

THE α -BROMOCYCLOHEXANONE RING: THE RELATIONSHIP BETWEEN ITS CONFORMATION AND THE ULTRAVIOLET AND INFRARED ABSORPTION OF THE KETO GROUP

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A series of diterpenoids whose C-ring was an α -bromocyclohexanone showed a discontinuity in the relationship between the Br—C—C=O torsion angle and the Br...O contact distance at about 50°, below which the Br...O distance remained effectively constant at about 3.0 Å. This effect is caused by the non-compressibility of the van der Waals radii of the Br and O atoms. Analysis of the parameters for all compounds in the Cambridge Data File containing an α -bromocyclohexanone ring confirmed this phenomenon. Once the Br...O distance approaches 3.0 Å, the Br—C—C and C—C=O angles are forced open to accommodate the Br...O compression strain as the torsion angle is further reduced. An approximate value of the Br...O distance, d in Å, can be estimated for any torsion angle, ϕ , by the empirical equation

$$d^2 = R - S \cos \phi + T \cos^2 \phi$$

where $R = 11.73$, $S = 3.62$ and $T = 0.75$. There is a linear relationship between the Br...O separation and both the infrared vibration frequency ν and the ultraviolet absorption wavelength λ_{\max} of the C=O group: the greater the distance, the lower is the frequency ν and longer the wavelength λ_{\max} . Thus measurement of the ultraviolet and infrared spectra of a compound containing an α -bromocyclohexanone system can yield information about the Br...O distance and hence the conformation of the six-membered ring. There are also systematic trends in the effect on the spectroscopic properties of the keto group that accompany changing the halogen from fluorine through to iodine. When the halogen is axial, its electronegativity has a maximum influence on the C=O vibration frequency by a 'through-bond' inductive process. When the halogen is equatorial, it exerts a steric compression on the non-bonded electrons in the 2p orbital of the oxygen atom. This enhances hybridization to the sp^2 state and this simultaneously strengthens the C=O bond and enlarges the $n \rightarrow \pi^*$ energy gap. This 'through-space' influence is simply a process of steric compression, dependent on the size of the halogen atom. It accounts well for all of the systematic trends in both infrared and ultraviolet frequencies of the C=O group when the halogen is equatorial and eclipses the C=O bond.

HISTORICAL INTRODUCTION

The use of shifts in the infrared and ultraviolet absorption frequencies of the keto group to determine conformation in α -bromo-substituted cyclohexanone systems has been widely discussed¹ and has even been used in students' practical work.² In a classic paper, Corey³ deduced that an axially substituted bromine atom had little effect on the vibration frequency of the keto group compared with that of the unsubstituted parent compound, whereas if the bromine was equatorial, the stretching frequency of the keto group was raised by about 20 cm^{-1} . In a detailed study of ultraviolet spectra, Cookson⁴ found that an axially substituted bromine atom caused a shift by about 25 nm to longer wavelength accompanied by an increase in absorption intensity. An equatorially substituted bromine pro-

duced, if anything at all, a small shift (*ca* 5 nm) to shorter wavelength compared with the parent cyclohexanone.

Subsequently it was found that an axial halogen atom α to the keto group in a cyclohexanone system could affect the sign of the Cotton effect relative to that of the parent ketone⁵ and the 'axial haloketone rule' was used to interpret the optical rotatory dispersion curve to yield the absolute configuration and conformation of the haloketone ring.

It has been generally accepted¹ that in the chair conformation non-bonded repulsions between the bromine at C-2 and the axial hydrogen at C-4 would tend to destabilize an axial bromine, whereas electrical repulsion between $\overset{+}{\text{C}}=\overset{-}{\text{O}}$ and $\overset{+}{\text{C}}-\overset{-}{\text{Br}}$ dipoles would destabilize an equatorial bromine atom because the dipoles

would be close to coplanar. For these reasons, solvent effects are dramatic for a simple halocyclohexanone. In non-polar solvents (e.g. octane, carbon tetrachloride) the halogen is axial, whereas in polar solvents (e.g. methanol, acetonitrile) the halogen is equatorial.² This emphasizes the ease with which the flexible cyclohexanone ring can flip from one chair conformation to the other. However, in polycyclic systems, such as steroids, fusion holds the ring rigid and prevents the ready flipping between chair configurations. Instead, to relieve strain, distortion of the ring can occur, and all conformations between chair and boat may be taken up.⁶

A case of an α -bromoketone A ring in a steroid taking up a boat configuration has been reported.^{1a} In the case of 2 α -bromo-2 β -methylcholestan-3-one, infrared and ultraviolet spectral measurements indicated that the bromine was 'axial', but the rotatory dispersion curve showed a negative Cotton effect, an apparent contradiction. With the A ring in a boat configuration, all spectral measurements were self-consistent.

THE IDEALIZED CONFORMATIONS

The conformation of the cyclohexane ring system has been discussed at great length.⁷ In cyclohexanone, the problem is more complex because the carbonyl group gives rise to two different types of boat and twist-boat forms.⁸ The conformation of both the cyclohexane and the cyclohexanone ring systems can be described in terms of either torsion angles⁹ or three pseudo-rotational parameters: Q , Θ and ϕ .¹⁰ However, it is difficult to translate these parameters into the well known terms such as 'chair' and 'twist-boat'. For this reason, the different possible conformers of the flexible boat form of the α -bromocyclohexanone ring are presented in detail below.

α -Bromocyclohexanone can take up two ideal chair conformations; in one the bromine is axial with the Br-C-C=O torsion angle equal to 120°, and in the other the bromine is equatorial with a Br-C-C=O torsion angle of 0°, the bromine eclipsing the oxygen (see Figure 1, structures 1a and 1b). If the cyclohexanone ring takes up a boat configuration, it becomes flexible and all possible torsion angles between 0 and 120° can be taken up. There are three ideal boat forms (see Figure 1, structures 2-4).

When the bromine is 'bowsprit' and the C=O is pseudo-equatorial, the torsion angle is 0° (Figure 1, structure 2a). When the bromine is 'flagpole' and the C=O is pseudo-equatorial, the torsion angle is 120° (Figure 1, structure 2b). When the bromine is equatorial and the C=O is pseudo-'bowsprit', the torsion angle is 0° (Figure 1, structure 3a). When the bromine is axial and the C=O is pseudo-'bowsprit', the torsion angle is 120° (Figure 1, structure 3b). When the bromine is equatorial and the C=O is pseudo-equatorial, the

torsion angle is 60° (Figure 1, structure 4a). When the bromine is axial and the C=O is pseudo-equatorial, the torsion angle is again 60° (but in the opposite sense) (Figure 1, structure 4b).

Consider now the ideal 'twist-boat' conformers. By suitably choosing the appropriate two-fold axis, it is easily seen that there are three pairs of conformers (see Figure 1, structures 5-7). With the O=C and C-4 defining the axis (Figure 1, structure 5), when the bromine is equatorial, the torsion angle is 30° (Figure 1, structure 5a); when the bromine is axial, the torsion

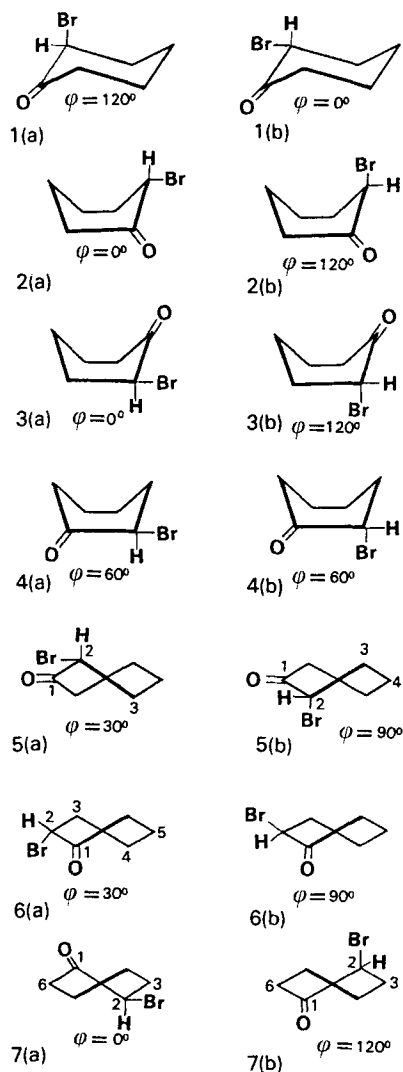


Figure 1. Br-C-C=O torsion angles, ϕ , for the idealized conformations of an α -bromocyclohexanone ring: 1a and b, chair; 2, 3 and 4a and b, boat; 5, 6 and 7a and b, twist boat. The pseudo-two-fold axes are horizontal, through ring atoms 1,4 in structure 5, 2,5 in structure 6 and 3,6 in structure 7

angle is 90° (Figure 1, structure 5b). When C-2, i.e. C-Br, and C-5 define the pseudo-two-fold axis, the O=C-C-Br torsion angle can again be either 30° or 90° (Figure 1, structures 6a and b). Finally, with C-3 and C-6 defining the two-fold axis, the torsion angle is 0° for the bromine pseudo-equatorial (Figure 1, structure 7a) and 120° when the bromine is pseudo-axial (Figure 1, structure 7b).

Examination of models shows that when the cyclohexanone ring is in the flexible boat conformation, it is possible by pseudo-rotating the ring to obtain any value between 0 and 120° for the Br-C-C=O torsion angle. Moreover, several different conformations lead to the same O=C-C-Br torsion angles of 0° and 120° , values found in both chair and boat conformations.

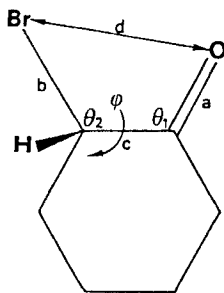
The energies of the different conformations of the cyclohexane ring system can be calculated by the methods of molecular mechanics¹¹ and, in particular, it has been shown that the difference in energy between the boat and twist-boat conformers is relatively small.¹² The interchange of the cyclohexanone ring through the various flexible twist-boat forms is a smooth, continuous pseudo-rotation rippling over a series of low energy barriers (Figure 2.3 in Ref. 13). These geometries and their relative energies are well reflected in the behaviour of models, both Dreiding framework and CPK van der Waals space-filling.

RELATIONSHIP BETWEEN THE Br...O SEPARATION AND THE Br-C-C=O TORSION ANGLE IN AN α -BROMOCYCLOHEXANONE RING

The Br...O distance (d) and the Br-C-C=O torsion angle (ϕ) for a rigid Br-C-C=O system are related by the equation

$$d^2 = a^2 \sin^2 \Theta_1 + b^2 \sin^2 \Theta_2 - 2ab \sin \Theta_1 \sin \Theta_2 \times \cos \phi + (c - a \cos \Theta_1 - b \cos \Theta_2)^2 \quad (1)$$

where a , b , c , ϕ , Θ_1 and Θ_2 are defined in the formula shown [see equation (2), Figure 1 in Ref. 3].



The crystal structures of the bromoketones of a series of closely related diterpenes^{14a-d} and a spirodiketone^{14e} have been determined. The relevant molecular parameters and spectroscopic data for these compounds are given in Table 1, and the values of the Br...O separation are plotted against values of the torsion angle (ϕ) in Figure 2. Equation (1), evaluated for the parameters $a = 1.22$, $b = 1.95$, $c = 1.52$ Å. $\Theta_1 = 119^\circ$, $\Theta_2 = 104^\circ$ is also shown in Figure 2 as the curved line. The curve, equation (1), fits the experimental results well for torsion angles between 100° and 60° . However, the three experimental results for torsion angles less than 40° have the same Br...O separation of about 2.97 Å, effectively independent of the torsion angle. If a horizontal line corresponding to this Br...O separation is extrapolated to the right, it intersects the curve of equation (1) at a torsion angle of about 50° ; thus, for any torsion angle of less than about 50° , the Br...O separation can be expected to be roughly constant at about 3.0 Å.

The sum of the van der Waals radii of oxygen (1.40 Å) and bromine (1.95 Å)¹⁵ is 3.35 Å, corresponding to the Br...O separation at a torsion angle of *ca* 90° , implying that the Br and O atoms are 'touching' even at this large torsion angle. As the ring conformation changes and the torsion angle decreases from

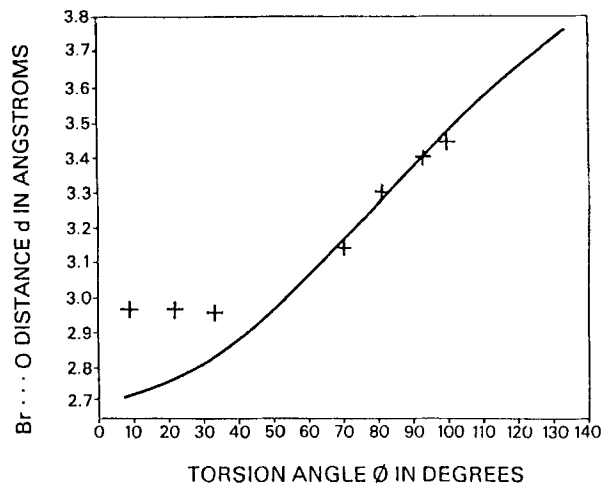
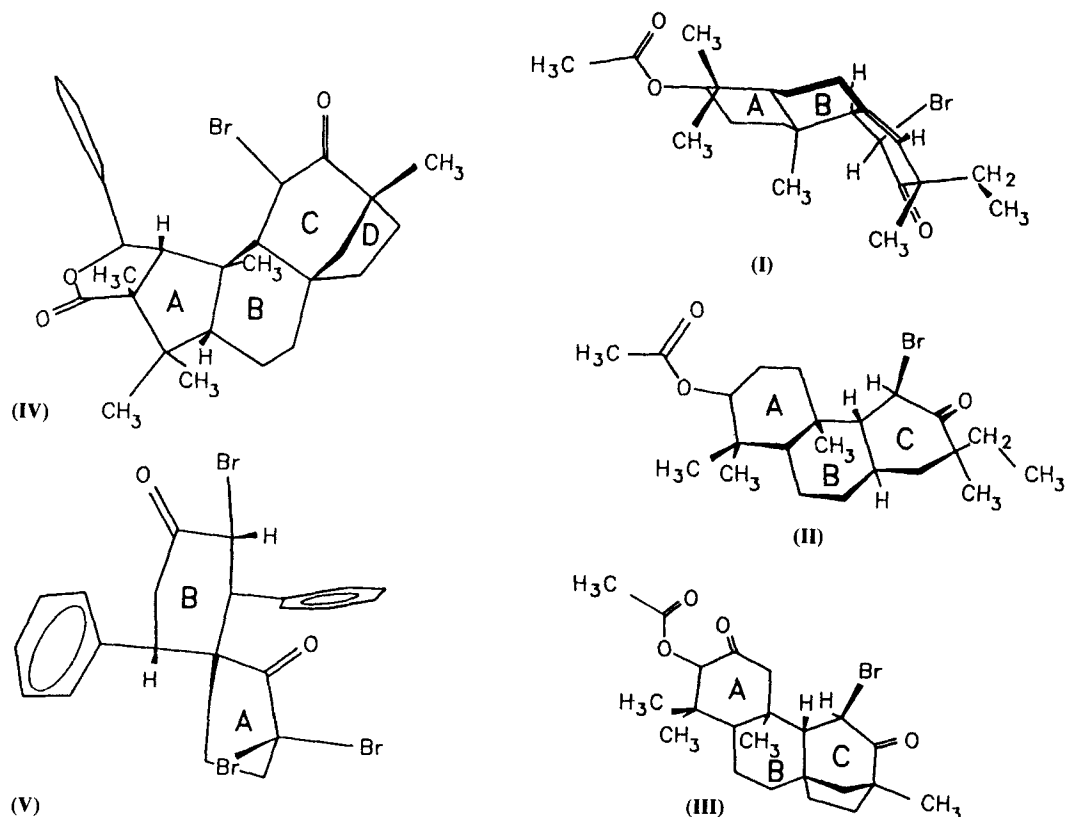


Figure 2. Plot of the Br...O separations and corresponding Br-C-C=O torsion angles for the compounds in Refs 14a-e (see Table 1). The curve through the points is defined by equation (1) with the parameters C=O = 1.22 Å, C-Br = 1.95 Å, C-C = 1.52 Å, O=C-C = 119° , Br-C-C = 104° . It is clear that the van der Waals radii of O and Br strongly resist further compression at $\phi = 50^\circ$, whereafter the Br...O separation remains roughly constant and it is the Br-C-C and O=C-C angles that now open as ϕ approaches zero. At $\phi = 0^\circ$, Br-C-C $\approx 109^\circ$, O=C-C $\approx 124^\circ$.

Table 1. Molecular parameters of the compounds I to V from Refs 14a-e (these are plotted in Figures 2, 6, 7 and 8)^a
Form G



Compound	$\phi(^{\circ})$	$d(\text{\AA})$	C=O(\AA)	C-Br(\AA)	C-C(\AA)	O=C-C($^{\circ}$)	Br-C-C($^{\circ}$)	IR (cm^{-1})	UV (nm) ^b	Name
IV	9	2.97	1.28	1.98	1.52	124	108	1725	284(86)	BRLACT
V	22	2.97	1.22	1.97	1.51	123	109	1720	{273(121)}	BPSUNO
V	33	2.96	1.21	1.95	1.52	119	109	1715	294(86)	AXBBEY
III	70	3.14	1.22	1.98	1.51	120	102	1705	{273(121)}	BPSUNO
V	81	3.30	1.21	1.95	1.52	119	105	1698	321(145)	ABIPIM
I	93	3.40	1.22	1.94	1.51	121	103	1695	325(78)	AXBPR0
II	99	3.44	1.24	1.94	1.54	115	104			

^aThe UV data for compound V (given in brackets) are not included in Figures 6, 7 and 8 because the values are artificially low owing to the proximity of the phenyl ring to the one carbonyl group.

^bMolar absorptivity (ϵ , $\text{l mol}^{-1} \text{cm}^{-1}$) in parentheses.

about 90° there is a gradual compression of the van der Waals radii of the Br and O atoms until a Br...O separation of *ca* 3.0 \AA is reached, corresponding to a torsion angle of *ca* 50° , at which stage further compression is energetically impossible and the bond angles O=C-C and Br-C-C begin to open to accommodate the compression strain. The cost in energy for these angular distortions is *ca* 0.4 kJ mol^{-1} per degree,¹⁶ giving a total of *ca* 4 kJ when the Br-C-C=O torsion angle $\phi = 0^{\circ}$,

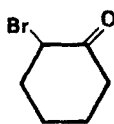
$\Theta_1 = 124$ and $\Theta_2 = 109^{\circ}$. This gradual opening of the O=C-C angle from 119° to about 124° and the Br-C-C angle from 104° to about 109° allows the Br...O separation to remain unchanged at about 3 \AA over a wide range of torsion angles. If the bond angles could not open, then the Br-C-C=O torsion angle could never become zero; the large van der Waals repulsion between Br and O would prevent it.

Under these conditions, there can be no simple linear

correlation between the observed Br—C—C=O torsion angle and the Br...O separation. Although the Br...O separation and the Br—C—C=O torsion angle must somehow be related, it follows from the comments about the data in Figure 2 and the various conformers in Figure 1, structures 2–7, that there is no unique conformation for a particular Br...O distance or Br—C—C=O torsion angle in an α -bromocyclohexanone ring.

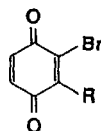
SURVEY OF THE LITERATURE

A search was made of the Cambridge Data File for the crystal structures of all compounds containing the grouping:



Tables 2–4 list the parameters a , b , c , Θ_1 , Θ_2 , d and ϕ (defined in the earlier structure shown) and the code name in the Data File for each structure whose atoms' positional parameters have been recorded. The observed Br...O separations are plotted against the Br—C—C=O torsion angles for these bromoketones in Figure 3. There are three distinct groups of compounds for which data are recorded, as follows.

Quinonoids



The quinonoids are shown in Figure 3 as Δ . In all cases they have Br...O separations close to 3.0 Å with a

small torsion angle of 6° or less. The mean Br—C(sp²) length is 1.89 Å and the Br—C—C angle is (naturally) opened to a mean of 116°, corresponding to the sp² hybridization. There are also a few compounds with 2-bromocyclohex-2-enone rings. In these rings, the C-1, -2, -3, -4 and -6 atoms and the O and Br atoms are close to coplanar with C-5 standing above the plane, thus giving a half-chair or couch conformation. Where atoms C-5 and either C-4 or C-6 are part of the *trans* ring fusion, the ring is very rigid and the C—Br and C=O groups are constrained to be coplanar.

Bromocamphors

Bromocamphors, which are shown in Figure 3 as \square , have Br...O between 3.20 and 3.33 Å, well separate from all the other compounds (the majority of the data are from structures containing 3-bromocamphor-sulphonate, where it has been used as a 'heavy atom' to give the absolute configuration of the compound). The line C through the points is given by equation (1) with the mean parameters $a = 1.20$, $b = 1.96$, $c = 1.52$ Å, $\Theta_1 = 126$ and $\Theta_2 = 110$ °. The range of Br...O distances is small, 0.13 Å, while the range of the Br—C—C=O torsion angle ϕ is about 23°. This remarkably large range of ϕ for the same moiety indicates that the energy required to change the torsion angle of the Br—C—C=O system is relatively small, i.e. the potential energy well is a broad, flat dish for this torsional motion.

The bond angles O=C—C and Br—C—C in the bromocamphors are greatly increased (126° from 120°, 110° from 105°, respectively) because the methylene bridge pulls C-1 and C-4 closer together than would be the case in the ideal boat without the bridging carbon atom. As C-1 and C-4 are forced towards each other, the substituents at C-2 and C-3 move away from each other, thus opening the O=C—C and Br—C—C angles over what would be observed in an unstrained

Table 2. Molecular parameters for compounds with a quinonoid structure^a

ϕ (°)	d (Å)	C=O (Å)	C—Br (Å)	C—C (Å)	O=C—C (°)	Br—C—C (°)	Name
0	2.99	1.20	1.88	1.46	121	117	DBANTQ
1	3.06	1.29	1.89	1.37	125	118	BANAPQ
1	3.05	1.22	1.91	1.40	124	118	BRMNQ
1	3.08	1.20	1.89	1.46	125	117	BRMNPQ
2	3.04	1.24	1.89	1.42	124	117	BANAQP
2	3.06	1.25	1.89	1.39	126	117	BANQMO
4	3.00	1.19	1.87	1.48	122	116	BRNAPQ
4	2.98	1.17	1.91	1.51	123	112	DBRNPQ
5	2.98	1.19	1.90	1.54	122	112	DBANTQ
5	3.02	1.24	1.87	1.43	121	119	DBRBZQ
6	2.83	1.15	1.86	1.45	124	110	TBBENQ
Mean	3.01	1.21	1.89	1.45	123	116	

^a Mean values of the parameters are given at the bottoms of the columns.

Table 3. Molecular parameters for compounds containing the camphor ring system

ϕ ($^{\circ}$)	d (\AA)	C=O (\AA)	C-Br (\AA)	C-C (\AA)	O=C-C ($^{\circ}$)	Br-C-C ($^{\circ}$)	Name
11	3.13	1.20	1.89	1.51	131	113	BBMNBO
13	3.10	1.18	1.89	1.50	126	115	BBMNBO (bridgehead)
21	3.15	1.25	1.93	1.48	127	114	TMBNBO
41	3.23	1.20	1.92	1.54	127	113	BRCMPH
46	3.23	1.22	1.93	1.49	126	113	TBRCAM
47	3.24	1.20	1.99	1.55	127	109	ENCOBC
48	3.27	1.18	1.95	1.51	126	113	ETBCAM
48	3.26	1.20	1.95	1.50	127	112	MEANBC
49	3.22	1.20	1.94	1.47	127	112	CLDRMY
53	3.29	1.21	1.95	1.52	127	111	BIFNUZ
54	3.25	1.18	1.96	1.54	126	110	BOFTOF
55	3.20	1.19	1.95	1.53	129	105	ENPTCA
57	3.32	1.20	1.99	1.55	126	110	RTUSMN
60	3.33	1.18	1.93	1.60	124	111	ENCOBC
61	3.31	1.30	1.91	1.40	124	115	ENPTCA
64	3.31	1.23	2.07	1.46	126	107	CLDRMY
Mean ^a	3.26	1.20	1.96	1.52	126	110	
Mean ^b	3.13	—	—	—	128	114	
Mean ^c	3.24	—	—	—	127	112	
Mean ^d	3.28	—	—	—	126	110	

^a Mean values for torsion angles between 41° and 64° .^b Mean values for the first three compounds (torsion angles, 11° , 13° and 21°).^c Mean values for torsion angles between 45° and 50° .^d Mean values for torsion angles between 50° and 65° .Table 4. Molecular parameters for all other compounds containing an α -bromocyclohexanone ring system

ϕ ($^{\circ}$)	d (\AA)	C=O (\AA)	C-Br (\AA)	C-C (\AA)	O=C-C ($^{\circ}$)	Br-C-C ($^{\circ}$)	Name
0	3.02	1.22	1.88	1.50	121	116	BAGTIM
0	3.18	1.17	1.90	1.45	128	119	BLUMSA
1	3.01	1.25	1.95	1.52	121	113	BRDEOC
1	3.03	1.22	1.89	1.52	124	114	BRFUSO
1	3.01	1.18	1.95	1.50	126	111	BRSANU
2	3.01	1.22	1.97	1.53	125	110	ABAXES
2	3.05	1.21	1.88	1.46	124	116	BAZCUA
2	3.05	1.20	1.87	1.51	121	117	BREBSA
3	3.02	1.14	1.92	1.53	122	114	BRSANT
3	2.99	1.21	1.89	1.48	120	116	BRSATO
3	3.08	1.26	1.89	1.52	123	115	BPDEDO
3	2.98	1.19	1.95	1.53	119	113	BHPULG
3	2.96	1.15	1.91	1.52	127	109	BRARBO
3	3.04	1.22	1.86	1.48	124	116	BRFUSO
4	3.06	1.21	1.87	1.49	123	116	BAZCUA
4	3.16	1.21	1.90	1.47	127	118	BOVVOX
4	3.04	1.21	1.90	1.48	123	116	BREASA
5	3.02	1.24	1.90	1.45	123	115	BAUSTD
5	2.99	1.15	1.88	1.59	123	111	BRMECH
6	2.94	1.16	1.93	1.55	121	111	BABDUD
6	2.96	1.23	1.92	1.53	121	111	KBHISB
6	3.00	1.20	1.96	1.48	128	109	DBMECH

(Continued)

Table 4. (Continued)

ϕ (°)	d (Å)	C=O (Å)	C—Br (Å)	C—C (Å)	O=C—C (°)	Br—C—C (°)	Name
6	2.97	1.20	1.96	1.55	122	110	DBMECH
6	3.02	1.21	1.96	1.46	129	110	MBXKAN
7	2.98	1.21	1.96	1.50	125	110	BCTCDO
8	2.94	1.22	1.91	1.43	119	116	BAUSTD
10	3.03	1.18	1.94	1.53	123	113	NPATOL
11	3.05	1.23	1.90	1.45	123	116	BAUSTD
13	3.03	1.28	1.93	1.57	120	112	BKHBZP
14	3.07	1.23	1.91	1.40	126	117	BAUSTD
14	3.01	1.25	2.01	1.50	115	116	BRHSNT
14	2.98	1.16	1.95	1.56	122	110	BRMENO
15	2.94	1.21	1.92	1.54	124	108	BIZYOY
16	3.00	1.22	1.88	1.60	116	115	DBDCCH
17	3.01	1.22	1.93	1.49	123	113	BBAXES
18	2.93	1.21	1.96	1.50	121	109	BMNHXO
20	3.05	1.24	1.93	1.50	122	113	EPCDBK
29	2.99	1.16	1.92	1.48	127	108	BABDUD
30	3.02	1.24	1.98	1.47	123	110	BMNOPO
36	3.02	1.21	1.97	1.53	123	107	OACBRT
40	3.06	1.22	1.90	1.34	123	116	DBDCCH
54	3.06	1.20	1.98	1.51	119	107	BPHCYB
57	3.18	1.20	1.95	1.55	122	107	BIJROB ^a
60	3.20	1.20	1.94	1.55	122	108	BIJROB ^a
61	3.19	1.23	1.95	1.48	123	108	PAFLEB
68	3.25	1.16	1.97	1.55	118	108	DBPINO
75	3.27	1.16	2.03	1.53	126	101	DBPINO
75	3.33	1.21	1.89	1.50	120	112	BRNOHA
82	3.33	1.21	1.99	1.52	120	104	BTCYDO
82	3.26	1.20	1.97	1.50	122	102	OPODCP
83	3.25	1.22	1.93	1.55	121	100	BPHCYB
84	3.36	1.19	1.99	1.52	120	105	DBCYOC
85	3.38	1.19	2.00	1.53	121	105	DBCYOC
85	3.35	1.19	1.98	1.56	117	105	BMHINO
85	3.35	1.21	1.99	1.54	120	109	BTCYDO
87	3.39	1.21	1.99	1.51	118	106	DBCYOC
88	3.43	1.21	1.99	1.47	122	107	DBCYOC
89	3.45	1.21	1.99	1.50	121	107	BTCYDO
90	3.46	1.21	1.97	1.51	121	107	BTCYDO
91	3.41	1.14	1.92	1.66	118	104	BANNEJ
92	3.42	1.19	1.98	1.59	119	103	BROHXN
95	3.35	1.22	1.94	1.55	120	99	BOXTOT
95	3.50	1.21	1.99	1.50	121	106	BMNHXO
97	3.43	1.23	1.97	1.53	118	102	BEMOTD
97	3.42	1.24	1.99	1.50	116	103	BKHBZP
98	3.53	1.22	1.96	1.52	120	107	BHMOIN
99	3.49	1.21	1.98	1.53	120	103	BANNAF
121	3.72	1.22	2.03	1.53	121	102	BOANDR
131	3.80	1.16	1.98	1.57	123	106	BRMENO
Mean ^b	3.02	1.21	1.92	1.50	123	113	
Mean ^c	3.40	1.20	1.97	1.53	120	105	

^a Bicyclo[2.2.2]octane.^b Mean values of parameters for ϕ up to 30°.^c Mean values of parameters for ϕ above 60°.

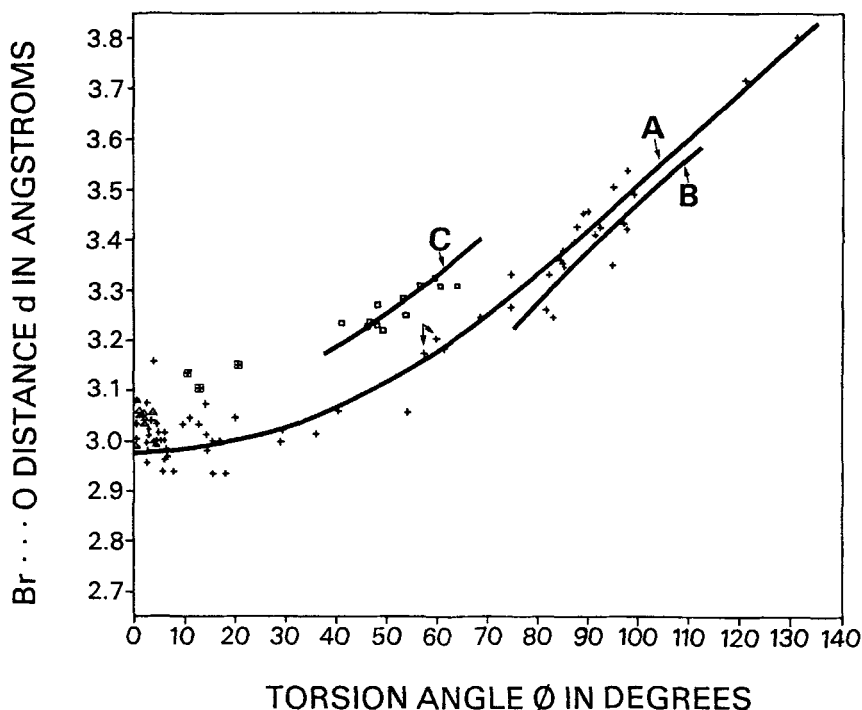


Figure 3. Plot of the Br...O separations and related torsion angles observed in crystal structures in the Cambridge Data File (see Tables 2-4). There are three distinct groups: bromo-substituted quinonoids, plotted as \square ; bromocamphorsulphonates, plotted as Δ ; and all other compounds containing an α -bromocyclohexanone ring systems, plotted as $+$. Curve C is defined by equation (1) with the parameters $C=O = 1.20 \text{ \AA}$, $C-Br = 1.96 \text{ \AA}$, $C-C = 1.52 \text{ \AA}$, $O=C-C = 126^\circ$, $Br-C-C = 110^\circ$ (average values, see Table 3). Curve B corresponds to the curve deduced for the data in Figure 2. Curve A is defined by the equation $d^2 = R - S \cos \phi + T \cos^2 \phi$, where $d = \text{Br}\cdots\text{O}$ distance, $\phi = \text{Br}-C-C=O$ torsion angle and R, S and T are constants defined by hand fitting the equation to the observed d values at $\phi = 0^\circ, 60^\circ, 90^\circ$ and 120° : $R = 11.73$, $S = 3.62$, $T = 0.75$. One molecule is a bicyclo[2,2,2]octane; its Br/O parameters are indicated by arrows. The three points (\oplus) with the shortest Br...O separation ($3.10\text{--}3.15 \text{ \AA}$) correspond to a camphor with a bridgehead bromine atom (bromine 'bowsprit') and are not included in the averaging in Table 3

cyclohexanone system in the boat conformation. The opening of the $Br-C-C$ and $O=C-C$ bond angles in this case is mainly a result of the innate strain within the ring system and is not caused by compression of the van der Waals radii of the Br and O atoms. In fact, the mean Br...O separation of 3.26 \AA is little different from the sum of the usual Br and O van der Waals radii.

A more detailed analysis of the data in Table 3 shows that there are three subgroups whose mean $Br-C-C$ and $O=C-C$ angles differ slightly but consistently: the bridgehead group, the camphors with ϕ between 45° and 50° and the camphors with ϕ between 53° and 64° . As the torsion angle ϕ increases, the angles $O=C-C$ and $Br-C-C$ gradually close; as ϕ decreases so the increasing Br...O compression opens the angles. This is

a *small* energy effect, but it is real and internally self-consistent.

The norbornane (bicyclo[2.2.1]heptane) system is a standard in the field of *molecular mechanics*,¹⁷ and the calculations are able to reproduce the observed very small angle of 94° at the bridging carbon, as well as the reduced 103° angles at C-2 and C-3 of the cyclohexane boat moiety.¹⁸ Calculation of the geometry of α -bromocamphor with the commercial program *ALCHEMY II*¹⁹ reproduced within 2° and 0.02 \AA the angles and distances actually observed, except for the $Br-C-C=O$ torsion angle, which always calculated close to 60° with the Br...O distance of 3.32 \AA . The smaller torsion angles close to 40° with the concomitant Br...O separations of about 3.25 \AA could not be attained. One may conclude that these observed confor-

mations of slightly higher energy are due to packing forces in the crystal.²⁰

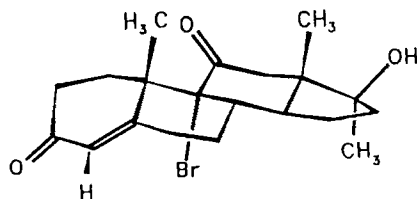
All others

The third group includes all other compounds where the Br atom is bonded to a tetrahedral sp^3 -hybridized carbon atom. These structural data are shown in Figure 3 as +. Curve B, corresponding to the calculated curve in Figure 2, falls close to but slightly below the data for the observed values of ϕ between 50 and 100°. There is clearly a relationship between d and ϕ over all values of ϕ from 0 to 120° and it must approximate the form of equation (1) for large ϕ , but give a larger d for small ϕ . The difference arises from compression and angle strain, and as these energies of deformation are of the form $E_\Theta = k(\Delta\Theta)^2$,¹⁶ it seems that a relationship between d and Θ should include a squared term. As the form of equation (1) is $d^2 = A - B \cos \phi$, the new equation will be:

$$d^2 = R - S \cos \phi + T \cos^2 \phi \quad (2)$$

This function is shown as line A in Figure 3 for $R = 11.73$, $S = 3.62$ and $T = 0.75$. The values of R , S and T were derived by fitting the curve to the appropriate average d ; at $\phi = 90^\circ$ for $R = 11.73$ ($d = 3.43 \text{ \AA}$); at $\phi = 0^\circ$ to give the approximate difference between S and T ; and at $\phi = 60$ and 120° to give separate values of S and T and hence the ratio S/T . Equation (2) was then evaluated, for different values over a small range of S and T (S between 3.5 and 3.7 and T between 0.6 and 0.9) until the curve best fitted the observed data for $\phi = 0-20^\circ$ and $\phi = 110-130^\circ$.

There are only a few examples with a large Br...O separation (over 3.4 Å) and an accompanying Br-C-C=O torsion angle exceeding 90°, corresponding to a conformation with the bromine atom axial. Where the bromine atom is axial, either the ring is distinctly flattened with ring torsion angles considerably smaller than 60° (e.g. compound BANNAF in Table 4) or the bromine is at a bridgehead of the fusion of the cyclohexanone ring and another six-membered ring (e.g. compound BOANDR in Table 4 and below).



One molecule contains a bicyclo[2.2.2]octanone skeleton, 3,3-dibromobicyclo[2.2.2]octan-2'-one (BIJROB in Table 2), marked with arrows in Figure 3). The Br...O separations and Br-C-C=O torsion

angles fit very well curve A, the general relationship for unstrained ring systems. The six-membered rings are almost perfect boats (with one C-CH₂-CH₂-C torsion angle = 10°) but there is no bad angle strain because atoms C-1 and C-4 are not forced together owing to the bridge being two-atom in this case. The bicyclo[2.2.2]octane system is known to be flexible, with a low barrier to pseudo-rotation resulting in a dynamic equilibrium in solution at room temperature. The lowest (shallow) energy minimum corresponds to a C-CH₂-CH₂-C torsion angle of about 12°. ^{11a,b,k} By taking up this conformation the molecule effectively minimizes its volume and, in keeping with the principle of maximum close-packing,^{16,20} this conformation is indeed observed in the crystal.²¹

DISTRIBUTION OF Br...O SEPARATIONS

In a review of molecular interactions in crystal structures, Murray-Rust²² reported over 200 Br...O separations and gave a bar graph of their distribution (see Figure 4). These data include both intra- and intermolecular contacts and, as is pointed out, there are very few of less than 3.0 Å, (only seven examples were given) and no significant peak at any interatomic separation, although Br...O separations between 3.2 and 3.3 Å were far more common than the shorter ones.

The data from Tables 1-4 are presented as a bar graph in Figure 5. The distribution of d values differs

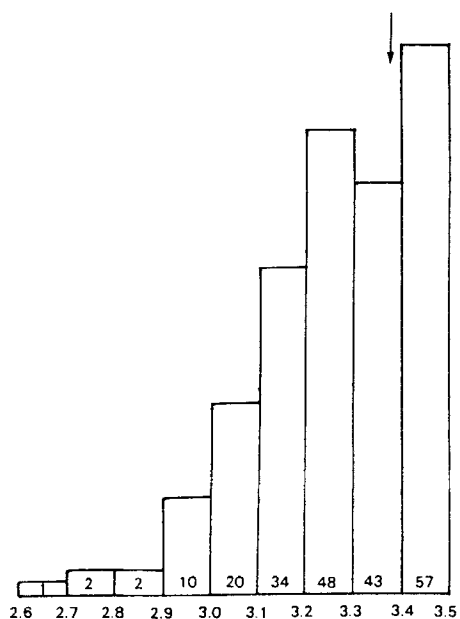


Figure 4. Distribution of Br...O contacts less than 3.5 Å in organic crystals. The arrow indicates the sum of the van der Waals radii. (Taken from Reference 22, p. 168, Figure 6)

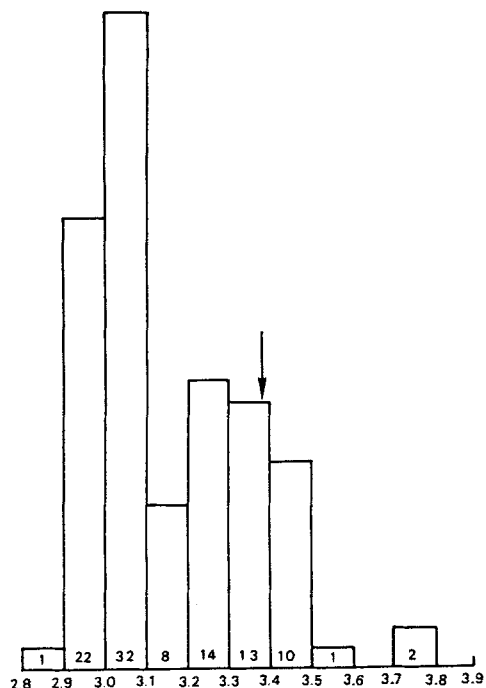


Figure 5. Distribution of intramolecular Br...O separations from the data in Tables 1-4. The number of contacts in each range is given at the base of the column. To allow easy comparison, the arrow is at the same position as chosen by Murray-Rust,²² see Figure 4. There are clearly two populations: those with Br...O \approx 3.0 Å, corresponding to an equatorial bromine that eclipses the C=O bond, and those with Br...O \approx 3.4 Å, corresponding to a bromine that is approximately axial in character, and does not eclipse the C=O group. The relatively large number of Br...O separations of 3.1 and 3.2 Å is an indication that twist-ring systems are more common than they are usually thought to be

markedly from that presented in Figure 4. There is a distinct peak near 3.0 Å (partly due to the bromoquinone compounds) and a second at about 3.3 Å (mainly due to the camphor derivatives). This large number of short intramolecular Br...O separations close to 3.0 Å corresponds to an equatorial position for the bromine atom in a chair conformation or a pseudo-equatorial position on one of the boat or twist-boat conformations of the cyclohexanone ring (see Figure 1, structures 2-7). This implies that in the past there has probably been an over-emphasis of the concept that repulsion between the $\overset{+}{\text{C}}=\overset{+}{\text{O}}$ and $\overset{+}{\text{C}}-\text{Br}$ dipoles would destabilize the chair form of the cyclohexanone ring when the 2-bromo substituent is equatorial and eclipses the C=O group.

CORRELATION WITH SPECTROSCOPIC DATA

If there is a correlation between the carbonyl vibration frequency in the infrared or the absorption wavelength in the ultraviolet, it cannot be linear for both Br...O separation and Br-C-C=O torsion angle, because the relationship between d and ϕ is far from linear (see Figure 3). However, the relationship may be linear for one geometric parameter. The observed data for compounds I-V are plotted against Br...O separation:

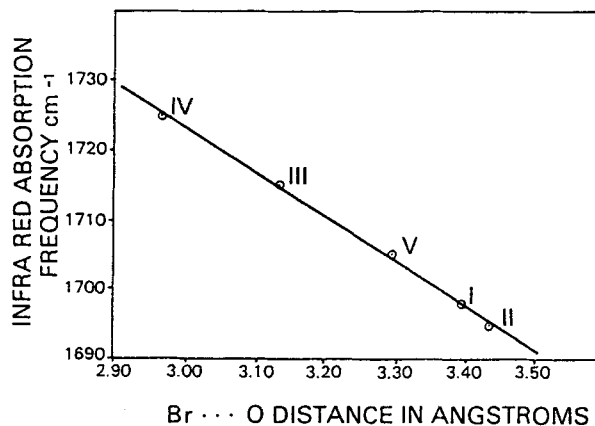


Figure 6. Relationship between the infrared absorption frequency of the keto group and the Br...O distance in the compounds in Refs 14a-e (see Table 1)

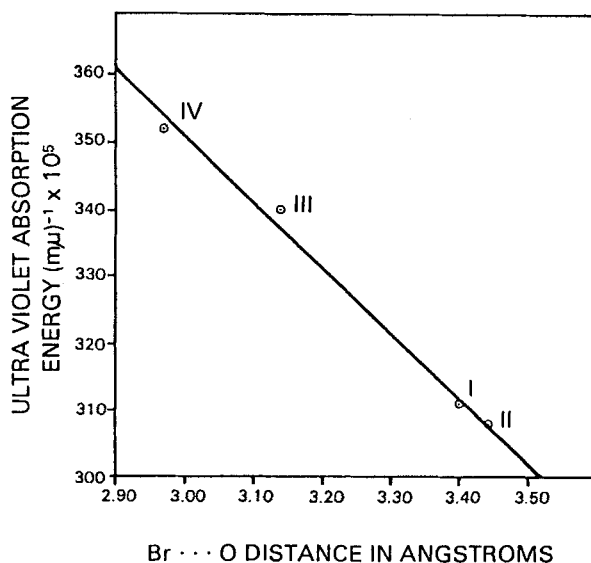


Figure 7. Relationship between the ultraviolet absorption energy of the keto group and the Br...O distance in the compounds listed in Refs 14a-d (see Table 1)

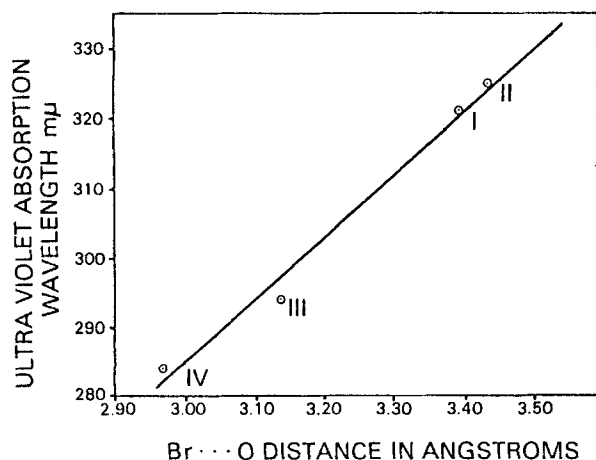


Figure 8. Relationship between the ultraviolet absorption wavelength of the keto group and the Br...O distance in the compounds listed in Refs 14a-d (see Table 1). The relationship is approximately linear because the range of wavelength is small

infrared vibration frequency in Figure 6, ultraviolet absorption energy in Figure 7 and ultraviolet wavelength in Figure 8. The lines joining the points in Figures 6 and 7 are linear, implying that in both cases the influence on the absorption is probably a 'through-space' interaction of the bromine atom with the keto oxygen (and not along the bonds).

IMPLICATION

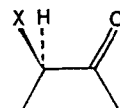
One may conclude that if no other constraints exist on the carbonyl group apart from the proximity of an α -bromine atom (e.g. no conjugation, or close contacts to a phenyl ring) then the shifts in the infrared and ultraviolet frequencies are linearly dependent on the Br...O distance. A high infrared frequency or short wavelength in the ultraviolet would characterize a short Br...O distance and hence a small torsion angle, and conversely a low infrared frequency or long ultraviolet wavelength would imply a large Br...O separation and hence a large torsion angle. This relationship appears to be generally applicable to all compounds containing an α -bromocyclohexanone system.

EXPLANATION OF THE SHIFTS IN THE VIBRATION FREQUENCY AND ULTRAVIOLET ABSORPTION ENERGY OF THE KETO GROUP

If an explanation of the shifts of the infrared and ultraviolet frequencies is to be of any value, then it must simultaneously account for the known effects not only of bromine, but of *all* of the halogens. This implies that

the model must account for both steric 'through-space' and electronic 'through-bond' processes.

In a naive sense, one may expect that substitution of the hydrogen atom α to a keto group by a halogen atom should have an effect on the bonding between the C and O atoms as a result of the change in the inductive effect of the α -substituent. This simple electronic effect would be directly related to the electronegativity of the atom and would be propagated by a 'through-bond polarization' process. Consider the following structure:



If one assumes that the effect of X on the atom O, and hence the C=O bond, is due only to the electronegativity of X, and is solely a 'through-bond' process and unaffected by the 'through-space' X...O distance, then atom X should have the same effect on the characteristics of the C=O group independent of whether its conformation be axial or equatorial.

The values of the spectral characteristics of the keto group in 3-fluoro-2-decalone²³ are given in Table 5. The large electronegativity of the F atom withdraws electrons thus, leading to a Δ^+ on the O atom with a resulting increase in C-O bond order and the C=O vibration frequency, and the effect is similar for both axial and equatorial substitution (Figure 9).

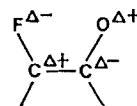


Figure 9. Relative charge distribution when the α -substituted halogen is fluorine

If this model is correct, then one would expect the effect on the vibration frequency of the C=O group to decrease as the electronegativity of the halogen decreases, i.e. going from F to Cl to Br. This indeed is

Table 5. IR and UV characteristics of the keto group in 3-fluoro-2-decalone²³

Compound	IR, ν (cm^{-1})	UV, λ_{max} (nm) ^a
Parent	1713	290(26)
Axial F	1729	300(48)
Equatorial F	1737	288(30)

^a Molar absorptivity (ϵ , $1 \text{ mol}^{-1} \text{ cm}^{-1}$) in parentheses.

Table 6. IR and UV characteristics of the keto group in axial 3-halo-2-decalones²³

Compound	IR, ν (cm ⁻¹)	UV, λ_{\max} (nm) ^a
Parent	1713	290(26)
Axial F	1729	300(48)
Axial Cl	1720	304(69)
Axial Br	1713	311(155)

^a Molar absorptivity (ϵ , l mol⁻¹ cm⁻¹) in parentheses.

true for the halogens in the axial position, as shown by the data in Table 6.²³

The trend of the ultraviolet absorption shows that a decrease in electronegativity corresponds to a larger value for λ_{\max} , i.e. to a decrease in the energy associated with this absorption. These trends show that two different electronic processes are simultaneously involved. One affects the bond order of the C=O group in the ground state and thus causes the shifts in the vibration frequency of the C=O group. The other must affect the energy gap between the filled bonding molecular orbital of highest energy (HOMO) of the C=O group and its empty antibonding orbital of lowest energy (LUMO), thus causing the change in λ_{\max} for the UV absorption.

The regular increase in λ_{\max} for the ultraviolet absorption suggests that it is the energy of the π^* C—O antibonding orbital that is decreasing, possibly as a result of interaction of the π^* lobe centred on the sp²-hybridized C atom with an appropriate empty orbital of the halogen atom to give an extended π^* orbital of lower energy.

Cantacuzene and co-workers²⁴ considered the effect on the ring conformation of the α -halocyclohexanone ring by the interaction between the empty π^* molecular orbital on the C=O group and the filled non-bonding p orbital on the axial halogen atom X. They concluded that 'there is better donation from (axial) fluorine into the empty (π^*) orbital of the carbonyl group'. If this explanation were correct, then the π^* orbital would gain electron density from the halogen atom and the net bond order of the C=O group would of necessity decrease, with a resulting decrease in the vibration frequency of the C=O group when the halogen atom is axially substituted. The experimental data shown above contradict this deduction.

THE EQUATORIAL CASE

When the halogen atom, X, is substituted equatorially and the C—X bond eclipses the C=O group, the halogen atom now can interact with the filled non-bonding p orbital on the oxygen atom (see Figure 11). Any changes in the spectroscopic properties of the C=O group with trends that differ from what is found for

axially oriented halogen atoms must therefore be caused by a 'through-space' interaction between the halogen atom and the oxygen atom.

The results for equatorially substituted halogen atoms²³ show that there is a new and different pattern (Table 7). The C=O vibration frequency is now considerably increased for all three halogens, and the difference between the frequencies for fluorine and bromine is smaller, only 7 cm⁻¹ compared with 16 cm⁻¹ for the halogen axial. The influence of the bromine is now larger, relatively, than that of the fluorine.

On the other hand, the energy of the ultraviolet absorption is now highest for the bromine equatorial and least changed for the fluorine equatorial. This is a complete reversal of what was found when the atoms were bonded axially and appears to be a contradiction.

The largest differences are seen for bromine. When it is equatorial it causes a marked increase in vibration frequency, yet it has a negligible effect on the C=O vibration frequency when it is axially placed. This strongly implies that a 'through-space' steric effect has come into play when the bromine is equatorial.

Figure 6 shows the changes in the infrared vibration frequency with change in Br...O separation. The shortest Br...O separation corresponds to the highest frequency of vibration of the C=O group: a short non-bonded Br...O distance strengthens the C=O bond. Simultaneously, this compression of the O atom by the Br atom increases the energy associated with the absorption of UV radiation (see Figure 7). These two effects are not simply related, as reference to the molecular orbitals in the energy level diagram in Figure 10 shows.

The electronic absorption of a keto group in the UV region is normally ascribed²⁵ to an n \rightarrow π^* transition, the excitation of an electron from a non-bonded p orbital centred on the O atom to the empty π^* antibonding molecular orbital associated with the C=O group (shown as NBp \rightarrow π^* in Figure 10). Hence the frequency of the UV absorption is determined by the NBp \rightarrow π^* energy gap (the $\pi \rightarrow \pi^*$ transition is of considerably higher energy and falls outside the scope of the present discussion).

The infrared absorption frequency is determined by

Table 7. IR and UV characteristics of the keto group in equatorial 3-halo-2-decalones²³

Compound	IR, ν (cm ⁻¹)	UV, λ_{\max} (nm) ^a
Parent	1713	290(26)
Equatorial F	1737	288(30)
Equatorial Cl	1733	282(38)
Equatorial Br	1730	276(85)

^a Molar absorptivity (ϵ , l mol⁻¹ cm⁻¹) in parentheses.

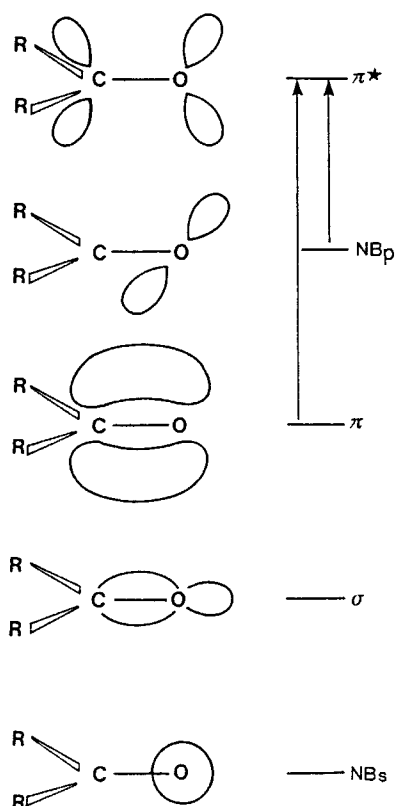


Figure 10. Energy levels for the carbonyl group. The shapes of the orbitals are shown schematically on the left and the order of energy levels is indicated on the right. The NBs orbital is essentially the 2s atomic orbital of the oxygen atom; the σ and π orbitals hold the C and O atoms of the CO group together and control its stretching frequency; the NBp orbital is essentially the 2p atomic orbital of the oxygen atom and is the filled orbital of highest energy. The π^* orbital is the empty molecular orbital of lowest energy. The energy gap from NBp to π^* corresponds to the lowest energy absorption in the ultraviolet region

the strength of the C=O bond, i.e. the bond order resulting from the sum of the σ and π bonds. Therefore, to explain the effects of the equatorial substitution of a bromine atom α to the keto group, these two apparently independent aspects of bonding must be reconciled.

There have been several molecular orbital treatments of the bonding in both open-chain and cyclic ketones of varying degree of complexity,²⁶ concentrating on different aspects such as the red shift induced by an axially substituted bromine atom,^{26a} the shifts of the ^{13}C NMR signals^{26b} and the conformation of the systems adjacent to the carbonyl group.^{26c} As many as four different electronic and orbital interactions have been considered to be taking place simultaneously, making it very difficult to visualize what is occurring to

the electrons and orbitals which are involved in the (generally accepted) $n \rightarrow \pi^*$ transition.²⁵

What is offered here is a simplistic model based on the treatments of the bonding in the H_2O ²⁷ and CO ²⁸ molecules which rest upon the large difference in energy between the 2s and 2p orbitals on the O atom. Assume that the oxygen 2s orbital is not initially involved in the bonding between the C and O atoms in the unsubstituted cyclohexanone ring. The one non-bonded pair of electrons on the O atom is thus in a simple atomic 2s orbital, whereas the second is in the atomic 2p orbital. The 2s pair are strongly held and the 2p pair, being considerably higher in energy, are therefore more easily excited. These two atomic orbitals are shown in Figure 10 as NBp and NBs. This large energy difference of about 800 kJ mol^{-1} (Ref. 29) militates against hybridization.

When the Br atom is equatorial, this 2p orbital containing the non-bonded pair of electrons on the oxygen lies in the plane of the Br-C-C=O moiety, and the lobes of this 2p orbital are perpendicular to the C=O bond. As a result, its electron density 'overlaps' with that of the Br atom, as shown in Figure 11(a). This is energetically unfavourable, because it amounts to the

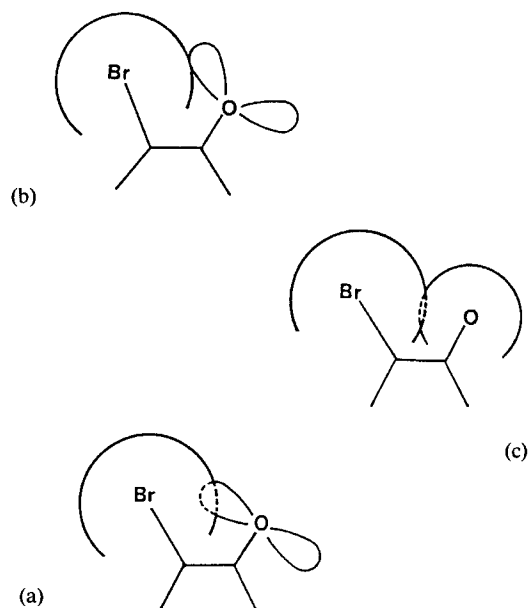


Figure 11. (a) Schematic diagram showing how the idealized atomic 2p orbital on the oxygen atom would penetrate the bromine atom's van der Waals surface. (b) Schematic diagram showing orbitals of idealized sp^2 geometry on the oxygen atom, and how they can better avoid the bromine atom. (c) Schematic diagram showing the overlap of the van der Waals radii of the O and Br atoms that must occur at $\phi \approx 50^\circ$ if the internal Br-C-C and O=C-C angles did not open to relieve the compression strain

interpenetration of van der Waals radii of the bromine and oxygen atoms [see Figure 17(c)], which is equivalent to contradicting the Pauli exclusion principle and hence is quantum mechanically not allowed. That the interaction between the O atom and the equatorially substituted Br atom cannot be attractive and must be repulsive is well shown in Figure 3 by the constancy of the Br...O separation for the torsion angles ϕ less than 50° . The Br and O atoms can be compressed no further, and the strain that results as ϕ drops to zero is taken up in opening the C—C—Br and the C—C=O bond angles.

As a result, the lobe on the oxygen atom will 'bend' out and away to minimize the compression strain. As the angle (lobe of 2p orbital)—O—C increases from 90° towards 120° , so the hybridization between this 2p orbital and the 2s orbital on the O atom becomes more and more favoured until it approaches the sp^2 state. [Figure 11(b)]. This now yields three sp^2 hybrid orbitals, one of which will be involved in bonding to the C atom, while the other two are 'non-bonding'. Thus the σ bond between the C and O atoms is no longer (sp^2)C—O(p) but now approaches (sp^2)C—O(sp^2). This change in hybridization on the O atom results in a concomitant increase in the strength of the C—O σ bond as a result of the enhanced overlap of the orbitals.³⁰ Hence the pressure of the Br atom on the O atom causes an increase in the C—O σ bond strength and hence will result in an increase of the C—O vibration frequency in the infrared relative to that of the C=O group in the parent compound.

This change in hybridization of the O atom simultaneously causes a lowering of the energy of the non-bonding sp^2 orbital below that of the original unhybridized atomic p orbital. This in turn results in a larger NBP $\rightarrow \pi^*$ energy gap, and hence a decrease in the wavelength of the UV absorption maximum. Hence this simple model simultaneously accounts for both the increase in the infrared vibration frequency and the

increase in the ultraviolet absorption wavenumber for the case where the bromine is equatorial and exerts significant compression strain on the oxygen of the keto group.

If the model is correct, then the trend that will be observed for changes in the axial atom will be controlled by its electronegativity (i.e. the degree of electronic 'hardness' or 'softness' of the atom). On the other hand, when the atom is equatorial, the bulk (or van der Waals size) of the atom will dictate the effect on the ultraviolet and infrared absorption of the C=O group. This implies that the atom which is 'softest' will yield the longest λ_{\max} in the ultraviolet, for the axially substituted case, while the largest atom will yield the shortest λ_{\max} for the equatorially substituted case, i.e. axial effects on the spectroscopic properties of the C=O group are primarily electronic and inductive, whereas equatorial effects are primarily steric.

These predictions can be tested by examining the influence of the iodine atom on the spectroscopic absorption by the carbonyl group. The pertinent electronegativities and van der Waals radii²⁹ of the atoms are as follows: F, 4.0, 1.35 Å; Cl, 3.0, 1.80 Å; Br, 2.8, 1.95 Å; I, 2.5, 2.15 Å; and H, 2.1, 1.20 Å. These data, taken together with the bonding model, lead to the following predictions. For an iodine atom equatorial, the vibration frequency of the C=O group should be lower than found for the bromine atom equatorial but higher than in the parent, while the λ_{\max} of the UVn $\rightarrow \pi^*$ transition should be shorter than in the bromine analogue, i.e. the energy will be higher.

One might expect that the large size of the iodine atom would probably prevent it from occupying an axial position on an ideal chair, but it could easily take up a pseudo-axial position (with an I—C—C=O torsion angle of about 90°) if the cyclohexanone ring were a twist-boat. Under these conditions, λ_{\max} will be longer than for the bromo analogue, and the vibration frequency will be lower than for the bromoketone.

Table 8. Spectroscopic data for brominated derivatives of cholestan-3-one, -2-one and lanostan-3-one^{31,1c}

Compound	IR, ν (cm^{-1})	UV, λ_{\max} (nm) ^a	Conformational assignment
Cholestan-3-one	1718	286	—
2 α -Bromcholestan-3-one	1733	282	Equatorial
2 α -Iodocholestan-3-one	1724	258	Equatorial
Cholestan-2-one	1712	280	—
3 α -Bromocholestan-2-one	1715	312	Axial
3 α -Iodocholestan-2-one	1708	na	Axial
Lanostan-3-one	1704	294	—
2 α -Bromolanostan-3-one	1726	289	Equatorial
2 α -Iodolanostan-3-one	1717	261	Equatorial
Lanost-8-en-3-one	1703	288	—
2 α -Bromolanost-8-en-3-one	1728	291	Equatorial
2 α -Iodolanost-8-en-3-one	1721	252	Equatorial

For α -iodocyclohexanone, the large I \cdots O non-bonded repulsion should favour the bulky iodine atom taking up the axial position. This indeed occurs in cyclohexane solution where NMR measurements show that ca 95% of the molecules adopt the conformation with the iodine atom axial, compared with 87% axial for the bromine analogue.²⁴ Although there is a paucity of data for α -iodoketones there are enough examples³¹ to allow an evaluation of the predictions (Table 8).

In all cases, an equatorial iodine causes not only a small but definite increase in the vibration frequency of the C=O group relative to that of the parent ketone, but also a marked decrease in λ_{\max} , i.e. an increase in the energy for the absorption. These results support this simplistic model of a combination of electronic and steric processes which is presented above.

CORRELATION OF SPECTROSCOPIC DATA WITH CONFORMATION

It is important to note that the critical parameter controlling the energies of the infrared and ultraviolet absorption is the non-bonded distance between the bromine and oxygen atoms; i.e. it is the Br \cdots O separation that can be estimated from the IR ν and UV λ_{\max} values. Even more important, as reference to Figure 1 will show, there are several different conformations of the α -bromocyclohexanone ring system which have torsion angles of 0° (corresponding to Br and O eclipsed and a Br \cdots O distance of about 3.0 Å). By the same token, there are several conformers in which the Br—C—C=O torsion angle is 90° or above.

The UV and IR characteristics of the keto group can thus differentiate between the extremes of Br and O close (i.e. Br \cdots O \approx 3.0 Å) (short λ_{\max} , large ν) and Br and O remote (i.e. Br \cdots O \approx 3.3 Å) (long λ_{\max} , small ν), but these results cannot immediately indicate whether the ring is a chair or a boat. Reference to Figure 1, structures 1a and 2a shows that identical Br \cdots O separations and Br—C—C=O torsion angles exist in both ideal chair and ideal boat. However, when the UV and IR results indicate an intermediate value for Br \cdots O (e.g. 3.1 Å), the ring can almost certainly be assigned a twist-boat conformation.

When the spectra indicate either of the extreme Br \cdots O separations, with the implication that the Br atom is either axial or equatorial, presumably with the ring in a chair conformation, not only is it possible that the ring may be a boat (Figure 1, structures 2–4) but in fact it is far more likely that the ring can be a twist-boat.

The twist-boat has several advantages energetically: there is great flexibility, and H/H eclipsing is minimized. In fact, it would be possible for the A ring in a steroid or triterpenoid system to have its α - and β -bromoketo derivatives *both* as twist-boats, with the corresponding UV and IR absorptions indicating either α

and β axial or α and β equatorial. This type of phenomenon will occur where other substituents on the cyclohexanone ring have sufficient steric bulk to prevent the ring taking up an ideal chair conformation.

Some possible examples of this phenomenon are discussed below.

Example 1

Two 2-bromo derivatives of an estran-3-one are known³² (ABAXES and BBAXES in Table 4). The value of the carbonyl stretching frequency was 1702 cm⁻¹ in the parent and 1728 cm⁻¹ in both the α and the β isomers. This implies that both derivatives have the minimum Br \cdots O separation of about 3.0 Å, which in turn implies that the A ring conformation in one will be a chair with the bromine equatorial whereas the other will have to be a boat (i.e. twist-boat) with a Br—C—C=O torsion angle close to zero.

The observed results are that the A ring in the 2 α -bromo compound is a chair, with a Br \cdots O distance of 3.0 Å and a Br—C—C=O torsion angle of 2° (see Figure 5 in Ref. 32), whereas the A ring in the 2 β -bromo compound is a twist-boat, with a Br \cdots O distance of 3.01 Å and a Br—C—C=O torsion angle of 17° (Figure 6 in Ref. 32). This particular conformation is close to the idealized form shown in Figure 1, structure 5a. The A ring cannot take up a chair conformation with the 2 β -bromine axial, because this would result in impossibly severe steric compression between the bromine atom and the axial methyl group on C-9 (the A/B ring fusion is *cis*). The 4 α -bromo compound had $\nu = 1727$ cm⁻¹, indicating again a short Br \cdots O distance (close to 3.0 Å), and hence this bromine atom would also be equatorial and ring A would be a chair.

Example 2

This is the classic case of the products that arise from the bromination of 2 α -methylcholestan-3-one.^{31,33,1c} The data are summarized in Table 9.

It is evident from these data that the Br \cdots O distances are short (about 3.0 Å) for the 2 α -bromo-4 α -methyl-

Table 9. IR and UV characteristics of the keto group in brominated cholestanones

Compound	IR, ν (cm ⁻¹)	UV, λ_{\max} (nm)
2 α -Methylcholestan-3-one	1711	
2 α -Bromocholestan-3-one	1733	
2 α -Bromo-2 β -methyl-(VI)	1712	313
2 β -Bromo-2 α -methyl-(VII)	1714	308
4 α -Bromo-2 α -methyl-(VIII)	1733	285
2 α -Bromo-4 α -methyl-(IX)	1733	
2 α -Bromo-4 α -bromo-	1756	

(IX) and 2α -methyl- 4α -bromo- compounds (VIII), indicating that in both cases the A ring is almost certainly a chair with the bromo and methyl groups equatorial. On the other hand, the spectral properties of the 2β -bromo- 2α -methyl- compound (VII) indicate that the Br...O distance is at least 3.3 Å and that the bromine is axial on an A ring that is probably a chair. The spectral characteristics of the 2α -bromo- 2β -methyl- compound (VI) indicate a maximum Br...O separation of about 3.4 Å i.e. the bromine is 'axial', chair or boat. In their original conclusion, Djerassi *et al.*^{33a} assigned a boat conformation to ring A with the Br axial, i.e. a conformation equivalent to that shown as Figure 1, structure 3b). However, it is far more realistic to assign the energetically more favoured twist-boat conformation to ring A, for example that shown in Figure 1, structure 5b, with the Br—C—C=O torsion angle of 90°, or even twisted as much as in Figure 1, structure 7b, to give a torsion angle of as large as 120°.

Moreover, inspection of a van der Waals radius (CPK) model shows that the 2α -methyl- 2β -bromo-compound also *cannot* have the bromine properly axial with the A ring in a regular chair conformation: the compression of the bromine atom by the methyl group at C-10 is too large. One is now forced to the conclusion that the conformation of the A ring in the 2α -methyl- 2β -bromo- compound could *also* be distorted away from a chair. Examination of a model shows that the likely conformation will lie between a flattened chair, i.e. couch³⁴ and a twist-boat of the form in Figure 1, structure 6b.

Example 3

2-Bromo-3,3,5,5-tetramethylcyclohexanone is used in an exercise for students to show how the UV and IR absorptions of the keto group change with the introduction of an α -bromine atom.^{2,35} The pertinent spectral data are given in Table 10.

The changes in the absorption spectra that result from changing the solvent from polar to non-polar are interpreted in terms of one chair conformation with the bromine axial very rapidly interconverting to a second chair form with the bromine equatorial (see Figures 2 and 3 in Ref. 2). This is physically unfavourable. The parent tetramethylcyclohexanone cannot easily adopt an ideal chair conformation because the 3,5-diaxial pair

of methyl groups would be uncomfortably close together (about 2.5 Å apart). By the same token, an ideal boat with the C=O as bowsprit is not favoured, again because of the significant repulsions between the 3-pseudo-axial and 5-pseudo-axial methyl groups. A chair is, of course, possible if the ring flattens, and the two axial methyl groups bend outwards to give a CH₃...CH₃ separation of about 3.2 Å. This would involve considerable molecular strain.^{35a} It seems, therefore, that in solution each of the two extreme conformations could probably be a twist-boat. The 'twist' conformation moves the methyl groups apart, thus eliminating the 3-CH₃...5-CH₃ repulsions and hence reducing the energy. At the same time, the much increased rotational flexibility of the twist-boat ring system enhances the entropy of the system.

The ease of pseudo-rotation between the ' $\phi = 0^\circ$ ' and ' $\phi = 120^\circ$ ' twist-boat conformers can be shown with both space-filling CPK and Dreiding models. It is evident that a rapid interconversion between the two twist boats is perfectly feasible because of the flexibility of the ring system in the boat and twist-boat conformations, as required by the spectroscopic evidence. One conformation (A) must have the Br...O separation of about 3.4 Å (Br—C—C=O torsion angle between 90° and 120°), whereas the other (B) would have Br...O *ca* 3.0 Å (Br—C—C=O torsion angle between 0 and 30°). The conformation A would approximate Figure 1, structure 6b, whereas B is probably close to (or between) Figure 1, structures 5a and 7a.

This process explains better the observed ease of conversion between the two isomers, while simultaneously fitting the spectroscopic characteristics. This example is probably best summarized by the statement that although the conformation of the cyclohexanone ring in each isomer may well be chair-like in the solid state,^{35c} it is likely that the ring becomes a twist-boat in solution.

It is interesting that Fétizon *et al.*³⁶ deduced from NMR spectroscopy that the parent ketone suffered an 'important deviation from a chair conformation', a conclusion in agreement with those above. The predilection for the flexible boat and twist-boat conformations at higher temperatures is well illustrated in recent x-ray crystal structure determinations of derivatives of bicyclo[3.3.1]nonan-9-one.³⁷ At temperatures between 130 and 145 K both of the six-membered rings are chairs. At room temperature, however, at least one

Table 10. IR and UV characteristics of the keto group in 2-bromo-3,3,5,5-tetramethylcyclohexanone

Compound	IR, ν (cm ⁻¹)	UV, λ_{\max} (nm)
Cyclohexanone	1712	285
3,3,5,5-Tetramethylcyclohexanone	1715	286
2-Bromo-3,3,5,5-tetramethylcyclohexanone	1715 (major), 1730 (minor) 1730 (major), 1715 (minor)	312 (in CCl ₄) 309, 292 (in CH ₃ CN)

becomes a boat, giving a population with the chair-boat conformation at about 25%. Similar results were deduced from a proton NMR study.³⁸

Example 4

The 2-bromo derivatives of lanostan-3-one and lanost-8-en-3-one have been prepared;³⁹ their spectral data are given in Table 11.

Comparison of these data with Figures 6 and 8 shows that the Br...O distances in all cases are close to 3.0 Å. Once again the A ring appears to be a chair with an equatorial bromine for both α - and β - bromo substituents. This is clearly impossible. Ring A for the 2 β -bromo isomers was originally assigned a boat conformation, but inspection of a space-filling (CPK) model shows that an ideal boat is overcrowded, and the true conformation of ring A (with Br...O ca 3.0 Å) is probably a twist-boat of the type shown in Figure 1, structure 7a (with the two methyl groups on site 4).

When lanostan-3-one is treated with an excess of bromine, a 2,2-dibromo compound is formed. The pertinent spectral data are given in Table 11. The intermediate value of 1716 cm⁻¹ for the keto stretching frequency implies that the Br...O separation far exceeds 3.0 Å, but falls significantly short of 3.4 Å. In other words, both Br-C-C=O torsion angles must be intermediate between 30 and 90°, probably close to 60°. The alternative model (as given by Cummins and Page)^{39b} of one bromine axial (Br...O = 3.4 Å, $\phi \approx 100^\circ$) and one bromine equatorial (Br...O = 3.0 Å, ϕ between 0 and 30°) cannot be correct, because the eclipsed Br-C-C=O system alone would afford an IR frequency of about 1730 cm⁻¹ and the addition of the second (axial) bromine would not have a significant effect on the C=O vibration frequency. However, two equatorial bromines (both Br...O $\approx 3.0^\circ$, $\phi \approx 0^\circ$) act in concert and cause a far higher C=O vibration frequency. This effect is clearly seen in the compounds 2-brom-(eq), 2,2-dibromo- (eq, ax) and

2,4-dibromo- (eq, eq) cholestan-3-one, 1733, 1735 and 1756 cm⁻¹, respectively.

The 2,2-dibromolanostan-3-one system is not directly comparable with the cholestan-3-one example because of the pair of *gem*-dimethyl groups at C-4. The possible cyclohexanone conformations are equivalent to Figure 1, structures 4a and 4b, but somewhat distorted towards 5a and 5b by the rigidity at the A/B ring fusion. A good conformation that minimizes all 1,3-non-bonded repulsions between the bromine atoms and methyl groups has the ring atoms C-1 to C-5 approximately coplanar, and is most simply described as a 'couch'.³⁴ The two Br-C-C=O torsion angles of about 60° and the corresponding Br...O distances of 3.2 Å suggest that the C=O vibration frequency should be considerably higher than the observed value of 1716 cm⁻¹, which is unusually low. This apparent anomaly appears to be due to the two methyl groups having simultaneously an inductive 'through-bond' effect on the electrons of the C=O bond in addition to a steric influence on the precise conformation of the cyclohexanone ring system. The depression of the C=O vibration frequency by the presence of a *gem*-dimethyl pair is clearly shown in the difference between the observed values in cholestan-3-one (1718 cm⁻¹) and lanostan-3-one (1704 cm⁻¹). A similar phenomenon is also seen in compounds VI and VII in Example 2 above.

There have been many applications of ¹³C NMR spectroscopy to the elucidation of molecular structure. Two in particular are germane to the present discussion. One^{40a} comments specifically about the difficulty of deducing correctly the conformation of twist conformers because of the flexibility of the rings. The second, about steroids,^{40b} comments that NMR data for bromo-steroids have rarely been reported. Their results show that substitution by bromine on C-2 causes a noticeable change in chemical shift, but that the difference between axial and equatorial substitution is small.

Table 11. IR and UV characteristics of the keto group in brominated lanostan-3-ones and lanost-8-en-3-ones^{1c}

Compound	IR, ν (cm ⁻¹)	UV, λ_{\max} (nm) ^a
Lanostan-3-one	1704	294
2 α -Bromolanostan-3-one	1726	289
2 β -Bromolanostan-3-one	1732	285
Lanost-8-en-3-one	1703	288
2 α -Bromolanost-8-en-3-one	1728	291
2 β -Bromolanost-8-en-3-one	1734	282
2,2-Dibromolanostan-3-one	1716	
Cholestan-3-one	1718	
2-Bromocholestan-3-one	1733	(Equatorial)
2,2-Dibromocholestan-3-one	1735	(Equatorial, axial)
2,4-Dibromocholestan-3-one	1756	(Diequatorial)

CONCLUSIONS

Both the infrared and ultraviolet spectral frequencies of the keto group in α -bromocyclohexanone systems correlate well with the non-bonded Br...O distance. The correlation is linear over the full 0.6 Å range of the Br...O distance, from 'axial' to 'equatorial' bromine: the values of λ_{\max} in the ultraviolet region span 40 nm and the values of ν in the infrared region span 30 cm^{-1} .

If the cyclohexanone ring is known to be a chair, then the spectral frequencies can indicate unequivocally whether the bromine atom is axial or equatorial.

Because the same pair of extreme Br...O separations (3.0 and 3.6 Å, corresponding to torsion angles of 0° and 120°) are found in both ideal chair and ideal boat conformations, it is not possible to decide whether or not either a boat or a chair conformation is present if only extreme values of the spectral frequencies are observed.

If intermediate values for the infrared and ultraviolet absorption frequencies are observed, they indicate that the Br...O separation will have an intermediate value, thus implying a torsion angle between about 30° and 90°. This can only be true for the boat-like conformations, which implies that a twist-boat is probably present. Twist-boats, in fact, are favoured.

If the estimated value of the Br...O separation and hence the derived value of the Br-C-C=O torsion angle are used in conjunction with space-filling (CPK; Leybold) and framework (Dreiding; FMM) models, it is possible to derive with confidence the actual conformation of the cyclohexanone ring system.

Finally, these results emphasize the value of recording both the frequency of the vibration of the C=O group in the infrared and the wavelength of the absorption of the C=O group in the ultraviolet region for a compound containing an α -bromocyclohexanone ring. These simple measurements can immediately yield valuable information about the Br...O separation, and hence also about the conformation of the six-membered ring.

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