Configuration and Conformation of Substituted Azetidines

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Studies of compounds such as 1-cyclohexyl-2-carbomethoxy-4-methylazetidine by H-1 nmr coupling constants, nuclear Overhauser effects, C-13 steric shifts, and N-15 nmr support the revised assignment of configuration for *cis/trans* isomers in a series of *N*-alkyl substituted azetidines. The *trans* isomer displayed spectral characteristics consistent with a planar or nearly planar ring. The *cis* isomer favors a puckered ring, with major substituents at C-2 and C-4 equatorial. Compounds lacking the C-4 methyl are also puckered. Puckering angles are estimated. In contrast, *trans*-1-cyclohexyl-2-carboxy-4-methylazetidine (a zwitterion) prefers a puckered ring, possibly implicating the time averaged effect of nitrogen inversion on ring shape. The N-15 spectra show a large difference in chemical shift between *cis* and *trans* isomers of the azetidines, although analogous aziridines show an even larger difference.

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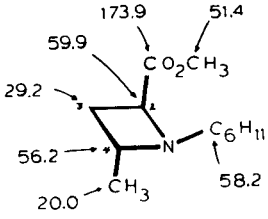
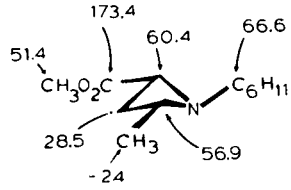
Introduction.

The conformation of azetidines (1,2), particularly azetidine-2-carboxylic acid (3), and related peptides (4-7), has been the subject of considerable interest in view of the biological properites of the molecules (8). The present study is concerned with the conformation and configuration of certain 1,2,4-trisubstituted azetidines (*cf.*, Charts I-III).

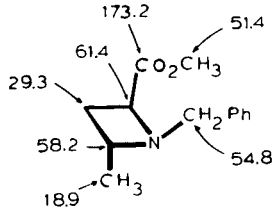
Chart I



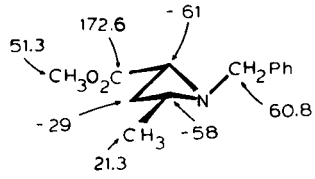
trans-1
(isomer A)



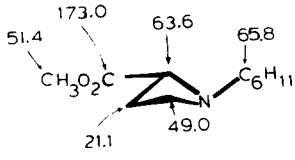
cis-1
(isomer B)



trans-3



cis-3



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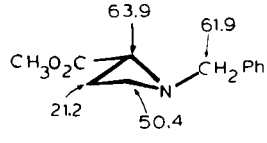

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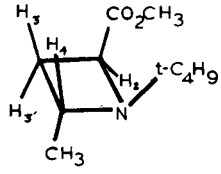
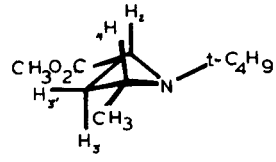
Chart II



trans-4
(isomer A)

$^3J_{23}$ = 5.3 Hz
$^3J_{23'}$ = 8.2
$^2J_{33'}$ -10.4
$^3J_{34}$ = 7.6
$^3J_{3'4}$ = 5.0

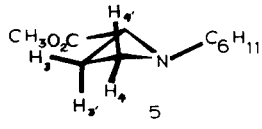


cis-4
(isomer B)

$^3J_{23}$ = 9.2 Hz
$^3J_{23'}$ = 8.2
$^2J_{33'}$ = -10.8
$^3J_{34}$ = 8.2
$^3J_{3'4}$ = 8.2

angle of pucker

Chart III



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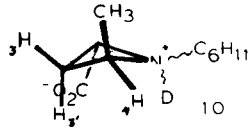

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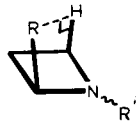
$^3J_{23}$ = 8.4 Hz
$^3J_{23'}$ = 9.0
$^2J_{33'}$ =-10.6
$^3J_{34}$ = 2.7
$^3J_{3'4}$ = 8.3
$^3J_{34'}$ = 8.4
$^3J_{3'4'}$ = 9.2
$^2J_{44'}$ = -7.0

$^3J_{23}$ = 9.6
$^3J_{23'}$ = 9.1
$^2J_{33'}$ =-10.6
$^3J_{34}$ = 3.8
$^3J_{3'4}$ = 8.8



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Before considering these molecules, it is worthwhile to review briefly previous work on four-membered rings in general (1). In 1,3-disubstituted cyclobutanes, the *cis* isomer is the more stable by a small factor. The preferred conformation involves pseudoequatorial substituents (9,10). The barrier to interconversion through the planar state in *ca.* 1 kcal/mole (9,11a,b,12,13). In solution, the angle of puckering (*cf.*, Chart II) ranges from 0-42° (11-14). The puckering angle is substantially larger for *cis*-1,3-disubstituted cyclobutanes and azetidines than for the *trans* isomers (9,10). Bauld and co-workers have suggested an explanation for puckering that involves an avoided contact between antibonding orbitals which would impinge upon one another in the center of the ring, if the ring were planar (15). Oxetane is planar, perhaps due to the reduction of the size of the orbitals in question by the electronegative oxygen (16). However, thietane and azetidine are puckered, although estimates of the puckering angle vary (12,16). Catalan and co-workers suggest that a puckering angle of 33° exists for azetidine, but also quote nmr data that indicate an angle of 15-20° (12). In azetidine-2-carboxylic acid, crystallographic data have disclosed an angle of 11°, but in azetidinium salts, planar as well as puckered forms have been observed (14,17). However, solid-state data do not necessarily reflect solution conditions (18). In azetidines as well as in cyclobutanes, the bowsprit hydrogens at C-2 and C-4 actually rotate toward one another slightly, although they remain within the attractive portion of the Morse potential (19). This minimizes the necessity for bent bonds. In azetidine, the barrier to ring inversion is also similar to cyclobutanes (12).

Results and Disscussion.

The configuration and conformation of certain *N*-alkyl-2-carbomethoxy-4-methylazetidines (**1-4**) (*cf.* Table I, Charts I, II) are investigated by a combination of spectral techniques (20). Table I also includes data for certain *N*-alkyl-2-carbomethylazetidines (**6-9**), which will serve as model compounds. In the azetidines **1-4**, one isomer termed isomer A, is characterized by downfield chemical shifts for H-2 and H-4 relative to carbomethoxyl (δ 4.3, 4.2 vs. 3.8 ppm, respectively, for **4**). The other isomer, termed isomer B, possesses upfield chemical shifts for H-2 and H-4 (δ 3.8 and 3.4 for **4**). In early work in this laboratory, isomer A of **4** was tentatively assigned the *cis* configuration based largely on infrared data (21). In later work, isomer A was reassigned the *trans* configuration based on the nmr anisotropy effects of carbonyl (22). This work also reported equilibration experiments from which isomer A of **4** appeared to be the less stable of the two isomers. However, recent work on **1-4** failed to corroborate this finding; for a series of *N*-alkylazetidines, isomer A strongly predominated under equilibrating conditions (20).

In view of the equilibration results, which are dissimilar to findings for 1,3-disubstituted cyclobutanes (9), and in view of the recently expressed uncertainity over the general theme of carbonyl anisotropy effects (22), it seemed advisable to reconsider the configuration assignments. Since previous work, an array of new techniques, *e.g.*, high-field H-1 nmr, C-13, and N-15 nmr had become available for application to the problem.

C-13 NMR Data.

Table I lists the C-13 chemical shifts for isomer A of **1-4** and for the model compound **5-9**. Isomers A were easily obtained pure from the equilibration experiments. Isomers B were observed only as mixtures with isomers A. Typical data for isomers B are illustrated in Chart I.

In **1-4**, the presence of a methyl group at C-4 causes *ca.*, 7 ppm downfield shifts for C-4 and a 7-8 ppm downfield shift for C-3, compared to **5-9**. These are rather typical *alpha* and *beta* effects for a methyl group (24). The strained nature of the four-membered ring has little effect in this particular case (25). The effect of methyl on C-2 (a *gamma* effect) is *ca.*, -3 ppm for both isomers. The *gamma* effect is usually interpreted in terms of a steric interaction (26). However, Seidman and Maciel have shown that the *gamma* effect is complex; conformational effects as well as the proximity of interacting groups are among the factors to be considered (27). Gorenstein believes that sterically induced bond angle changes may be the most significant factor in the upfield *gamma* shifts (28). Thus, changes in the degree of puckering in isomer A relative to isomer B may account for the unexpectedly similar *gamma* effect of the two isomers. On a purely steric basis, only the *trans* isomers should show an upfield shift, as the methyl group is near in space to the C-2 hydrogen only in this isomer. However, as shown in structure **11** (Chart III), the C-4-methyl makes contact with the C-2 hydrogen through a 90° angle. The original theory of Grant and co-workers for the steric shift proposed a cos θ dependence of observed shift on contact angle. For a maximum effect, an angle of contact of 180° is required, whereas for a 90° angle, the effect should be minimal. Thus, even by the older theory, it is not surprising that the trans isomer shows a small effect (26).

A classic *gamma* effect is observed in the chemical shifts of the *N*-alkyl groups (*i.e.*, the *alpha* carbon). In isomer A of **1-4**, a strong upfield shift is noted for N-C(α). In isomers B, the chemical shift is similar to that of the model compounds, **6-9**. If isomers B are indeed *cis*, the preferrred conformation of the *N*-alkyl group is likely to be equatorial, and thus *trans* to the equatorial C-2 and C-4 substituents. Due to the fact that the azetidine ring is less puckered than cyclohexanes, the interaction of the *N*-alkyl group with the C-2 and C-4 substituents should be rather

small compared to the interaction of gauche substituents in a 1,2,3-trisubstituted cyclohexane. Although nitrogen is rapidly inverting, a preference can and does exist for a particular orientation of the *N*-alkyl group. For the *trans* isomer, no matter which invertomer is occupied, the N-C(α) group will impinge on some other large group, either C-4 methyl or the C-2 carbomethoxyl. The strong upfield shift of the alpha carbon in isomers A is consistent with this unavoidable steric interaction. The magnitude of this *gamma* effect (6-7 ppm) is sizable, although not as large as found in similarly substituted aziridines (*ca.*, 9 ppm) (29). The larger magnitude of the shift in aziridines is partially due to the short N-C ring bonds (1.47 Å) compared to azetidines (1.44 to 1.52 Å) (4,17).

Since the C-4 methyl interacts with N-C(α) in isomers A, causing a steric shift of C(α), the inverse is also expected, *i.e.*, an upfield shift for methyl. An upfield shift (-3 ppm) is indeed observed in isomers A compared to isomers B. The smaller magnitude of this shift reflects the preferred orientation of the *N*-alkyl group near carbomethoxyl and *trans* to methyl (29).

H-1 Data.

The most direct proof of configuration should be a nuclear Overhauser effect (nOe) (30). This involves radiofrequency irradiation of a certain group, and observation of the intensity of neighboring hydrogen(s) to which excitation energy is transferred. As the nOe drops off as the sixth power of internuclear separation, no signal enhancement is expected if the irradiated and the observed hydrogens are distant. In the present case, a mixture of isomer A and isomer B of **1** was investigated. Irradiation of C-4 methyl led to some difficulty because of noise on the integration circuit. Also, H-2 and H-4 have similar chemical shifts in isomer A, and it is difficult to distinguish the effect of H-2 from the certain effect on H-4. However, by visual observation of the intensity changes (*cf.*, Fig. 1), the effect was unmistakable. The signal intensity of H-2 in isomer A underwent a strong signal enhancement, providing H-2 to be *cis* to C-4-methyl. In isomer B, H-2 underwent a smaller change. These results corroborate the assignment of isomers A as *trans*.

The H-1 nmr coupling constants verify these assignments. The results of the LAOCON3 computer simulation of spectra from the separated isomers of the *N-t*-butylazetidine, **4**, are shown in Chart II (31). The 360 MHz spectrum of **1** (isomer A) and the 90 MHz spectra of **2** and **3** (both isomers) exhibited similar coupling constants. The interpretation of the coupling constants follows the work of Whipple and Evanega (32). In strained four-membered rings, for which the Karplus relationship is inapplicable (33), H-1 coupling constants were determined for a series of molecules whose exact geometry was known from crystallographic data. Thomas and Williams showed that rather similar parameters were present for azetidines of proven geometry (34). The data of Escale *et al.*, on 1,3-disubstituted azetidines is also quite similar (35).

Large coupling constants from hydrogens such as H-2 and H-4 (to *both* H-3 and H-3′ (*cf.*, Chart II) (36) were shown to occur when H-2 and H-4 are axial in a puckered ring. Coupling constants of a uniform 8 Hz magnitude are indeed present for isomer B. This observation identifies H-2 and H-4 as axial and therefore *cis*; the large substituents at C-2 and C-4 must be equatorial and also *cis*.

In isomer A (*cf.*, Chart II), the coupling constants from H-2 to H-3 and to H-3′ are dissimilar (5.2 and 8.3 Hz, respectively). The coupling constants from H-4 to H-3 and H-3′ and reversed in magnitude (7.6 and 5.0 Hz). The geometry of H-2 with respect to H-3 is similar to H-4 with respect to H-3′. Thus H-2 and H-4 must be *trans*.

C-13 nmr coupling constants to H-1 follow a similar geometric dependence as H-1–H-1 couplings, although the C-13 data are subject to greater uncertainties (37). These spectral parameters were briefly investigated for certain of the azetidines. Observation of the coupled C-13 spectra of CO_2CH_3 of *trans*-**3** disclosed line separations of *ca.*, 4 Hz, which appeared as a clean septet. Selective decoupling from CO_2CH_3 (and also from H-2) gave a triplet. Thus, CO_2CH_3 is split by H-3 and by H-3′ by similar degrees, *ca.*, 4 Hz. For CH_3, line separations of 1.5, 3.2, and 4.9 Hz were observed in the coupled spectrum. Selective decoupling from H-4 preserved the larger splittings which represent the couplings for CH_3 to H-3 and H-3′. These are also of intermediate magnitude, and are roughly analogous to the couplings between H-4 and H-3 and H-3′. This suggests a similar geometry of CH_3 and of H-4 with respect to H-3 and H-3′. The methyl group of the *cis* isomer appeared as a 2 × 3 × 4 pattern in the coupled spectrum. The splittings of interest are *ca.*, 1 Hz, *ca.*, 1 Hz and 4.6 Hz. The 1 Hz and the 4 Hz splittings probably are couplings to H-3′ and H-3, respectively. Previous work has shown that coupling between equatorial hydrogens is small (35), and this observation appears to carry over to equatorial C-13–H-1 nuclei as well.

With regard to the precise geometry of the four-membered rings, three research groups have published on the use of various nmr parameters to predict the degree of puckering. In contrast to the findings of Gamba and Mondelli, (40) Fomochev, *et al.*, find that ^4J is negative for couplings between both *cis* and *trans* transannular hydrogens (*e.g.*, H-2 and H-4), but larger in magnitude for trans hydrogens (41). Fomochev, *et al.*, find that ^4J(*trans*) diminishes from -1.3 to 0.4 Hz, as the puckering angle diminishes from 21 to 6°. In **1-5**, very sharp nmr peaks were observed, indicative of small long-range coupling. For *trans*-**3**, the line width at half-height for H-2 is 1.02 Hz, compared to 0.95 Hz for *cis*-**3**. The width at half-height is

0.48 Hz for the standard, hexamethyldisiloxane. Thus, the combined ^4J values from H-2 to H-4 and to N-CH_2Ph is on the order of 0.5 Hz. On this basis the degree of puckering would appear to be small. The electronegative nitrogen in the azetidine ring may reduce couplings, however.

Abraham and co-workers have correlated ^3J values (also ^2J values) with puckering angles in a series of cyclobutanes of known geometry (38). For cyclobutanol, in which the puckering angle is *ca.*, 30°, ^3J(ax-ax) is 10.4 Hz and ^3J(ax-eq) is 7.9-9.7 Hz. Escale, *et al.*, find similar values (35). For smaller puckering angles, smaller coupling constants are observed. In the case of *cis*-**4**, the ^3J(ax-ax) values of 8.2-9.2 Hz are similar to Escale's data for compounds having 23-26° puckering angles (35). For the *trans* isomer, the data (Chart II) are not dissimilar to values quoted by Abraham for a planar ring (38). However, it would be difficult to distinguish the average of two slightly puckered conformations from a truly planar form.

Other Data.

The compound lacking the C-4-CH_3 group, 1-cyclohexyl-2-carbomethoxyazetidine (**5**) was briefly investigated. The H-1 data are recorded in Chart III. The data are roughly similar to the data reported by Thomas and Williams for 2-carboxyazetidine (34). One of the chief differences is $^3J(3,4)$ = 2.7 Hx in **5**, compared to 6.0 Hz for analogous protons in 2-carboxyazetidine. Although both values are consistent with equatorial hydrogens, the geometry in the two cases must be somewhat different. Thomas and Williams showed that the greater the degree of puckering, the greater the divergence between the coupling constants of trans hydrogens, *e.g.*, the equatorial hydrogens, H-3 and H-4 vs. the axial hydrogens, H-3′ and H-4′ (34). A coupling constant of 2.7 Hz is similar to data reported by Abraham (2.3 Hz) for a substituted cyclobutane having a dihedral angle of *ca.*, 105° between the coupling hydrogens, and a puckering angle of *ca.*, 30° (38). However, for a planar ring, and dihedral angle of 125°, the coupling constant is *ca.*, 3.5 Hz. Extrapolating between these extremes, a puckering angle for **5** in the range of 15-20° seems likely.

The geminal coupling constant, $^2J(4,4')$ = -7 Hz, is exceptionally low in absolute magnitude, although $^2J(3,3')$ is normal. The $^2J(4,4')$ values were varied considerably using the LAOCON3 simulation program, but the calculated spectrum never fit the observed spectrum adequately if higher $^2J(4,4')$ values were used. In 2-carboxyazetidine (a zwitterion), analogous protons showed ^2J = -10.6 Hz. It seems likely that the low value in **5** is a lone pair effect. Cookson has shown that positive enhancements of ^2J occur when one hydrogen of the CH_2 group is located at a dihedral angle of 0° or 180° from the lone pair (39). In **5**, puckering of the ring indeed would place H-4′ near the optimum 180° angle from the lone pair, thus shifting $^2J(4,4')$ nearer zero. In **5**, H-4′ is shielded by 0.5 ppm compared to H-4. This shielding may also be explained by a delocalization effect involving the lone pair.

Compound **10**, 1-cyclohexyl-2-carboxy-4-methylazetidine is also zwitterionic. It is of interest to see the effect of localizing the *N*-cyclohexyl group in a particular state, as opposed to the rapidly inverting state of nitrogen as occurs in the free amine, **1**. In **10**, the very large $^3J(2,3)$ and $^3J(2,3')$ are suggestive of an axial hydrogen in a puckered ring. The unusual feature of the spectrum is the small $^3J(3,4)$ (3.8 Hz). This is consistent with equatorial hydrogens H-3 and H-4. This required that C-4-CH_3 be axial. However, the nOe on H-2 caused by irradiation of methyl is only + 10%. Prehaps the relatively small magnitude of the effect is due to the fact that the *N*-cyclohexyl group is locked in a position such that some of the cyclohexyl hydrogens lie near H-2 and methyl. These hydrogens would "drain off" the irradiation energy that would otherwise affect the population of H-2 energy levels (30). In the case of **1**, the rapidly inverting *N*-cyclohexyl group would have a shorter correlation time with H-2, and thus a smaller effect.

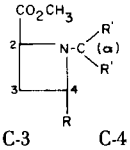
It is perhaps surprising that methyl assumes an axial or pseudoaxial position, and carboxylate an equatorial position. However, Eliel and others have shown that the solvation of carboxylate anions strongly enhances their space demands, and thus their tendency to occupy the least hindered environment (40). It is also of interest that **10** is puckered but *trans*-**1** is effectively planar.

The reason that the *trans* isomers are more stable than the *cis* isomers in **1-4** awaits the knowlegde of the exact geometry and the non-bonded interactions in these molecules. Present indications are that the *N*-alkyl group plays a role. The inward rotation of H-2 and H-4, in order to reduce the bent bonding characteristics of the ring bonds, would compress the *N*-alkyl group in the *cis* isomers (*cf.*, structure **12**), which would create strain. The fairly low steric shift of the *N*-alkyl group of the *trans* isomer compared to similar aziridines might also be due to a more nearly planar configuration at nitrogen in the *trans* azetidine. This would reduce eclipsing interactions between the *N*-alkyl group and methyl or carbomethyoxy.

In order to test the possibility of a different shape of nitrogen in the two azetidine isomers, natural abundance N-15 spectra were run on several compounds (43). In N-15 nmr, the chemical shift of nitrogen is often not highly dependent on which isomer is observed, *e.g.*, in the 1-alkyl-2-nitro-1-propanols. In the case of the *N*-*t*-butyl-2-benzoyl-3-phenylaziridines, the chemical shifts of the *trans* isomer is 24 ppm downfield of the *cis* isomer. This may be explained by three-ring hyperconjugation, in which a no-bond resonance structure exists which places a positive charge on nitrogen and a negative charge on carbonyl

Table I

C-13 Chemical Shifts in ppm of Substituted Azetidine in Deuteriochloroform



Compound	N-R Substituent	R	C-2	C-3	C-4	R	CO	CO_2CH_3	N-C(α)	R'
1 (f)	c-C_6H_{11}	CH_3	59.9	29.2 (b)	56.2	20.0	173.9	51.4	58.2	
2 (f)	iso-C_3H_7	CH_3	60.4	28.7	56.6	20 (b)	173.9	51.4	49.8	*ca.*, 20 (a)
3 (f)	Ph-CH_2	CH_3	61.4	29.3	58.2	18.9	173.2	51.4	54.8	
4 (e,f)	*t*-C_4H_9	CH_3		27.8	54.7	21.2		48.9		24.8 (g)
5	c-C_6H_{11}	H	63.6	21.1 (b)	49.0		173.0	51.4	65.8	
6	iso-C_3H_7	H	63.9	20.6 (b)	49.5		173.2	51.6	57.7	*ca.*, 20.6 (a)
7	Ph-CH_2	H	63.9	21.2	50.4		172.3	51.2	61.9	
8	Ph_2-CH	H	64.5	20.9	(c)		172.6	51.3	77.3	
9	*t*-C_4H_9	H	57.9	20.1	43.2		173.7	52.4 (d)	51.5 (d)	

(a) Diastreotopic methyls. (b) Tentative assignment, many other alkyl absorptions nearby. (c) Missing, probably superposed with CO_2CH_3. (d) Could be reversed. (e) Very rough values, determined from an extremely dilute sample. (f) *Trans* isomers (Isomer A). (g) Methyl.

(29,43). In addition, this effect increases the C-N bond order. In the *cis* isomer, a steric shift by the C-2 and C-3 substituents on the lone pair should produce strong shielding of N-15.

In the case of the azetidines, **1**, a substantial difference between isomers is also observed. The peak at 74 ppm is assigned to the trans isomer, and that at 64 to the *cis*. For *trans*-**3**, the chemical shift is 71 ppm, and for **5**, the chemical shift is 60 ppm. As **5** lacks a C_4-CH_3 group, the downfield shifts of **1** and **3** are due to a *beta* effect (41). With regard to *cis* and *trans*-**1**, a steric effect on the lone pair should occur in the *cis* isomer (44). This effect should not be as severe as for the aziridines, as the equatorial substituents in the azetidines are not eclipsed with the lone pair. The substantial chemical shift difference between *cis* and *trans* isomers is suggestive of a variation in the state of nitrogen.

Spectra.

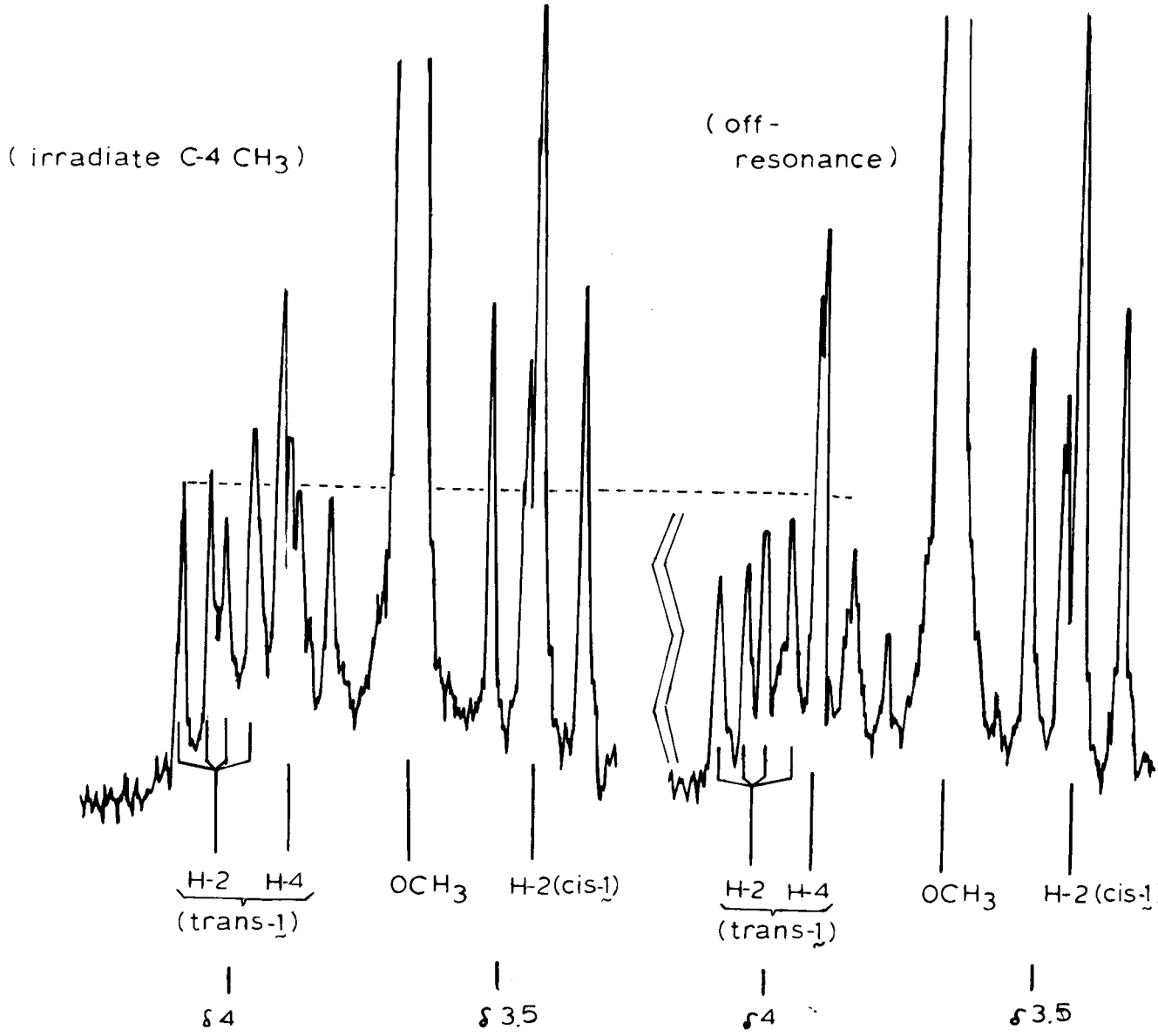
In H-1 nmr spectra were run on a Varian EM-390, an XL-100, or less frequently, on a A-60D. The spectra of **1** and **5**, were also run by the Colorado State Regional NMR Center on a Nicolet 360 MHz instrument [not 220 MHz as previously reported (24)]. The H-1 spectra were taken in 2-6% w/v solutions in deuteriochloroform at normal probe temperature, which ranges from 22-26° on the various instruments. The zwitterion, **10**, was run in deuterium oxide, using TSP as the internal standard. The coupling constants were determined from suitable expansions of the spectral region in question. The spectrometers had been recently calibrated.

The nOe effects were determined using samples deoxygenated by nitrogen entrainment (nitrogen was passed through until about half the solvent was evaporated). The nOe's were run on the XL-100, as a deuterium lock was available, although decoupler-integrator difficulties were present. The methyl group was irradiated using a trial-and error search technique to identify the frequency that afforded the greatest response. Similarly, the optimum power level for the decoupler was established (usually 99db low power, or slightly less than 1 watt). The best integration results (an average of 7 determinations) gave a 4 % enhancement for H-2 on irradiation of methyl in the compound later established as trans. The other isomer showed a 1% decrease in intensity of H-2, compared to the intensity observed on irradiation of an empty region of the spectrum. The effects on signal intensity (Figure 1) were more striking.

The long range coupling constant investigations were run on the EM-390, using a multiply filtered solution, and using 0.5 ppm as full scale with very slow scan speeds.

The following represent the results of an iterative fit of the spectra of **4**, and other compounds using LAOCON3. For *trans*-**4** (isomer A), the computer generated plot was superimposable on the original spectrum in the H-3 and H-3′ region, which contains all of the important data. The RMS error for the best fit was 0.156; the probable errors in the data sets are: for $^3J(2,3)$ = 5.3 Hz, 0.062; for $^3J(2,3')$ = 8.2 Hz, 0.061; for $^2J(3,3')$ = -10.4 Hz, 0.042; for $^3J(3,4)$ = 7.6 Hz, 0.062; and for $^3J(3',4)$ = 5.0 Hz, 0.060. For *cis*-**4** (isomer B), the computer generated plot was also superimposible on the original. The RMS error was 0.133, with probable errors in the data sets: for $^3J(2,3)$ = 9.2 Hz, 0.053; for $^3J(2,3')$ = 8.2 Hz, 0.051; for $^2J(3,3')$ = -10.8 Hz, 0.036; for $^3J(3,4)$ = 8.2 Hz, 0.053, and for $^3J(3,4')$ = 8.2 Hz, 0.051.

The zwitterion, **10**, was also fitted by iterative techniques: RMS error, 0.202; probable error in data sets: chemical shifts of H-2, H-3, and H-3′, 0.059, 0.044, and



Nuclear Overhauser effect, comparing the signal enhance ment of H-2 on irradiation of CH_3 (left spectrum), with the signal on irradiation of an irrelevant position (right spec trum).

0.136 respectively; $^3J(2,3)$ = 9.3 Hz, 0.077; $^3J(2,3')$ = 9.6 Hz, 0.088; for $^2J(3,3')$ = -11.9 Hz, 0.064; $^4J(1,4)$ = -01 Hz, 0.105, $^5J(1,CH_3)$ = 0.0 Hz, 0.117; $^3J(3,4)$ = 8.9 Hz, 0.086; $^3J(3',4)$ = 3.3 Hz, 0.108. A few additional attempts were made by trial-and-error in order to attain a better fit of the spectrum; these led to the data reported to Chart III.

The most difficult case was **5**. About 20 attempts were made by trial-and-error in order to attain a reasonable fit of the 90 MHz spectrum. However, it developed that the computer generated plot was not accurate. Stick plots were made by hand, which fit the original spectrum adequately, although the error in data probably is larger than the other data reported herein. For **1**, and **5**, the 360 MHz spectra did not carry large enough expansions in order to observe the coupling constants accurately.

The C-13 data were obtained on an XL-100 using the following procedure: 5000 transients were collected using a tip angle of *ca.*, 45°, and an acquisition time of 0.8 s, which with the present system, gives an error in line position of 1.25 Hz. The center line of deuteriochloroform was taken as the standard, *i.e.*, 76.9 ppm from TMS, the ultimate standard against which the data of Table I are

given. The spectra were run in deuteriochloroform at an approximate concentration of 0.1 g/ml. In order to observe C-13–H-1 coupling constants, a solution of 0.3 g/ml was necessary. A 1000 Hz window was used, with a 4 s acquisition time (error in line position, 0.25 Hz). The tip angle was *ca.*, 70°, and about 10 K of transients were necessary. The spectra were not simulated.

The N-15 spectra were taken on a Varian XL-100, using not less than 1 g of substrate in 3 ml of nitromethane (whose resonance was taken as 380 ppm from ammonia, the ultimate standard). The tip angle was *ca.*, 23°; 10 K of transients were collected at a spectral width of 5 KHz. The solutions contained about 100 mg of $Cr(acac)_3$; the pulse repetition rate was 5.8 s.

The following chemical shifts for *trans*-**1** (at 360 MHz) afforded certain corrections of data given in an earlier paper (20). δ 1.2 (m, 6, cyclohexyl), 1.28 (d, 3, CH_3), 1.66 (m, 4, cyclohexyl), 1.94 (m, 1, H-3′), 2.33 (m, 1, H-3), 2.57 (m, 1, H-α), 3.72 (s, 3, OCH_3), 3.94 (m, 1, H-4), and 4.11 (m, 1, H-2). For **5**: (*ca.*, 3% w/v in deuteriochloroform, at 360 MHz): δ 1.0-1.3 (m, 6, cyclohexyl), 1.5-1.8 (m, 4, cyclohexyl), 2.07 (m, 1, H-3), 2.22 (m, 1, H-3), 2.31 (q, 1, H-α), 2.90 (m, 1, H-4′), 3.42 (m, 1, H-4), 3.67 (t, 1, H-2) and 3.73 (s, 1, OCH_3). For **10**, (deuterium oxide at 100 MHz): δ 1.1-1.4 (m, 6, cyclohexyl), 1.65 (d, 3, CH_3), 1.7-2.0 (m, 4, cyclohexyl), 2.31 (m, 1, H-3), 2.64 (m, 1, H-3′), ca. 3.25 (broad, s, 1, H-α), ca. 4.5 (m, 1, H-4), and 4.69 (t, 1, H-2).

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