Chiroptical Studies. Part 98.[1] The Short-wavelength Circular Dichroism of Ketones in 2,2,2-Trifluoroethanol

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C.d. curves in the range 205—185 nm for a series of 67 chiral ketones, in 2,2,2-trifluoroethanol (TFE) as solvent, show marked differences from those in hexane. A red-shift of the c.d. maximum, averaging 7 nm, is normally accompanied by a significant change in $\Delta\varepsilon$, or in many cases by an inversion of its sign. The values of $\Delta\varepsilon$ in TFE are analysed in the usual empirical way to derive 'group increments' ($\delta\Delta\varepsilon$) which can be used to calculate $\Delta\varepsilon$ for *trans*-decalones and their extended polycyclic derivatives in TFE.

It is suggested that c.d. curves previously reported for the same ketones in hexane may result from super-imposition of two absorption bands. One is presumed to derive from the $n \longrightarrow \sigma^*$ (or $n \longrightarrow 3s$) transition, which would be blue-shifted in TFE to beyond the range of observation with the available instruments, exposing the red-shifted component which has not been assigned, but which appears to derive from a transition not previously recognised. An attempt is made to derive the separate c.d. characteristics of the two transitions by comparing the values of $\Delta\varepsilon$ in TFE with those in hexane.

OUR empirical analysis of c.d. data in the region 185—200 nm for chiral ketones in hexane solution [2] revealed c.d.–structure relationships which differ significantly from those at *ca.* 290 nm ($n\to\pi^*$ transition).[3] Two features of that earlier work suggested that further study would be desirable.

(i) C.d. data for compounds of the 'all-*trans*' extended decalone type, with structures including up to four 6-membered rings, seemed best interpreted empirically on the basis of a novel kind of octant rule in which the two natural symmetry planes of the carbonyl group are supplemented by a third sector boundary surface some 3—4 Å behind the carbon atom of the carbonyl group. Structural features in front of that surface (*i.e.* closer to the carbonyl group) generally exhibit octant-consignate behaviour, while any rings behind the surface exhibit weak but significant octant-dissignate behaviour (Figure 1). It was suggested [2] that this curious empirical finding might result from the presence of two super-imposed electronic transitions, one characterised by short-range consignate effects of perturbing groups, and the other by dissignate effects which attenuate more gradually with distance from the carbonyl group.

(ii) A change of solvent from hexane to acetonitrile produced a small red-shift (2—3 nm) of the c.d. band, observed near 190 nm, although acetonitrile and all other polar solvents are known to cause a blue-shift of the $n\to\pi^*$ (290 nm) band. The blue-shift has been attributed partly to stabilization of the ground state n-orbital by its association with the polar solvent,[4] and partly to the inability of the solvent shell to relax around the excited molecule in the brief time taken for the electronic transition.[5] In discussing possible assignments of the '190 nm' c.d. band, it was pointed out [2] that transitions of $n\to\sigma^*$ or $n\to3s$ (Rydberg) type would be expected to undergo a blue-shift in polar solvents for similar reasons: indeed a blue-shift is observed in the u.v. absorption band immediately below 200 nm, for acetone and similar ketones, when the ketone is transferred from the vapour phase or hydrocarbon solution into a polar solvent.[6] In 2,2,2-trifluoroethanol (TFE) solution in particular, the

absorption band for acetone (probably a mixed $n\to\sigma^*/n\to3s$ transition) shifts to 171 nm, compared with 185 nm in hexane and 196 nm in the vapour phase.[6] C.d. bands for the $n\to\pi^*$ transition of steroidal ketones have been observed typically to shift from *ca.* 296 nm in hexane to *ca.* 283 nm in TFE.[7]

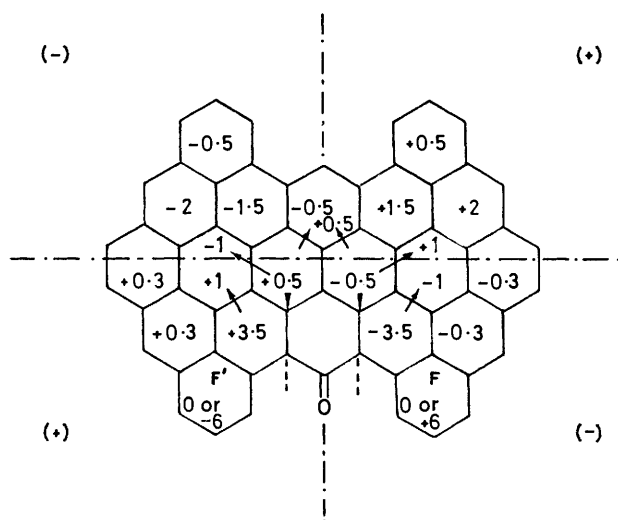The present study was intended to test the hypothesis

FIGURE 1 For solutions in hexane: c.d. contributions ($\Delta\varepsilon_H$) of cyclohexane rings in 'all-*trans*' compounds of extended decalone type (taken from ref. 2). Notes: (a) Arrows indicate the manner of connection of rings where different values apply. (b) —·—·—·— indicates apparent sector boundaries. (c) Rings F and F' (in geometric front octant): zero contribution when the oxo group is in a terminal ring (*e.g.* 5α-cholestan-1-one); ±6 units when the oxo group is in a 'middle' ring (±3 units if the 'front octant' ring is five-membered)

that the '190 nm' c.d. band for ketones in hexane solution is normally a composite of two overlapping bands, one of which is red-shifted in polar solvents, and the other strongly blue-shifted in the manner described above. It was unfortunately not possible to examine the region of the spectrum below about 183 nm with available instrumentation, so the presence of a blue-shifted component of the c.d. could not be directly confirmed.

It nevertheless seemed a safe assumption in view of the reported changes in u.v. absorption spectra of simple ketones.[6] C.d. associated with the steroid skeleton[8] may in any case preclude any informative study much below 183 nm. The objective of the present work was, therefore, to gather data on the red-shifted component of

40 °C showed no significant variations in $\Delta\varepsilon$ over this range. Values of $\Delta\varepsilon$ in hexane $(\Delta\varepsilon_H)^2$ are given for comparison, together with the observed red-shifts $(\lambda_T - \lambda_H)$, and the differences in Cotton effects between hexane and TFE. The apparent change in Cotton effect $(\Delta\Delta\varepsilon)$ is recorded as $\Delta\varepsilon_H - \Delta\varepsilon_T$ rather than as $\Delta\varepsilon_T - \Delta\varepsilon_H$, on the

TABLE 1

C.d. data at 24 °C for trans-decalones and related compounds, in 2,2,2-trifluoroethanol (TFE) and hexane as solvents. ($\Delta\varepsilon$ values in parentheses were calculated by summing group increments)

Compound [a]	Hexane		TFE		Difference $\Delta\Delta\varepsilon = \Delta\varepsilon_H - \Delta\varepsilon_T$	Wavelength shift $(\lambda_T - \lambda_H)/$ nm
Solvent:	$\Delta\varepsilon_H$	λ/nm	$\Delta\varepsilon_T$	λ/nm		
Monocyclic						
(3R)-3-Methylcyclohexanone (1)	+1.0 (+0.5)	185	−0.5 (−0.5)	188	+1.5 (+1)	+3
trans-1-Decalone derivatives						
(4aS,8aS)-trans-1-Decalone (2)	+3.6 (+3.5)	188	−1.9m (−2)	189	+5.5 (+5.5)	+1
(4aS,8aR,9aS,10aR)-Perhydroanthracen-1-one (3)	+3.9m (+3.8)	187	−1.9m (−2)	188	+5.8 (+5.8)	+1
4′-Oxo-2α,3β-Tetramethylene-5α-cholestane (4)	−4.2m (−4.1)	194	+0.9m (+2)	196	−5.1 (−6.1)	+2
5α-Oestran-4-one [b] (5)	−3.2m (−4.8)	188	+4.0m (+4)	195	−7.2 (−8.8)	+7
5α-Cholestan-4-one [b] (6)	−5.6m (−6.3)	191	+3.0m (+3)	201	−8.6 (−9.3)	+10
3α-Methyl-5α-cholestan-4-one [b] (7)	−1.7 (−2.3)	194	+3.4 (+3.5)	198	−5.1 (−5.8)	+4
5-Methyl-5α-cholestan-4-one [b] (8)	0.0 (+0.2)	—	+0.8m (+1)	201	−0.8 (−0.8)	?
3β-Acetoxy-des-D-5α,13β(H)-androstan-14-one (9)	0.0 (0.0)	—	+4.0m (+4)	189	−4 (−4)	?
D-Homo-5α-androstan-17a-one (10)	−5.5m (−5.2)	189	−5.0m (−5)	195	−0.5 (−0.2)	+6
17α-Methyl-D-homo-5α-androstan-17a-one (11)	−6.1m (−5.7)	190	−6.3m (−6.5)	192	+0.2 (+0.8)	+2
5α-Cholestan-1-one [c] (12)	+6.8m (+6.5)	189	+6.0 (+6)	198	+0.8 (+0.5)	+9
trans-2-Decalone derivatives						
(4aR,8aR)-trans-2-Decalone (13)	−0.5m (−0.5)	190	+1.0m (+1)	190	−1.5 (−1.5)	0
(4aS,8aR,9aR,10aR)-Perhydroanthracen-2-one (14)	+1.5 (+1)	185	+2.8 (+3)	194	−1.3 (−2)	+9
(4aS,5aR,6aR,10aR,11aR,12aR)-Perhydronaphthacen-2-one (15)	+2.0sh (+1.5)	187—190	+4.2m (+4.5)	193	−2.2 (−3)	ca. +4
(4aR,4bS,8aR,10aS)-Perhydrophenanthren-3-one (16)	−1.0m (−0.5)	195	−7.2m (−7)	194	+6.2 (+6.5)	−1
Des-D-5α,13β(H)-androstan-2-one (17)	+4.5m (+4.5)	189	−1.4m (−2)	198.5	+5.9 (+6.5)	+9.5
5α-Cholestan-2-one [b] (18)	+4.9 (+2.5)	188	−5 (−4)	194	+9.9 (+6.5)	+6
3β-Methyl-5α-cholestan-2-one [b] (19)	−1.6 (+0.5)	192	−3.6 (−5)	196	+2 (+5.5)	+4
3,3-Dimethyl-5α-cholestan-2-one [b] (20)	+1.8m (0)	184	−3.7m (−5)	195	+5.5 (+5)	+11
D-Homo-5α-androstan-2-one (21)	+2.2 (+2.5)	190	−1.7 (−4)	198	+3.9 (+6.5)	+8
17β-Hydroxy-5α-oestran-3-one (22)	Insoluble	—	−2.1m (−2)	195	ca. +2.1 (+2)	?
17β-Acetoxy-5α-oestran-3-one (23)	0.0 (0.0)	—				
5α-Cholestan-3-one (24)	−0.5 (0.0)	192	−2.4 (−2)	198	+1.9 (+2)	+6
2,2-Dimethyl-5α-cholestan-3-one (25)	−0.9 (−2.5)	198	−0.9m (−3)	200	0 (+0.5)	+2
17β-Acetoxy-2α-methyl-5α-androstan-3-one (26)	−2.8 (−2)	186	−4.6 (−3)	187	+1.8 (+1)	+1
17β-Acetoxy-4α-methyl-5α-androstan-3-one (27)	+1.6 (+2)	190	−1.1sh (−1)	200	+2.7 (+3)	+10
17β-Acetoxy-4β-methyl-5α-androstan-3-one (28)	0.0 (+0.5)	—	−2.6m (−2)	188	+2.6 (+2.5)	?
6α-Methyl-5α-cholestan-3-one (29)	0.0 (0.0)	—	−1.2m (−2)	205	+1.2 (+2)	?
6β-Methyl-5α-cholestan-3-one (30)	−2.4m (−3)	187	−1.8m (−1.5)	200	−0.6 (−1.5)	+13
3′-Oxo-2α,3β-tetramethylene-5α-cholestane (31)	−0.7m (−1)	193	−3.5m (−3) ca. 195		+2.8 (+2)	ca. +2
4,4-Dimethyl-5α-cholestan-3-one (32)	+1.6 (+2.5)	192	−1.2 (−1)	198	+2.8 (+3.5)	+6

[a] Sources of compounds are acknowledged in ref. 2 and in earlier papers of this series. [b] 'Calculated' values of $\Delta\varepsilon$ assume a six-membered ring D. [c] 'Calculated' values include $\delta\Delta\varepsilon = 0$ (in hexane) for the front-octant ring C; see ref. 2.

the c.d. To maximise the observed effects, TFE was chosen as the polar solvent. Trial experiments revealed a moderately large red-shift of c.d. maxima compared with hexane (mean shift ca. +7 nm).

Tables 1 and 2 record short-wavelength c.d. data ($\Delta\varepsilon_T$), with TFE as solvent, for a representative set of 67 chiral ketones selected from among those used in the earlier study. Measurements were made at the instrument temperature of 24 °C, but trial experiments at 10 and

assumption that $\Delta\varepsilon_H$ represents the algebraic sum of two c.d. curves, one of which is strongly blue-shifted (to <180 nm) in TFE, while the other is left exposed and is redshifted. The difference $\Delta\Delta\varepsilon$ is, therefore, taken tentatively as an estimate of the magnitude of $\Delta\varepsilon$ for the presumed hidden (blue-shifted) c.d. band, while $\Delta\varepsilon_T$ is taken as a crude estimate of the separate Cotton effect at the red-shifted absorption band. This oversimplification assumes (a) that the separated c.d. bands no longer have

TABLE 2

C.d. data at 24 °C for miscellaneous ketones, in TFE and hexane as solvents ($\Delta\varepsilon$ values in parentheses were calculated by summing group increments)
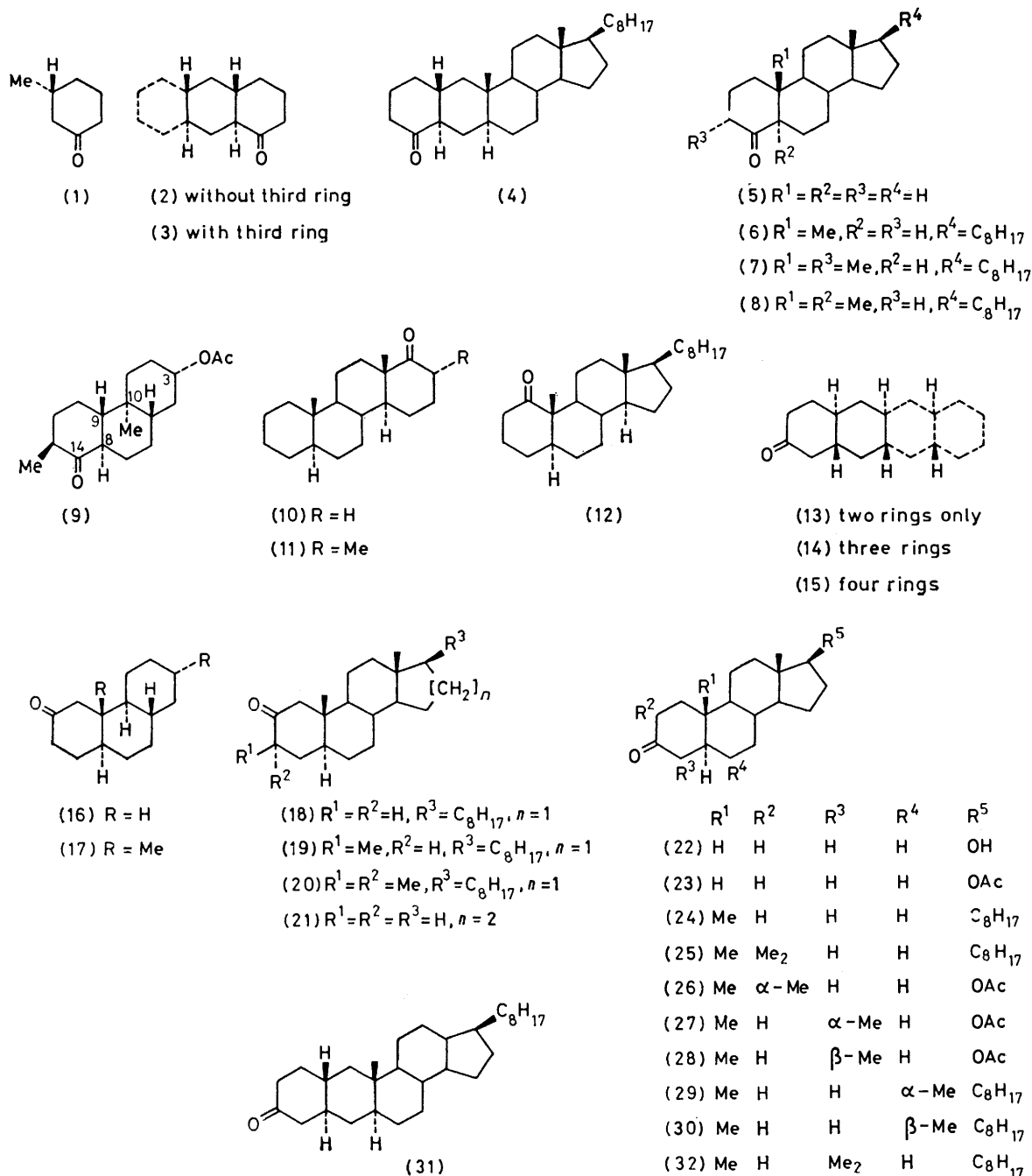
Solvent:	Hexane		TFE		Difference $\Delta\Delta\varepsilon = \Delta\varepsilon_H - \Delta\varepsilon_T$	Wavelength shift $(\lambda_T - \lambda_H)$ nm
Compound [a]	$\Delta\varepsilon_H$	λ/nm	$\Delta\varepsilon_T$	λ/nm		
Middle-ring ketones						
5α-Oestran-6-one (33) [b]	+2m (+4)	195	+1.5m (+5)	198	+0.5 (−1)	+3
D-Homo-5α-androstan-6-one (34)	+5.2m (+5.5)	192	+3.0m (+6)	200	+2.2 (−0.5)	+8
3β-Acetoxy-5α-cholestan-6-one (35) [b]	+4m (+5.5)	192	+4m (+6)	200	0 (−0.5)	+8
5-Methyl-5α-cholestan-6-one (36) [b]	0.0 (−1)	—	+5.5 (+8)	190	−5.5 (−9)	?
3β-Methoxy-5-methyl-5α-cholestan-6-one (37) [b]	+2.4 (−1)	186	+1.2m (+8)	198	+1.5 (−9)	+12
3β-Acetoxy-5-chloro-5α-cholestan-6-one (38) [b]	+5.4 (?)	190	+3.7 (?)	190	+1.7 (?)	0
Des-D-5α,13β(H)-androstan-7-one (39)	+1.0m (+3)	192	−0.7m (−1)	198	+1.7 (+4)	+6
5α-Androstan-7-one (40) [c]	−0.1 (0.0)	188	−3.1m (−4)	194	+3.0 (+4)	+6
5α-Cholestan-7-one (41) [c]	−0.8 (0.0)	185	0.0 (−4)	—	−0.8 (+4)	?
3α-Acetoxy-5α-cholestan-7-one (42) [c]	−3.5 (0.0)	186—190	−3.5m (−4)	191	0 (+4)	(+)
3β-Acetoxy-5α-cholestan-7-one (43) [c]	−4 (0.0)	186	−4m (−4) [c]	187—189	0 (+4)	ca. +2
3α-Hydroxy-5α-cholestan-7-one (44) [c]	−3.5 (0.0)	187	−2.5m (−4)	187—194	−1 (+4)	(+)
3β-Hydroxy-5α-cholestan-7-one (45) [c]	0.0 (0.0)	—	0.0 (−4)	—	0 (+4)	
3β-Acetoxy-4,4,14α-trimethyl-5α-cholestan-7-one (46) [d]	0.0 (?)		{ 1.5m (?) { +3.5	205 183	+1.5 (?)	
5β-Pregnane-11,20-dione (47)	+5.6 (+7 [e])	189	+3.6m (+9)	194	+2.0 (−2)	+5
3β-Acetoxy-5α,25R-spirostan-11-one (48) [f]	+3.7 (?)	197	+1.7m (?)	193	+2.0 (?)	−4
5α-Androstan-12-one (49) [b]	+3.0 (+2)	185	+2.7m (−2.5)	194	+0.3 (+4.5)	+9
3β-Acetoxy-5α,25R-spirostan-12-one (hecogenin acetate) (50) [b]	+8 (+5)	185	+3.5sh (+0.5)	190	+4.5 (+4.5)	+5
3α-Acetoxy-5β-cholestan-12-one (51) [b]	+8.5m (+6)	191	+8.4m (+6.5)	194.5	+0.1 (−0.5)	+3.5
5β-Cholan-12-one (52) [b]	+10.5 (+6)	188	+7.6m (+6.5)	195.5	+2.9 (−0.5)	+7.5
***cis*-Decalone derivatives**						
(6c3eq [g])						
5β-Cholestan-3-one (53)	+0.9	190	+0.8sh	190	+0.1	0
5-Methyl-5β-cholestan-3-one (54)	−3.3	188	+1.0m	198	−4.3	+10
(6c2ax [g])						
5β-Cholestan-6-one (55)	+9.0	188	+4.0m	190	+5	+2
3β-Acetoxy-5β-cholestan-6-one (56)	+4.1	183	+4.2m	190	−0.1	+7
3α-Methyl-5β-cholestan-6-one (57)	+5.0	189	+6.0	192	−1	+3
(−)-Valeranone (58)	+7.6	187	+8.0	185	−0.4	−2
Cyclopentanone and hexahydroindanone derivatives						
(3R)-3-Methylcyclopentanone (59)	−5.7	190	−1.2	185	−4.5	−5
5α-Androstan-15-one (60)	+1.8	195	−1.6sh	193	+3.4	−2
5α,13α-Androstan-15-one (61)	−1.4	185	−4.5sh	187—190	+3.1	(+)
5α,14β-Androstan-15-one (62)	−3.0	186	−0.6sh	196	−2.4	+10
5α-Androstan-17-one (63)	−9.5	191—195	−10.5	187	+1	(−)
3β-Hydroxy-4,4,14α-trimethyl-5α-androstan-17-one (64)	+5 (MeCN)	187	{ −3.2m { +3.5	197.5 183	+8.2	+10.5 } −4 } ?
3β-Acetoxy-5α-androstan-16-one (65)	+3.5	193	+3.6	187	ca. 0	−6
3β-Hydroxy-5α-androstan-16-one (66)	+3.0 (MeCN)	193	+4.0sh	192	−1	−1
Miscellaneous						
5β-Pregnan-20-one (67)	−2.0m	188	−2.5m	196	+0.5	+8

[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1. [c] Assuming $\delta\Delta\varepsilon = -3$ (hexane) for a five-membered ring D in a front octant: *cf.* −6 for the corresponding six-membered ring D (Figure 1; see also ref. 2). [d] There is no clear basis for assessing the effect of the 14α-methyl group. [e] See ref. 2. [f] Structure too complicated to attempt a calculation of $\Delta\varepsilon$. [g] See ref. 3.

any significant overlap (Figure 2), and (b) that the separate magnitudes of $\Delta\varepsilon$ for the two bands are additive and invariant with solvent. Neither assumption, of course, can be justified quantitatively, either from the available evidence or theoretically.

ated difference $\Delta\Delta\varepsilon$ which is tentatively assumed to derive from the blue-shifted transition.

C.d. Data in TFE.—The following sections analyse the c.d. characteristics in TFE solution of the different classes of ketones, according to structural type. Table 1

(1)

(2) without third ring

(3) with third ring

(4)

(5) $R^1 = R^2 = R^3 = R^4 = H$

(6) $R^1 = Me, R^2 = R^3 = H, R^4 = C_8H_{17}$

(7) $R^1 = R^3 = Me, R^2 = H, R^4 = C_8H_{17}$

(8) $R^1 = R^2 = Me, R^3 = H, R^4 = C_8H_{17}$

(9)

(10) R = H

(11) R = Me

(12)

(13) two rings only

(14) three rings

(15) four rings

(16) R = H

(17) R = Me

(18) $R^1 = R^2 = H, R^3 = C_8H_{17}, n = 1$

(19) $R^1 = Me, R^2 = H, R^3 = C_8H_{17}, n = 1$

(20) $R^1 = R^2 = Me, R^3 = C_8H_{17}, n = 1$

(21) $R^1 = R^2 = R^3 = H, n = 2$

	R^1	R^2	R^3	R^4	R^5
(22)	H	H	H	H	OH
(23)	H	H	H	H	OAc
(24)	Me	H	H	H	C_8H_{17}
(25)	Me	Me_2	H	H	C_8H_{17}
(26)	Me	α-Me	H	H	OAc
(27)	Me	H	α-Me	H	OAc
(28)	Me	H	β-Me	H	OAc
(29)	Me	H	H	α-Me	C_8H_{17}
(30)	Me	H	H	β-Me	C_8H_{17}
(32)	Me	H	Me_2	H	C_8H_{17}

(31)

Viewing the data in Tables 1 and 2 as a whole, most of the compounds show a change in the observed magnitude of $\Delta\varepsilon$ between hexane and TFE, and many show a change of sign. Perhaps more significantly, even more of the ketones show a sign reversal between $\Delta\varepsilon_T$ (in TFE; attributed to the red-shifted transition) and the calcul-
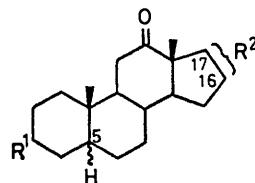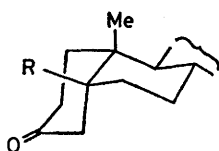
contains the data for compounds of ' all-*trans* ' extended decalone type, which, as experience [2,3] has shown, yield the most useful information for the derivation of symmetry rules. C.d. data for steroidal ' middle ring ' ketones, and miscellaneous others, are collected in Table 2.
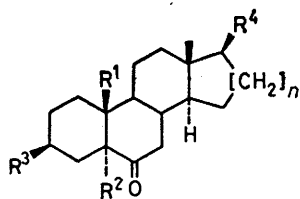
	R^1	R^2	R^3	R^4	n
(33)	H	H	H	H	1
(34)	Me	H	H	H	2
(35)	Me	H	AcO	C_8H_{17}	1
(36)	Me	Me	H	C_8H_{17}	1
(37)	Me	Me	MeO	C_8H_{17}	1
(38)	Me	Cl	AcO	C_8H_{17}	1
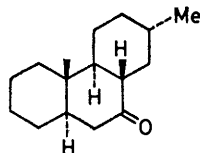
(39)
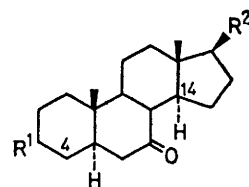
(40) $R^1 = R^2 = H$

(41) $R^1 = H, R^2 = C_8H_{17}$

(42) $R^1 = \alpha - OAc, R^2 = C_8H_{17}$

(43) $R^1 = \beta - OAc, R^2 = C_8H_{17}$

(44) $R^1 = \alpha - OH, R^2 = C_8H_{17}$

(45) $R^1 = \beta - OH, R^2 = C_8H_{17}$

(46) as (43), with 4,4,14-Me$_3$
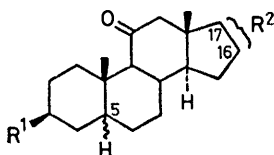
(47) $R^1 = H, R^2 = 17\beta - COCH_3, 5\beta - H$

(48) $R^1 = AcO, R^2 = $ rings E and F

of (25R)-spirostan, 5α-H

(49) $R^1 = R^2 = H, 5\alpha - H$

(50) $R^1 = \beta - OAc, R^2 = $ rings E and F

of (25R)-spirostan, 5α-H

(51) $R^1 = \alpha - OAc, R^2 = 17\beta - C_8H_{17}, 5\beta - H$

(52) $R^1 = H, R^2 = 17\beta - CHMe(CH_2)_2Me, 5\beta - H$

(53) R = H
(54) R = Me
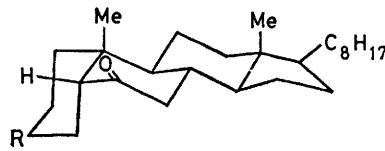
(55) R = H
(56) R = β-AcO
(57) R = α-Me
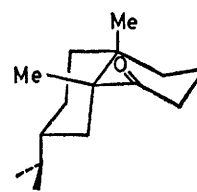
(58)
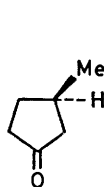
(59)
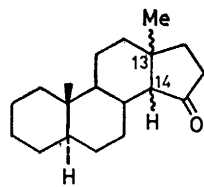
(60) 13β, 14α
(61) 13α, 14α
(62) 13β, 14β
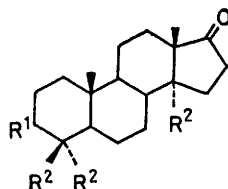
(63) $R^1 = R^2 = H$
(64) $R^1 = HO, R^2 = Me$
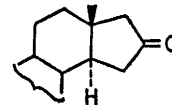
(65) 3β - AcO, 5α - H
(66) 3β - HO, 5α - H
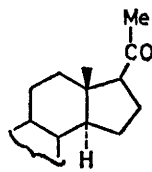
(67)

(a) trans-*Decalones and their extended derivatives.*
Both *trans*-1- and *trans*-2-decalone show a reversal in
the sign of $\Delta\varepsilon$ between hexane and TFE, but the addition
of further rings and/or alkyl substituents leads to in-
stances both of sign retention and of sign reversal in each
series.

The contributions of additional rings, and of methyl

units in TFE (*cf.* 10 units in hexane [2]), in the consignate
sense. The effect of a ' β '-axial methyl group depends as
usual [3] upon the class of decalone. These and other
methyl substituent effects in TFE, which are generally
small, are collected in Table 3. This Table also lists
methyl group increments, $\delta\Delta\varepsilon_H$, in hexane, and the dif-
ferences $\delta\Delta\varepsilon_H - \delta\Delta\varepsilon_T$.
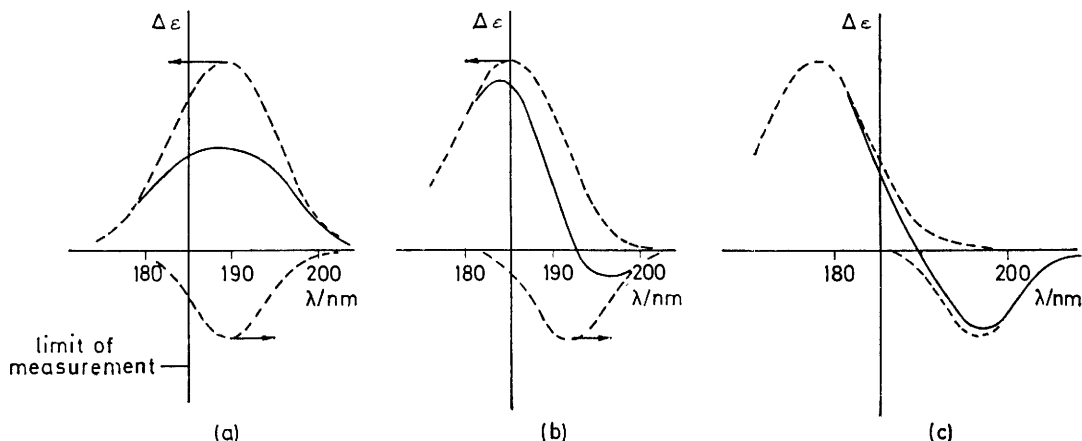

FIGURE 2 Overlapping Gaussian curves, illustrating the changing pattern of profiles of the resultant composite curve as the com-
ponent curves move apart in the directions indicated. ———— experimental curve; — — — — — — — postulated component Gaus-
sian curves. (a) Superimposed maxima; (b) effect of partial solvent shift: note the displaced small (negative) maximum near 198
nm; (c) solvent-separated curves, displaying virtually true maxima

substituents close to the carbonyl group, were estimated
in the usual way [2,3] by subtracting the value of $\Delta\varepsilon$ for the
parent decalone from that for each tricyclic or substituted
derivative. The same procedure of pairwise comparisons
was applied subsequently to determine contributions of
fourth rings. The assumption of additivity of con-
tributions, although not wholly valid, has proved to be a
reasonable approximation in previous studies.[2,3] In this
way the pattern of relationships between structure and
c.d. for all-*trans* arrays of six-membered rings for solu-
tions in TFE was estimated to be that illustrated in
Figure 3. By comparing values of $\Delta\varepsilon$ in hexane (Figure
1) with those in TFE, the derived pattern for the
difference $\Delta\Delta\varepsilon$ ($= \Delta\varepsilon_H - \Delta\varepsilon_T$) is that shown in Figure 4.

Although all the numerical values of ring increments
recorded in these Figures must be treated as only crude
estimates, the *signs* of ring increments in Figures 3 and 4
show encouraging consistencies. The TFE data in
Figure 3 appear to correspond to a ' reverse-octant ' rule
(*i.e.* all ring contributions dissignate,[9] with respect to the
conventional octant rule [10] in right-handed Cartesian
co-ordinates [3]). In contrast, the ' difference ' data
(Figure 4) for those rings in rear octants correspond to the
signs which would be expected on the basis of an octant
rule (consignate),[9] whereas the absence of a sign reversal
between front and rear octants suggests a quadrant
rather than octant rule (see discussion, p. 1818).

Contributions from methyl substituents were also
derived by inspection of the available data. A methyl
group at the ' α '-axial ring junction position in a *trans*-
1-decalone component contributes only a modest 1—2

It was surprising to find that most methyl group in-
crements are consignate in TFE, despite the octant-
dissignate pattern for rings. The largest and therefore
most reliable of the methyl group increments in the
' difference ' column (α-axial methyl at ring junction) is
also consignate, in this case following the sign pattern

TABLE 3

Estimated increments ($\delta\Delta\varepsilon$) for methyl substituents

	Solvent:	Hexane $\delta\Delta\varepsilon_H$		TFE $\delta\Delta\varepsilon_T$		Differ- ence $\delta\Delta\varepsilon_H - \delta\Delta\varepsilon_T$	
For cyclohexanones and *trans*-1-decalones							
α-*Ax.* (at ring junction)		10	(con [a])	1	(con)	9	(con)
α-*Ax.* (at tert. carbon)		4	(dis [a])	0.5	(dis)	3.5	(dis)
α-*Eq.*		0.5	(con)	1.5	(con)	1	(dis)
β-*Ax.* (in absence of α-*ax.* Me)		1.5	(con)	1	(con)	0.5	(con)
β-*Ax.* (in presence of α-*ax.* Me)		5	(con)	4	(con)	1	(con)
β-*Eq.*		0.5	(con)	0.5	(dis)	1	(con)
γ'-*Ax.*[b]		4	(dis)	1.5	(con)	5.5	(dis)
For *trans*-2-decalones							
α-*Ax.*		0.5	(dis)	~0		0.5	(dis)
α-*Eq.*		2	(con)	1	(con)	1	(con)
β-*Ax.* (at ring junction)		5	(con)	5	(con)	0	
γ'-*Ax.*[b]		3	(dis)	0.5	(con)	3.5	(dis)

[a] Con = consignate; dis = dissignate. [b] γ'-axial, in posi-
tions corresponding to 6β-Me in a 3-oxo-5α-steroid.

found for ring contributions, although the appreciable
dissignate contributions of ' α '-axial methyl groups at
tertiary carbon (*e.g.* 3α-Me in a 4-oxo-5α-steroid), and of
γ'-axial methyl groups (*e.g.* 6β-Me in a 3-oxo-5α-steroid)

reflect their contributions in hexane solution,[2] and remain unexplained.

Values of $\Delta\varepsilon$ calculated for each compound by summation of appropriate ring and substituent increments are included (in parentheses) in Table 1. Agreement with experimental values is reasonable for the great majority
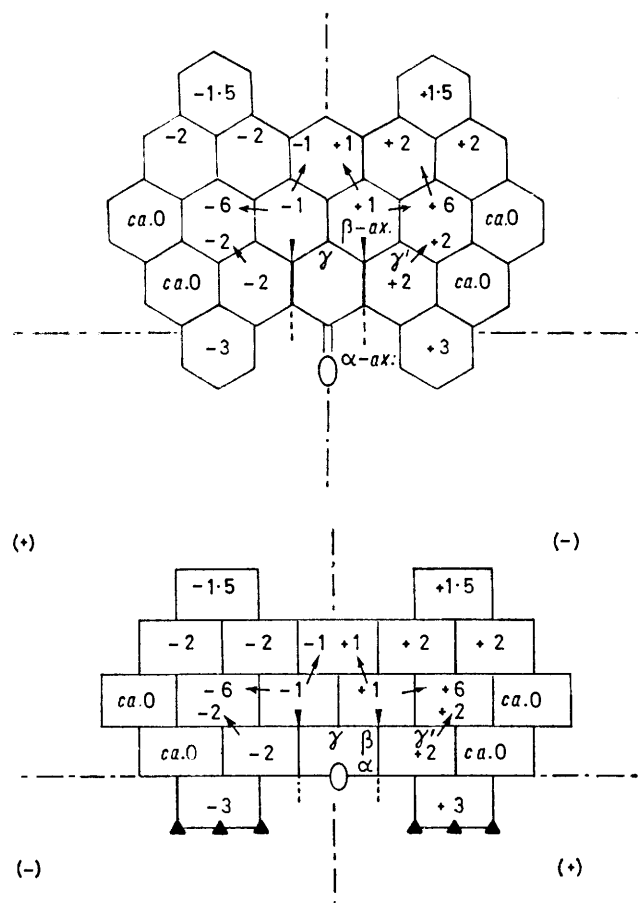
FIGURE 3 For solutions in TFE: c.d. contributions ($\Delta\varepsilon_T$) of cyclohexane rings, with classical 'octant' projection. [See notes (a) and (b) below Figure 1.] ▲ indicates carbon atom in a front octant. Signs in parentheses refer to 'octant consignate' behaviour (rear octants)

of compounds, although not as close as corresponding estimates have been for $n{\to}\pi^*$ c.d. data.[3]

(b) '*Middle-ring*' and *miscellaneous ketones* (*Table* 2). Values of $\Delta\varepsilon$ for 'middle-ring' ketones of extended *trans*-decalone type show much less sensitivity to change of solvent than those in Table 1. In qualitative terms, their approximate invariance arises from the mutual cancellation of effects of reversing (in opposite directions) the signs of the major contributions from rings both to the left and to the right of the carbonyl group. Quantitative correlations between experimental values of either $\Delta\varepsilon_T$ or $\Delta\Delta\varepsilon$ and the values calculated by summing group increments are generally rather poor. Calculated values of $\Delta\varepsilon_T$, for example, are too large for the various 6-oxo steroids. They are reasonably close or too negative for the 7-oxo steroids, where substituents at C-3 appear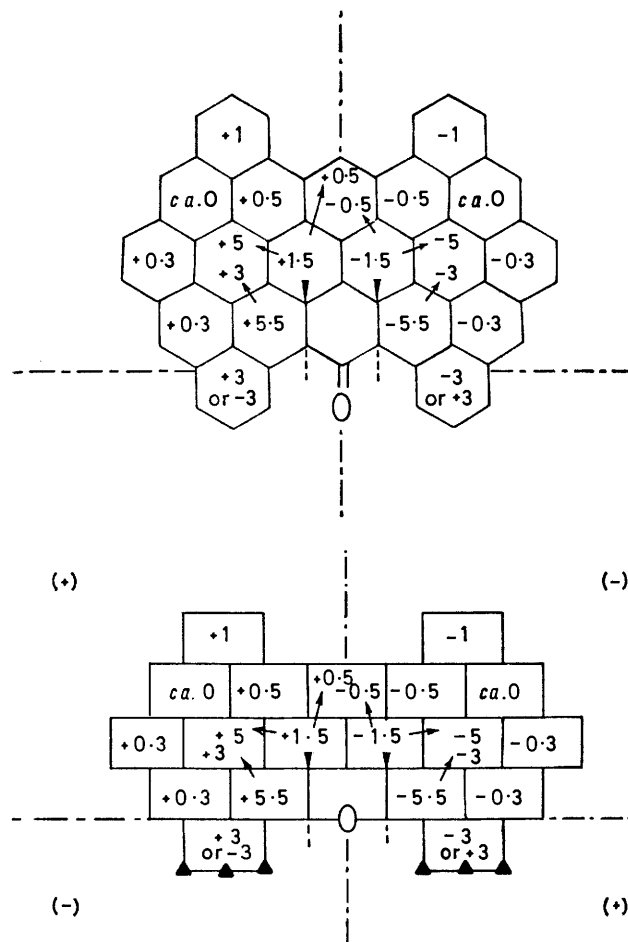 to have pronounced effects. There is a large positive deviation for 5β-pregnane-11,20-dione. One of the four 12-oxo steroids (5α-androstan-12-one) gives a calculated value of the wrong sign, but there is some regularity in that each of the calculated values shows a shift towards the negative. Corresponding discrepancies occur between calculated and experimental values of $\Delta\Delta\varepsilon$. These effects may stem, in part, from assumptions in the calculations that the five-membered ring D is equivalent in its effect to a cyclohexane ring, and that the 17β-side-chain in 12-oxo steroids can be regarded as making the contribution of a front octant ring. Rather poorer additivity for 'middle ring' ketones, however, was also a feature noted in our previous study for hexane solutions,[2] and for the $n{\to}\pi^*$ transition.[3]

Data for only six compounds of *cis*-decalone type

FIGURE 4 Differences between ring contributions in hexane and those in TFE ($\Delta\Delta\varepsilon = \Delta\varepsilon_H - \Delta\varepsilon_T$). (See notes below Figures 1 and 3.) Increments for 'front octant' rings: first value applicable when the oxo group is in a terminal ring; second value when oxo group is in a middle ring. Corresponding values when the front octant ring is five-membered are 0 and 5 units

(Table 2) do not permit extraction of a set of group increments for such compounds, but generally show rather small solvent effects. Only 5-methyl-5β-cholestan-3-one shows a change of sign. The seven compounds of hexahydroindanone type also, for the

most part, exhibit only minor solvent variations, and some are anomalous in exhibiting a small blue-shift in TFE. 3-Methylcyclopentanone also showed a blue-shift. No attempt to analyse this limited set of data seemed justified. The c.d. maximum for 5β-pregnan-20-one is red-shifted in TFE, but hardly alters in magnitude.

Further Work.—The effect of TFE in reversing signs of Δε for 5α-oestran-4-one and 5α-cholestan-2-one was additionally examined by recording the c.d. curves of these ketones in hexane containing increasing small proportions of TFE. For both ketones the change in Δε was progressive, though non-linear, with the concentration of TFE (Table 4) suggesting an equilibrium between associated and non-associated molecules (acetone and TFE are reported [11] to associate strongly in the vapour or in CCl$_4$, where Δ$G°$ is *ca.* −5 kcal mol^{-1}). The change in the c.d. curve with initial small concentrations of TFE was very pronounced, the c.d. sign reversals being effectively complete at 1% TFE. Experimental inaccuracies in measurements of Δε and the uncertainties inherent in overlapping curves precluded any attempt at accurate evaluation of equilibrium constants from c.d. data, but it is clear that association is very substantial even at low percentage concentrations of TFE (in solutions containing 0.5% TFE, the TFE : steroid molar ratio was *ca.* 30 : 1 for 5α-cholestan-2-one and *ca.* 50 : 1 for 5α-oestran-4-one).

A similar series of c.d. measurements with 5α-cholestan-3-one, and varying proportions of TFE in hexane, showed an increase in the (negative) value of Δε, without change of sign: the wavelength of the c.d. maximum remained essentially constant (192 ± 2 nm) up to 2% TFE, the limit for this experiment. Over the same range of concentrations the $n{\rightarrow}\pi^*$ c.d. band shifted progressively from 298 nm in hexane to 290 nm with 2% TFE (*cf.* 280 nm in 100% TFE), while Δε became increasingly positive. This blue-shift of the $n{\rightarrow}\pi^*$ band provides some measure of the effect of TFE in associating with the carbonyl group.

A more limited set of experiments was carried out with trifluoroacetic acid (TFA)–hexane mixtures. As expected from its greater acidity, TFA was effective in even smaller concentrations than TFA in shifting the c.d. curves (Table 4), although the effects were qualitatively similar. With 5α-cholestan-2-one the c.d. curve contained two maxima of opposite signs even at 0.025% TFA, and sign inversion was virtually complete at 0.05%. 5α-Cholestan-3-one showed a sharp increase in Δε even at very low TFA concentration. The $n{\rightarrow}\pi^*$ bands for these two ketones [7] showed the expected strong blue-shift and enhanced Δε with added TFA.

I.r. examination of a solution of 5α-cholestan-3-one in TFE confirmed that the carbonyl group is intact even after 20 h, so that hemiacetal or acetal formation is not a contributing factor in the c.d. changes, even with this most reactive type of steroid ketone. The only change in the carbonyl region of the i.r. spectrum was from a sharp peak at 1 716 cm^{-1} (in CS$_2$) to a broad and fine-

structured absorption band with principal maxima at 1 692 and 1 682 cm^{-1} in TFE; the shift is entirely compatible with the formation of a hydrogen-bonded ketone–TFE complex. T.l.c. confirmed that the 5α-cholestan-3-one was unchanged after being in solution in TFE.

TABLE 4

Changes in c.d. of ketones (at 24 °C) with increasing proportions of TFE or TFA in hexane

% TFE (v/v)	Δε [a]	λ$_{max}$/nm [b]	Δε [a]	λ$_{max}$/nm [b]
(1) 5α-Oestran-4-one 0	−3.2	188		
0.1	−2.2	188		
0.15	−1.8	188	+0.2	201
0.2	−1.6	188	+0.4	200
0.25	−1.2	188	+0.4	200
0.3	−1.0	188	+0.5	199
0.4	*ca.* −0.5	188	+0.9	197
0.5	*ca.* 0.0	188	+1.3	195
1.0			+1.5	195
3.0			+2.3	195
5.0			+2.7	195
100			+4.0	195
(2) 5α-Cholestan-2-one 0	+4.9	188		
0.1	+2.9	188		
0.2	+2.4	188		
0.25	+1.8	188	−0.3	198
0.3	+1.7	188	−0.6	198
0.4			−0.9	197
0.5			−1.25	197
0.8			−1.9	196
5			−2.8	195
100			−5.0	194
% TFA (v/v)				
0.0125	+2.5	188		
0.025	+1.9	188	−0.6	197.5
0.05	*ca.* 0		−1.0	197
0.1			−1.0	197
0.2			−1.2	196
0.25			−1.9	195
(3) 5α-Cholestan-3-one **% TFE (v/v)**				
0	−0.5	192		
0.1	−1.3	190		
0.25	−1.5	192		
0.5	−1.8	192		
2.0	−1.5	194		
100	−2.4	198		
% TFA (v/v)				
0.0063	−1.2	192		
0.0125	−1.8	194		
0.025	−2.1	195		
0.1	−2.1	194		
0.4	−2.1	195		

[a] Δε is the mean of duplicate or triplicate runs, with probable error in the range 10—20% due to instrument ' noise ' and measurements of small volumes. [b] λ$_{max}$. Estimated within ±2 nm from rather broad maxima.

Association between 5α-cholestan-2-one and TFE was also evident from ^{13}C-n.m.r. spectra. In solution in [^{2}H$_{12}$]cyclohexane the carbonyl ^{13}C signal was at 206.1 p.p.m. (relative to Me$_4$Si as internal standard) but with added TFE the signal moved progressively downfield (*e.g.* to 208.4 p.p.m. with 1% TFE; 214.0 p.p.m. with 5%

TFE) owing to electron depletion by hydrogen bonding. Other ^{13}C signals were shifted only marginally if at all by added TFE.

In the c.d. study, an additional point of interest and probable significance emerged from a detailed inspection of the set of curves obtained with increasing proportions of TFE for 5α-oestran-4-one. The shrinkage of the negative c.d. band, which initially had its maximum at *ca.* 188 nm, close to the limit of measurement, was accompanied by the appearance of the positive c.d. as a second and distinct band on the longer-wavelength side (*ca.* 201 nm) when the TFE concentration reached 0.15%. Further increases in the TFE concentration caused the positive c.d. band to grow at the expense of the negative, while the wavelength of the positive maximum of the curve moved gradually from 201 nm to its final position at 195 nm, which was reached at 0.5% TFE. This pattern of shifting curve profiles, with maxima differing from those of the individual component curves,[12] is exactly what would be expected from the postulated gradual separation of two initially overlapping c.d. peaks of opposite signs (Figure 2). Although an alternative explanation could lie in the solvated and unsolvated forms of the ketone showing totally different c.d. characteristics in what is essentially a single electronic transition, it is then difficult to explain the red-shift of a band believed to originate in a transition from the oxygen *n*-orbital, for reasons already discussed. Moreover the simple solvation argument would not offer any clear explanation of the peculiar third boundary surface (Figure 1) for c.d. data in hexane. The concept of two separate transitions, with the c.d. characteristics implied in Figures 3 and 4, removes the need for such a boundary surface.

U.v. Absorption Spectra in TFE.—The u.v. absorption curves of 5α-cholestan-2-one and -3-one, and of 5α-oestran-4-one, were recorded in TFE between *ca.* 220 and 186 nm. They revealed a broad but weak shoulder on a steeply rising background curve. No shoulder was detectable in hexane solution. An attempt at curve resolution by comparison of the experimental curves in TFE with smoothed ' background ' curves, treated as providing baselines, suggested that the shoulder was in each case caused by the presence of a weak absorption band of approximately Gaussian shape centred at 198—200 nm, with molar extinction coefficient (ε) in the range 300—450. This is much weaker than would be expected for the $n{\rightarrow}\sigma^*$ transition (compare $\varepsilon_{186} = ca.$ 3 000 for the background curves). The observed c.d. in TFE is clearly associated with this weak absorption band, which does not appear to have been recognised previously, and apparently has no counterpart in the spectrum of acetone or other simple ketones in TFE.[6]

DISCUSSION

The c.d. characteristics estimated by difference ($\Delta\Delta\varepsilon = \Delta\varepsilon_H - \Delta\varepsilon_T$) for the band which is here presumed to be blue-shifted, should be those corresponding to a transition of $n{\rightarrow}\sigma^*$ type (or $n{\rightarrow}3s$, or mixed $n{\rightarrow}\sigma^*/3s$). The

signs of increments $\Delta\Delta\varepsilon$, derived above, follow a quadrant rule, which according to Buckingham and Stiles[13] can be derived, with the observed signs, from a theoretical treatment of the $n{\rightarrow}\sigma^*$ transition based upon the Kirkwood approach. It therefore seems reasonable to assign the part of the c.d. band which appears to be blue-shifted in TFE, beyond the range of measurement, to a transition of $n{\rightarrow}\sigma^*$ or $n{\rightarrow}\sigma^*/3s$ type.

This leaves the problem of assigning the c.d./u.v. band which appears at 197—200 nm in TFE. It has mainly octant-dissignate c.d. characteristics for ' all-*trans* ' systems of fused cyclohexane rings, but methyl substituents exert generally consignate and very weak effects. Only for ' β '-axial methyl groups is the contribution strongly consignate. No red-shifted c.d. band was observed for five-membered ring ketones. The apparent absence of a red-shifted absorption band for acetone[6] suggests that it only appears if the ketonic molecule is of reasonably complex structure. To be red-shifted in TFE, the transition should be to a more highly polarised state, which suggested that it has substantial charge-transfer character, either intramolecular or between solvent and solute. No electronic transition near 200 nm with these characteristics appears to have been identified for ketones. A very recent theoretical treatment (' random phase approximation ')[14] of pentan-3-one suggested the possibility that the second lowest singlet excited state, excluding Rydberg states, is derived from a $\sigma{\rightarrow}\pi^*$ transition rather than from the more generally accepted[2] $n{\rightarrow}\sigma^*$. The $\sigma{\rightarrow}\pi^*$ transition could conceivably show the c.d. characteristics identified here, but is seemingly of too high energy (*ca.* 8.9 eV[14]) to appear at 200 nm.

Further study is needed, but in the meantime the c.d. solvent effect in TFE opens a new and potentially useful possibility for empirical comparisons of c.d. for new ketones with data for compounds of known structures and absolute configurations.

EXPERIMENTAL

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