooctanone was seeded in neon at stagnation pressures of 5 bar and conducted to the vacuum chamber, where it was polarised with 4 chirped microwave pulses of 4 μs length. After each excitation pulse, molecular relaxation signals (free inductions decays, FIDs) were collected for 20 μs by our digital oscilloscope. The time domain spectrum was converted to the frequency domain using a fast Fourier-transform algorithm with a Kaiser-Bessel window. 1.4 million FIDs were coherently added to produce the spectrum of Fig. 2. The spectra of cyclooctanone seeded in helium and argon as carrier gases were collected with the same set up. Molecular pulses of 1000 μs duration were used when neon was used as carrier gas, and of 600 μs duration when helium and argon were used.

The conformational landscape of cyclooctanone was first sampled using molecular mechanics (MM+), with an energy limit of 84 kJ/mol, which yielded eleven conformations. The geometry of the conformational minima was then optimized at the M062X, B3LYP-D3BJ and MP2 levels of theory with the 6-311++G(d,p) basis set using Gaussian09.[58] The DFT and *ab initio* calculations returned ten distinct conformations (Fig. 1), as one of the initial crown conformers converged to distorted crown. Harmonic vibrational calculations at the three levels of theory were also carried out to determine whether all the minima are local minima in the potential energy surface, and obtain zero-point corrections and Gibbs free energies of the conformers. Rotational constants, dipole moments and relative energies of all predicted conformers are collected in Table 1 and Tables S1-S2.

Conflicts of interest

There are no conflicts to declare.

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References

1 S. I. Chan, J. Zinn, J. Fernandez and W. D. Gwinn, Trimethylene oxide. I. Microwave spectrum, dipole moment, and double minimum vibration, *J. Chem. Phys.*, 1960, **33**, 1643–1655.

2 D. O. Harris, H. W. Harrington, A. C. Luntz and W. D. Gwinn, Microwave spectrum, vibration-rotation interaction, and potential function for the ring-puckering vibration of trimethylene sulfide, *J. Chem. Phys.*, 1966, **44**, 3467–3480.

3 F. A. Cotton and B. A. Frenz, Conformations of cyclobutane, *Tetrahedron*, 1974, **30**, 1587–1594.

4 G. G. Engerholm, A. C. Luntz, W. D. Gwinn and D. O. Harris, Ring puckering in five-membered rings. II. The microwave spectrum, dipole moment, and barrier to pseudorotation in tetrahydrofuran, *J. Chem. Phys.*, 1969, **50**, 2446–2457.

5 T. Ogata and K. Kozima, Microwave Spectrum of Cyclohexene, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 1263–1265.

6 Y. Ohnishi and K. Kozima, Microwave spectrum of cyclohexanone, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 1323–1325.

7 J. Laane, Origin of the ring-puckering potential energy function for four-membered rings and spiro compounds. A possibility for pseudorotation, *J. Phys. Chem.*, 1991, **95**, 9246–9249.

8 K. S. Pitzer and W. E. Donath, Conformations and Strain Energy of Cyclopentane and its Derivatives, *J. Am. Chem. Soc.*, 1959, **81**, 3213–3218.

9 S. J. Han and Y. K. Kang, A pseudorotation model and ring-puckering of cyclopentane, *J. Mol. Struct. THEOCHEM*, 1996, **362**, 243–255.

10 H. Kim and W. D. Gwinn, Ring Puckering in Five-Membered Rings. III. The Microwave Spectrum, Dipole Moment, and Structure of Cyclopentanone, *J. Chem. Phys.*, 1969, **51**, 1815–1819.

11 H. J. Geise, H. R. Buys and F. C. Mijlhoff, Conformation of non-aromatic ring compounds, *J. Mol. Struct.*, 1971, **9**, 447–454.

12 D. Cremer and K. J. Szabó, in *Conformational Behavior of Six-Membered Rings*, 1995, pp. 59–135.

13 E. Díez, A. L. Esteban, F. J. Bermejo, C. Altona and F. A. A. M. de Leeuw, Relationships between torsional angles and ring-puckering coordinates. Part II, *J. Mol. Struct.*, 1984, **125**, 49–65.

14 K. Tamagawa, R. L. Hilderbrandt and Q. Shen, Molecular Structure of Cyclopentanone by Gas-Phase Electron Diffraction, *J. Am. Chem. Soc.*, 1987, **109**, 1380–1383.

15 H. R. Barton, The conformation of the steroid nucleus., *Experientia*, 1950, **6**, 316–320.

16 J. Dommen, T. Brupbacher, G. Grassi and A. Bauder, Microwave Spectra of Isotopic Species and Substitution Structure of Cyclohexane, *J. Am. Chem. Soc.*, 1990, **112**, 953–957.

17 J. Dillen and H. J. Geise, The molecular structure of cyclohexanone determined by gas-phase electron diffraction, including microwave data, *J. Mol. Struct.*, 1980, **69**, 137–144.

18 J. R. Durig, R. M. Ward, A. R. Conrad, M. J. Tubergen, K. G. Nelson, P. Groner and T. K. Gounev, Microwave, Raman, and infrared spectra, r0structural parameters, conformational stability, and vibrational assignment of cyanocyclohexane, *J. Mol. Struct.*, 2010, **967**, 99–111.

19 J. L. Alonso, Microwave Spectrum of Cyclohexanone, *J. Mol. Struct.*, 1981, **73**, 63–69.

20 J. Dillen and H. J. Geise, an Investigation of the Molecular Structure of Cycloheptanone By Gas Phase Electron Diffraction J., *J. Mol. Struct.*, 1981, **72**, 247–255.

21 M. K. Jahn, D. A. Dewald, M. Vallejo-Lõpez, E. J. Cocinero, A. Lesarri, W. Zou, D. Cremer and J. U. Grabow, Pseudorotational Landscape of Seven-Membered Rings: The Most Stable Chair and Twist-Boat Conformers of ε-Caprolactone, *Chem. - A Eur. J.*, 2014, **20**, 14084–14089.

22 V. Prelog, Conformation and Reactivity of Medium-sized Ring Compounds, *Pure Appl. Chem.*, 1963, **6**, 545–560.

23 R. Rudman and B. Post, Polymorphism of Crystalline Cyclooctanone and Cyclononanone, *Mol. Cryst.*, 1968, **3**, 325–337.

24 P. Groth, On the Cry stal Structure of Cyclododecanone, *Acta Chem. Scandanavica*, 1979, **33 A**, 203–205.

25 F. A. L. Anet, A. K. Cheng and J. J. Wagner, Determination of conformational energy barriers in medium- and large-ring cycloalkanes by proton and carbon-13 nuclear magnetic resonance, *J. Am. Chem. Soc.*, 1972, **94**, 9250–9252.

26 F. A. L. Anet, P. J. Degen and J. Krane, Dynamics of eight-membered rings. 1,3-Dioxocane and its gem-dimethyl derivatives, *J. Am. Chem. Soc.*, 1976, **98**, 2059–2066.

27 F. A. L. Anet, Dynamics of Eight-Membered Rings in the Cyclooctane Class, *Dyn. Chem.*, 1974, **45**, 169–220.

28 B. H. Rubin, M. Williamson, M. Takeshita, F. M. Menger, F. A. L. Anet, B. Bacon and N. L. Allinger, Conformation of a Saturated 13-Membered Ring, *J. Am. Chem. Soc.*, 1984, **106**, 2088–2092.

29 G. G. Brown, B. C. Dian, K. O. Douglass, S. M. Geyer, S. T. Shipman and B. H. Pate, A broadband Fourier transform microwave spectrometer based on chirped pulse excitation, *Rev. Sci. Instrum.*, 2008, **79**, 1–13.

30 A. P. S. Narula, The search for new amber ingredients, *Chem. Biodivers.*, 2014, **11**, 1629–1638.

31 P. Kraft, Design and Synthesis of Violet Odorants with Bicyclo [6.4.0] dodecene and Bicyclo [5.4.0] undecene Skeletons, *Synthesis (Stuttg).*, 1999, **4**, 695–703.

32 T. Aono and M. Hesse, 62. Synthesis of 14-Membered Lactones from Cyclooctanone, *Helv. Chim. Acta*, 1984, **67**, 1448–1452.

33 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. Mcphail, Plant Antitumor Agents.VI.The Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor

Agent from Taxus brevifolia2, *J. Am. Chem. Soc.*, 1971, **93**, 2325–2327.

34 P. Appukkuttan, W. Dehaen and E. Van Der Eycken, Microwave-assisted transition-metal-catalyzed synthesis of N-shifted and ring-expanded buflavine analogues, *Chem. - A Eur. J.*, 2007, **13**, 6452–6460.

35 H. M. C. Ferraz, F. I. Bombonato, M. K. Sano and L. S. Longo, Natural occurrence, biological activities and synthesis of eight-, nine-, and eleven-membered ring lactones, *Quim. Nova*, 2008, **31**, 885–900.

36 N. L. Allinger, C. H. Langley and J.-H. Lii, Molecular Mechanics Calculations on Carbonyl Compounds. III. Cycloketones, *J. Comput. Chem.*, 2001, **22**, 1451–1475.

37 N. L. Allinger, K. Chen, M. Rahman and A. Pathiaseril, Molecular mechanics (MM3) calculations on aldehydes and ketones, *J. Am. Chem. Soc.*, 1991, **113**, 4505–4517.

38 T. C. Rozada, G. F. Gauze, F. A. Rosa, D. C. Favaro, R. Rittner, R. M. Pontes and E. A. Basso, The conformational analysis of 2-halocyclooctanones, *Spectrochim. Acta Mol. Biomol. Spectrosc.*, 2015, **137**, 176–184.

39 T. C. Rounds and H. L. Strauss, Vibration, rotation spectra, and conformations of cyclooctanone, *J. Chem. Phys.*, 1978, **69**, 268–276.

40 J. K. G. Watson, in *Vibrational Spectra and Structure*, 1977, pp. 1–89.

41 H. M. Pickett, The fitting and prediction of vibration-rotation spectra with spin interactions, *J. Mol. Spectrosc.*, 1991, **148**, 371–377.

42 R. S. Ruoff, T. D. Klots, T. Emilsson and H. S. Gutowsky, Relaxation of conformers and isomers in seeded supersonic jets of inert gases, *J. Chem. Phys.*, 1990, **93**, 3142–3150.

43 M. Jung, Conformational Analysis of Cyclooctanone: Evidence from 13C Nuclear Magnetic Resonance, *Bull. Korean Chem. Soc.*, 1991, **12**, 224–227.

44 G. M. Florio, R. A. Christie, K. D. Jordan and T. S. Zwier, Conformational preferences of jet-cooled melatonin: Probing trans- and cis-amide regions of the potential energy surface, *J. Am. Chem. Soc.*, 2002, **124**, 10236–10247.

45 J. Kraitchman, Determination of Molecular Structure from Microwave Spectroscopic Data, *Am. J. Phys.*, 1953, **21**, 17–24.

46 P. Kraft, J. A. Bajgrowicz, C. Denis and G. Fra, Odds and Trends : Recent Developments in the Chemistry of Odorants, *Angew. Chemie - Int. Ed.*, 2000, **39**, 2980–3010.

47 Z. Kisiel, PROSPE - Programs for ROtational SPEctroscopy, *Spectrosc. from Sp.*, 2001, 91–106.

48 O. V. Dorofeeva, V. S. Mastryukov, N. L. Allinger and A. Almenningen, The molecular structure and conformation of cyclooctane as determined by electron diffraction and molecular mechanics calculations, *J. Phys. Chem.*, 1985, **89**, 252–257.

49 A. C. Legon, Equilibrium Conformations of Four- and Five-Membered Cyclic Molecules in the Gas Phase: Determination and Classification, *Chem. Rev.*, 1980, **80**, 231–262.

50 T. Iijima, Zero-point Average Structure of a Molecule Containing Two Symmetric Internal Rotors. Acetone, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3526–3530.

51 F. Gámez, B. Martínez-Haya, S. Blanco, J. C. López and J. L. Alonso, High-resolution rotational spectroscopy of a cyclic ether, *J. Phys. Chem. Lett.*, 2012, **3**, 482–485.

52 F. Gámez, B. Martínez-Haya, S. Blanco, J. C. López and J. L. Alonso, Microwave spectroscopy and quantum chemical investigation of nine low energy conformers of the 15-crown-5 ether, *Phys. Chem. Chem. Phys.*, 2012, **14**, 12912–12918.

53 C. Pérez, J. C. López, S. Blanco and M. Schnell, Water-Induced Structural Changes in Crown Ethers from Broadband Rotational Spectroscopy, *J. Phys. Chem. Lett.*, 2016, **7**, 4053–4058.

54 P. Clarke, R. Black and M. Iqbal, Investigation of Transannelation Reactions Across a Cyclononene Ring, *Synlett*, 2010, **2010**, 543–546.

55 N. Wang, Q.-S. Gu, Z.-L. Li, Z. Li, Y.-L. Guo, Z. Guo and X.-Y. Liu, Direct Photocatalytic Synthesis of Medium-Sized Lactams through C-C Bond Cleavage, *Angew. Chemie Int. Ed.*, 2018, 14225–14229.

56 D. Loru, M. A. Bermúdez and M. E. Sanz, Structure of fenchone by broadband rotational spectroscopy Structure of fenchone by broadband rotational spectroscopy, *J. Chem. Phys.*, 2016, **145**, 074311-8.

57 D. Loru, M. M. Quesada-Moreno, J. R. Avilés-Moreno, N. Jarman, T. R. Huet, J. J. López-González and M. E. Sanz, Conformational Flexibility of Limonene Oxide Studied By Microwave Spectroscopy, *ChemPhysChem*, 2017, **18**, 268.

58 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09 Revis. E.01*, 2010.