Conformation Preferences in Nitro-alcohols: Possible Donor–Acceptor Interactions

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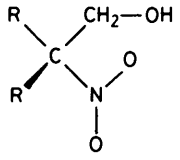
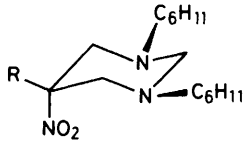
By means of ^{1}H and ^{13}C n.m.r. coupling constants, dilution studies, the effect of solvent, and limited i.r. studies, the configuration and conformation in a group of diastereoisomeric nitro-alcohols, such as 3-nitrobutan-2-ol are assigned. The question of interest concerns the effect of intramolecular hydrogen bonding between nitro and hydroxy on conformation. This effect proved to be weak. The OH n.m.r. signal was split into a doublet, in certain cases; the magnitude of the splitting was not indicative of prevalent hydrogen bonding, in agreement with hydroxy chemical shift, and with vicinal proton coupling constants. The ^{15}N chemical shifts were similar to nitromethane, and not sensitive to the state of isomerism. Deuterium for hydrogen exchange occurred at the carbon bearing the nitro group with high retention of configuration.

In an early study of the conformation of vicinal nitro-alcohols [*e.g.* (1)], Urbanski concluded that the NO_2 and OH functions were either gauche or eclipsed.[1] Intramolecular hydrogen bonding was believed to be the reason for this conformational preference. Flett, Kuhn, and their co-workers found that the i.r. $\Delta\nu$ was of the order of 15—30 cm^{-1} in 2-nitroethanol, *i.e.* hydrogen bonding was weak.[2] However, Urbanski's dipole moment data were suggestive of a strong conformational preference. Ungnade and Kissinger interpreted the i.r. data in a 2-nitro-1,3-diol in terms of an interesting effect: the nitro-group was believed to inhibit intramolecular hydrogen bonding between the two hydroxy-groups.[3] Similarly, an intermolecular hydrogen bond between alcohols was thought to be inhibited by nitromethane. The nitro and alcohol functions were considered to engage in an unspecified type of interaction that is responsible for the inhibition. This work was sharply criticized by Schleyer and his co-workers.[4] Under high resolution conditions, new hydroxy i.r. absorptions occur in the presence of the nitro-group. These peaks were considered to be due to $NO_2 \cdots HO$ hydrogen bonding. These peaks lie very close to the free hydroxy absorption.[5] The reason that a weak $NO_2 \cdots HO$ interaction is able to overcome a stronger $HO \cdots HO$ hydrogen bond was ascribed to proximity effects, despite the fact that a six-membered hydrogen bonded ring occurs in either case.

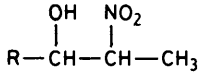
In other work, Urbanski and his co-workers found that the nitro-group prefers the axial position in certain 5-nitro-1,3-dioxans, oxazine, and hydropyrimidines, *e.g.* (2). The nitro group lies gauche to both ring hetero-atoms. This preference is reduced when an acceptor, *e.g.* boron, replaces C_2. A similar conformational preference, *i.e.* the tendency for the halogens of vicinal dihalides to be gauche was studied by Lowe and by Wolfe and his co-workers.[6,7] This preference was termed the 'gauche effect' by Wolfe, who at one time considered an attractive $X \cdots X$ interaction to be the possible source of the conformational preference. Phillips and Wray showed that the effect is more pronounced for the more electronegative halogens.[8] Several quantum mechanical reasons for the preference have been advanced, which lack agreement as to the origin of the effect.[9-11] Pople and his co-workers, and also Brunck and Weinhold suggest that the $X \cdots X$ interaction *per se* is repulsive. The gauche preference arises essentially from a hyperconjugative type of interaction of X with appropriately oriented vicinal hydrogens.[9] However, other molecules, *e.g.* butanedinitrile, also prefer the gauche orientation.[12,13] It is questionable whether the carbon of cyanide is sufficiently electronegative to enable the interaction to take place. It is not known at present whether the dinitriles



(1)



(2) R = Me, Et, Pr^n



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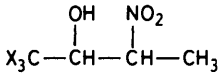
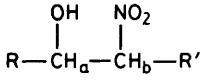
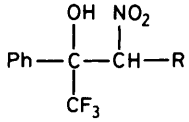


(4)



(5) R = R' = CH_3
(6) R = Pr^i, R' = CH_3
(7) R = CF_3, R' = CH_3
(8) R = CCl_3, R' = CH_3
(9) R = CBr_3, R' = CH_3
(10) R = p-$O_2NC_6H_4$, R' = C_2H_5
(11) R = p-$O_2NC_6H_4$, R' = Pr^i



(12) R = CH_3
(13) R = H

are gauche for some other reason, or if the hyperconjugative effect is in fact incorrect. Abraham and his co-workers have shown that special explanations are unnecessary in order to explain the conformational preferences in a group of fluorocarbons.[14] Force-field calculations adequately foretold the conformation. In other

work, Abraham and his co-workers have demonstrated the extreme solvent dependence of similar polar molecules. In one case, an attractive halogen–vicinal hydrogen interaction was postulated.[15]

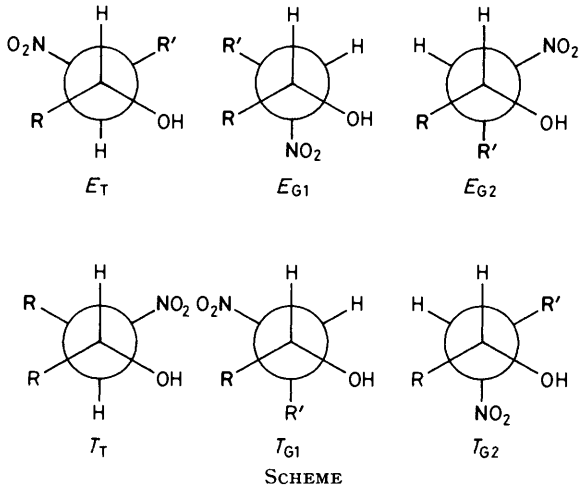
The present study concerns nitro-alcohols of general structures (3) and (4). Several aspects are of interest: (i) the effect of hydrogen bonding on molecular conformation as studied by n.m.r. (in particular, the effects of strong hydrogen bonding solvents, and also studies on congeners incapable of hydrogen bonding); (ii) comparison of non-hydrogen groups, *e.g.* CX_3, with methyl; (iii) investigation of $^{13}C \cdots {}^1H$ n.m.r. coupling constants for CX_3 groups; (iv) ^{15}N n.m.r. studies; and (v) brief experiments on deuterium–hydrogen exchange.

In the molecules of interest, the evidence for conformation involves ^1H coupling constants, ^{13}C chemical shifts, and $^{13}C \cdots {}^1H$ coupling constants. Regrettably, separations of the diastereoisomers by preparative g.l.c. have not been possible in our hands, although analytical separations were accomplished. Thus, i.r. data were possible only on a few compounds which were obtained diastereoisomerically pure by other means.

As in previous studies, $^3J_{ab}$ values of 10—13 Hz are taken as an indication of a strong preference for *trans*-vicinal protons; $^3J_{ab}$ of 1—3 Hz indicate gauche protons.[16] Intermediate values are due to a mixture of conformers, or due to a high weight of a conformer with highly skewed dihedral angles. Vicinal $^{13}C \cdots {}^1H$ coupling constants of 5—7 Hz are found for *trans*-nuclei, and 0—2 Hz are found for gauche nuclei if carbon is sp^3. Lemieux and his co-workers have warned of possible anomalies in ^{13}C coupling constants, and these data must be regarded as less reliable.[17]

3-Nitrobutan-2-ol (5) was intended as a reference molecule against which the behaviour of the trihalogenomethyl compounds could be compared. However, (5) itself proved to be unusual. Condensation of nitroethane with acetaldehyde gave the two diastereoisomers of (5) in a 60 : 40 ratio. The isomers exhibited separate, split OH signals at high concentration (20% w/v $CDCl_3$ solutions). However, the magnitudes of the $^3J_{OH-H_a}$ splittings (*ca.* 6 Hz) are indicative of rotational averaging. The maxima and minima of $^3J_{HO-H}$ have been shown to follow a Karplus relationship, with magnitudes rather similar to the more familiar H–C–C–H couplings.[18] Strangely, as the concentration of the solution is decreased, OH broadens, splitting is lost, and the two signals coalesce. Even at −69° at 1% w/v, splittings were not observed. Only with freshly prepared (5) in purified $CDCl_3$ were splittings again found at 1% w/v, *i.e.* 6.1 and 4.7 Hz respectively. The splittings at high concentration are presently believed to be due to a dimeric structure. In a test molecule (12), the apparent molecular weight determined by osmometry was 6% high from data taken in 1—3% w/v solutions in benzene. Investigations of the n.m.r. chemical shift in other solvents, *e.g.* CCl_4 and CS_2 were not informative. The chemical shift of OH in these solutions (single, broad peaks) is δ 2.28 and *ca.* 2.0, respectively, somewhat above the theoretical limit for an unassociated OH in a non-polar solvent, δ *ca.* 0.9.[19]

The configuration and conformation of the hydrocarbon backbone of the molecule will be discussed with reference to the Newman projections shown in the Scheme (*E* = *erythro*, *T* = *threo*). The overlapping multiplets of the two isomers were simplified by spin decoupling from methyl. The major isomer showed a $^3J_{ab}$ of *ca.* 7.8 Hz (Table 1), indicative of a sizeable population of a conformer with *trans*-vicinal hydrogens, *i.e.* E_T or T_T. The minor isomer exhibited a $^3J_{ab}$ of 3.7 Hz, which indicates a strong preference for conformer(s) with gauche hydrogens. These values were later confirmed in high field spectra. The effect of moving to the powerful hydrogen bonding solvent, $[^2H_6]$DMSO, is rather small. Both isomers exhibit slightly larger $^3J_{ab}$ values in this



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solvent. In contrast, vicinal diols show a more profound change on moving to more polar solvents. The *erythro*-isomer, in particular, undergoes a *ca.* 2 Hz increase in $^3J_{ab}$ due to break-up of the internal hydrogen bond and population of conformer E_T.[20] However, in weakly hydrogen bonded systems, *e.g.* sulphide-alcohols, $[^2H_6]$-DMSO has little effect.[21] The hydrogen bond is not a compelling force in the determination of conformation, and the break-up of this hydrogen bond thus has little effect.

Observation of the $^{13}CH_3$ splittings permitted an assignment of configuration. For the minor isomer $^3J_{CH_3'-H_a}$ is rather large, 3.3 Hz. The population of conformers having *trans*-methyl and hydrogen nuclei (either T_{G1} or E_{G2}) is moderately high. If T_{G1} is indeed substantially populated, the other methyl, CH_3, should exhibit a similar coupling constant, as both methyls are *trans* to their respective hydrogens. However, $^3J_{CH_3-H_b}$ (2.2 Hz) is substantially smaller. These data can be accommodated by conformer E_{G_2} of the *erythro*-configuration.

In the minor isomer, R′ = CH_3' lies upfield in chemical shift (12.2 p.p.m.) compared with the analogous methyl in the major diastereoisomer (15.5 p.p.m.). This difference is consistent with conformer E_{G_2} for the minor isomer, as

R′ = CH_3′ lies gauche to two major groups and should suffer a steric shift. Again T_{G1} is unacceptable, as *both* methyls would be expected to lie upfield due to their congested environment. However, CH_3 (*ca.* 18 p.p.m.) lies down-field in both isomers.

For the major isomer, the large $^3J_{ab}$ suggests that roughly equal proportions of conformers T_T and T_{G2} are present. The moderately small $^3J_{CH_3-H}$ values are consistent with this assignment, as the methyl groups and their respective vicinal hydrogens are gauche in both T_T and T_{G2}. It is noteworthy that both diastereoisomers favour conformers having gauche NO_2 and OH functions, as suggested by the early work of Urbanski.[1] The conformational preferences are roughly similar to 1,2-dialkylethane diols, in which an attractive interaction (hydrogen bonding in the case of the diols) overcomes the tendency for the alkyl groups to be *trans*.[21] However, for (5), neither the chemical shift of OH, nor the OH splitting is indicative of prevalent internal hydrogen bonding. For *erythro*-(5), $^3J_{OH-H_a}$ would be *ca.* 1 Hz if intramolecular hydrogen bonding were important and if conformer E_{G2} is populated. In certain sulphoxide-alcohols, similar values have been observed.[22]

Compound (6), 2-methyl-4-nitropentan-3-ol, is similar to (5), but conformational preferences are more pronounced despite the presence of the larger isopropyl group. In particular, $^3J_{CH_3'-H_a}$ of one isomer is 3.7 Hz, one of the higher values seen (methyl is rarely *trans* to a hydrogen).[23] The same methyl lies even more strongly upfield (11.8 p.p.m.) than its counterpart in the other diastereoisomer (16.1 p.p.m.). In view of these data and the low $^3J_{ab}$, the *erythro*-configuration is indicated, with a preference for E_{G2}. The *threo*-isomer again occupies T_T and T_{G2} about equally. Each of these conformers permits the isopropyl group to occupy a reasonably strain free environment.

TABLE 1

^1H and ^{13}C n.m.r. coupling constants

Compound		$^3J_{ab}$ ($CDCl_3$)/Hz 20%	10%	1%	$^3J_{ab}$ ([$^2H_6$]-DMSO)[d]/ Hz	$^3J_{HO-H_a}$ ($CDCl_3$)/Hz 20%	1%	$^3J_{HO-H_a}$ ([$^2H_6$]-DMSO)[d]/ Hz	$^3J_{CH_3'-H_a}$ ($CDCl_3$)[c]/ Hz	$^3J_{R-Hb}$ ($CDCl_3$)[c]/ Hz
(5)	*T*[a]	7.8	7.7	7.5	8.1	6.3	6.1		2.3	2.1
	E[b]	3.7	3.6	3.4	4.1	*ca.* 5	4.7		3.3	2.2
(6)	*T*	7.6	7.5	7.3	8.4		4.8	6.5	1.8	
	E	3.6	3.4	3.4	4.1		7.2	6.9	3.7	
(7)	*T*	7.4	7.5	7.1	7.1			*ca.* 7	1.8	*ca.* 0
	E	*ca.* 3	*ca.* 3	*ca.* 3	3.8			*ca.* 6	3.2	*ca.* 0
(8)	*T*	5.1	5.1	4.9	6.2		*ca.* 5	*ca.* 6	2.2	1.7
	E	3.1	3.1	3.1	3.2		*ca.* 5	*ca.* 6	2.1	3.7
(9)	*T*	4.5		4.4	6.2				1.7	2.0
	E	3.0	2.9	3.0	2.8				2.0	3.7
(10)	*T*		8.5	8.1	8.6	5.2	4.5	4.9		
(11)	*T*?	6.7	6.4	6.2	7.9	6.9	7.8	5.1		

[a] *threo*-Isomer. [b] *erythro*-Isomer. [c] A concentrated solution, *ca.* 33% w/v, is necessary in order to observe these coupling constants. [d] The concentration effect is small.

TABLE 2

Chemical shifts[a]

Compound	Isomer	^{13}C [δ (p.p.m.)] C_a	C_b	R	R′	^1H (δ) H_a	H_b	R	R′
(5)	*T*	68.1	88.6	18.7	15.5	4.15	4.48	1.28	1.56
	E	68.9	86.8	18.4	12.2	4.36	4.51	1.25	1.56
(6)	*T*	76.9	84.5	29.5[b]	16.1	3.69	*ca.* 4.6	1.7[b]	1.51
	E	77.2	86.3	30.7[b]	11.8	3.87	*ca.* 4.6	1.7[b]	1.51
(7)	*T*	70.1	78.1	123.1	15.7	4.44	*ca.* 4.8		1.68
	E	71.3	78.1	123.1	12.2	4.76	*ca.* 4.8		1.68
(8)	*T*	78.1	83.1	99.1	18.5	4.41	*ca.* 5.2		1.83
	E	80.9	82.1	100.2	14.4	5.00	*ca.* 5.2		1.77
(9)	*T*	82.9	84.1	45.4	19.4	4.38	*ca.* 5.2		1.91
	E	81.8	83.8	47.4	15.3	5.02	*ca.* 5.2		1.81
(10)	*T*					5.19	4.62	8.24	1.2—2.1 (CH_2)
								7.58	0.91 (CH_3)
(11)	*T*?					5.32	4.59	8.21	2.14 (CH)
								7.57	1.05 (CH_3)
									1.02 (CH_3)

[a] ^{13}C Chemical shifts were taken at an approximate concentration of 30% (w/v) in $CDCl_3$. ^1H chemical shifts were observed at 20—10% (w/v) in $CDCl_3$. The centre line of the $CDCl_3$ pattern was taken as the ^{13}C standard at δ 76.9 p.p.m from tetramethylsilane. [b] Methine carbon and hydrogen.

In (6), hydroxy splitting was noted at high dilution using purified solvents. The $^3J_{OH-H_a}$ values of 7.2 and 4.8 Hz are roughly similar to the splittings in [$^2H_6$]DMSO, *i.e.* 6.9 and 6.5 Hz.

In the trihalogenomethyl compounds (7)—(9), the increased acidity of the hydroxy-group, with consequent rapid exchange, made observation of hydroxy-splittings difficult. However, splittings could be observed for the trichloromethyl compound in both $CDCl_3$ and in [$^2H_6$]-DMSO, and for the trifluoromethyl compound in [$^2H_6$]-DMSO. The magnitudes of the splittings (Table 1) are unexceptional and again not indicative of a restriction of conformation by intramolecular hydrogen bonding.

In other respects, the trihalogenomethyl compounds are quite different from one another. Investigation of (7) proceeded with difficulty. As with (5), the H_a and H_b resonances are not well separated. Splittings by ^{19}F provided an additional complication. The latter were identified by observation of ^{19}F (among others, a $^5J_{CF_3-CH_3}$ of 1.2 Hz was observed for both isomers). Spin decoupling from methyl simplified the ^1H spectra sufficiently that $^3J_{ab}$ could be approximated, as the ^{19}F splittings were then known. Nonetheless, $^3J_{ab}$ for one isomer could only be roughly determined, *ca.* 3 Hz. For this diastereoisomer, $^3J_{CH_3-H_a}$ is 3.6 Hz. These data strongly suggest the *erythro*-configuration and conformer E_{G2}. The *threo*-diastereoisomer ($^3J_{ab}$ 7.4, $^3J_{CH_3-H_a}$ 1.8 Hz) again prefers conformers T_G and T_{G2}, similar to (5) and (6). It is somewhat surprising that the introduction of CF_3 did not result in a larger effect. The methyl group is ' fluorophobic '. Fluorocarbons and hydrocarbons are insoluble in most proportions, probably due to the lack of polarizability interactions in the perfluoroalkane molecules.[24] The non-bonded interactions of these two types of groups must be unfavourable. Thus, a lower population of conformers such as E_{G2}, in which CH_3 and CF_3 are gauche, might have been expected.

It had been hoped that the splittings of the $^{13}CF_3$ group could be used as evidence for conformation. However, the $^{13}CF_3$ resonances were nearly superposed. Only a single sizeable splitting of 4.6 Hz plus a small splitting of the order of 0.7 Hz were evident in the coupled spectra. Exchange experiments were attempted in order to tell which splitting is $^2J_{CF_3-H_a}$ and which is $^3J_{CF_3-H_b}$. The results were suggestive of the larger splitting being ^2J although these results were not conclusive. A model compound, 2,2,2-trifluoroethanol, shows a $^2J_{CF_3-H}$ of *ca.* 3 Hz. Thus, present indications are that the larger splitting in (7) is ^2J. The very small ^3J value is consistent with the predominately gauche CF_3 and H_b in the major conformers, E_{G2} and T_T and T_{G2}. The effect of the electronegativity of fluorine is not known, but indications are that $^3J_{CF_3-H_b}$ should be enhanced.[25]

The trichloromethyl and tribromomethyl compounds (8) and (9) are quite different from (7). Both (8) and (9) show substantially smaller $^3J_{ab}$ values (*ca.* 5 Hz) than (7) (7.4 Hz), for the isomer presumed to be *threo*. The $^3J_{CH_3-H_a}$ values are again *ca.* 2 Hz, indicating that conformers with gauche CH_3 and H_a groups are preferred. The proof that the isomer in question is *threo* is derived from the splittings of $^{13}CCl_3$ and $^{13}CBr_3$. In the former case, splittings of 1.7 and *ca.* 0.5 were observed, and in the latter case, the values were 2.5 and 0.5 Hz. For (8), the larger of the two splittings disappeared upon deuterium for H_b exchange, proving that $^3J_{CCl_3-H_b}$ is *ca.* 2 Hz. In the case of the *erythro*-isomer, $^3J_{CCl_3-H_b}$ is similarly identified as 3.7 Hz. For the *threo*-isomer, the combination of $^3J_{ab}$ (intermediate in magnitude), $^3J_{CH_3-H_a}$ (small), and $^3J_{CX-H_b}$ (small) is consistent with a combination of conformers T_T and T_{G2} that is rather larger in weight of T_{G2} than previous cases. The reason for the apparent reversal in magnitudes of ^2J and ^3J in the CX_3 splittings between (7) and (8) is unknown.

For the erythro isomers of (8) and (9), the combination of $^3J_{ab}$ (small), $^3J_{CH_3-H_b}$ (small), and $^3J_{CH_3-Hb}$ [quite sizeable, 3.7 for (8) and 4.5 Hz for (9)] requires a conformer with gauche hydrogens and *trans* CX_3 and H_b groups. Only E_{G1} fits these data. None of the *threo*-conformers, individually or in combination, is easily accommodated. It is noteworthy that CX_3 as well as OH are now gauche to NO_2 in both isomers of (8) and (9), despite steric problems for CX_3 in E_{G1}.

Compound (10) was obtained diastereoisomerically pure. The purity stems from a second-order asymmetric transformation during synthesis, which merely means that the least soluble isomer of an equilibrating system happens to precipitate.[26] The identity of this single isomer is probably *threo*. A related aromatic nitro-alcohol 1-phenyl-2-nitropropan-1-ol exhibited $^3J_{ab}$ values rather similar to (5)—(7), *i.e. ca.* 8 and *ca.* 4 Hz for the two isomers. The single isomer of (10) exhibits a $^3J_{ab}$ of 8.5 Hz similar to the *threo* isomer of (5)—(7). The preferred conformers are quite likely T_T and T_{G2}. As in the case of (5), (10) showed splittings of the hydroxy resonance at high concentration (4.5 Hz at 20% w/v, $CDCl_3$). This splitting was lost on dilution, but reappeared at low concentration (4.9 Hz, 1% w/v, $CDCl_3$). These coupling constants are similar to those observed in [$^2H_6$]DMSO.

The i.r. spectrum of (10) avoids the ambiguity associated with spectra of mixtures of isomers. For (10), i.r. peaks were observed at 3 617 cm^{-1} (s), and at 3 609 cm^{-1} (w, br) at 0.2% w/v CCl_4. This certainly does not suggest strong intramolecular hydrogen bonding. However, another aromatic nitro-alcohol, 3-methyl-2-nitro-1-(4-nitrophenyl)butan-2-ol (11), was also obtained nearly diastereoisomerically pure. The conformational preference for T_{G2} is more pronounced ($^3J_{ab}$ 6.5 Hz). The isopropyl group appears from models to be less hindered in this conformer. At low concentration, $^3J_{OH-H_a}$ is larger (7.8 Hz) than for other compounds of this study. In T_{G2}, molecular models suggest that a dihedral angle of *ca.* 120—150° pertains for OH and H_a. Furthermore, the isopropyl group forces the nitro-group to lie edgewise toward OH. In the i.r., hydroxy-peaks were observed at 3 611 (m, br) and at 3 539 (m, br). The latter is suggestive of an intramolecular hydrogen bond of moderate strength.

The trifluoromethyl compound (12) also was obtained diastereoisomerically pure. Over a concentration range down to 0.2% w/v in CCl_4, no free hydroxy was observed. At low concentration, only a broad peak at 3 510 cm^{-1} was found. Similar results were observed for (13) in which only one isomer is possible. In these trifluoromethyl compounds, the enhanced acidity and therefore the enhanced donor ability of the hydroxy group evidently facilitates hydrogen bonding. Similar results would be expected for (7)—(9), and indeed (8) shows $\bar{\nu}_{OH}$ 3 610 (s) and 3 502 (s) cm^{-1} (spectra run on mixed isomers).

The pattern that emerges from the i.r. and ^1H and ^{13}C n.m.r. results indicates a variable tendency for intramolecular hydrogen bonding. Whether or not hydrogen bonding exists, a strong tendency for the nitro and hydroxy functions to be gauche exists. The latter observation is amplified by study of the acetate derivative of (5). The ^1H and ^{13}C coupling constants were extremely similar for the acetate and the parent alcohol, indicative of similar conformational preferences. The preference for gauche nitro and oxygen functions stems from some other influence that occurs in addition to hydrogen bonding, if any.

The tendency for CX_3 to be gauche to NO_2 when X = Br or Cl (not F) raises the question of a possible charge-transfer interaction. In view of the well known ability of amines to complex with nitro functions, either through a charge-transfer interaction or through a two-electron donor–acceptor interaction,[27-30] it is possible that the OH group may have a similar interaction with NO_2. Charge-transfer interaction has an identifiable, but often rather small effect on the ^1H and ^{13}C spectra of the molecules involved.[27] In order to investigate the group directly involved in such complexation, if any, ^{15}N spectra were studied. The sensitivity of ^{15}N spectra to even small amounts of unpaired electron density *via* n–π^* processes is well known.[31] The chemical shift of pyridine nitrogen is extremely sensitive to lanthanide shift reagents. The enormous shifts quite likely are due to contact as well as pseudocontact interactions, which involve the placement of unpaired electron density at the nucleus in question.[31]

In view of the similarity in chemical shift of *o*-nitrophenol ($\Delta\bar{\nu}$ *ca.* 300 cm^{-1}) and *p*-nitrophenol, hydrogen bonding appears to have a small effect on the $^{15}NO_2$ chemical shift.[31] Similarly, the literature suggests that $^{15}NO_2$ in substituted nitrobenzenes is unresponsive to electron donation or withdrawal.[31] For (5), the $^{15}NO_2$ resonances of the two isomers (396 and 395 p.p.m. from $^{15}NH_3$) were similar to nitromethane (380 p.p.m.) and not too sensitive to a change from nitromethane as solvent to a nitromethane : DMSO mixture (2 : 1) (395 and *ca.* 393 p.p.m.). In the case of (6), the two isomers were found at 396 and 397 p.p.m., which suggests that a change in alkyl substitution also has little effect. The chemical shift of nitroethane and 1-nitro-3-methylbutane are also similar (391 and 388 p.p.m.). The trifluoromethyl compound (7) showed two closely spaced peaks at 388 p.p.m., compared to 390 and 391 p.p.m. for (8). The latter changed slightly to *ca.* 292 p.p.m. in nitromethane–DMSO (1 : 1). The ^{15}N spectra were not indicative of any unusual effects whatsoever.

Exchange Experiments.—Deuterium–hydrogen exchange was originally attempted with little thought of eventual success. A retrocondensation was expected, and indeed this occurred for the aromatic nitro-alcohols. Decomposition also occurred for the sensitive CBr_3 compound (9). The other difficulty was possible equilibration. In the 1930s, soon after deuterium became available, Ingold and his co-workers investigated the rate of bromination, racemization, and deuterium exchange in a chiral ketone.[32] The equivalent rates of these processes was indicative of a planar intermediate. The lack of stereochemistry eliminated interest for many years until Cram and Wingrove showed that chiral sulphones, as well as other molecules yielding stabilized carbanions, exhibited different rates of racemization and exchange.[33] It was suggested that $R(R')C^-(XO_2)$ anions were capable of preservation of geometry, in contrast to $R(R')C^-(XO)$ anions.[34] In the present case (XO_2 = NO_2), this finding appears to be upheld. In the case of the CCl_3 compound (8) the *threo*-isomer exchanged deuterium for hydrogen completely while the *erythro*-isomer was in its first half-life (essentially one third exchanged). There was no apparent change in the intensities of other ^1H or ^{13}C peaks between the two isomers. The results in either pyridine–D_2O or [$^2H_6$]DMSO –D_2O mixtures (with a trace of piperidine as catalyst) were very similar.

In the case of (5), the rates of exchange of the two isomers were more nearly equal. The *erythro*-isomer exchanged slightly more rapidly. For (6), sizeable differences again occurred. After one half-life of exchange of the *threo*-isomer, the *erythro*-isomer had barely reacted. Compound (7) exchanged so rapidly that comparisons were impossible. Both H_a and H_b diminished in intensity.

The apparent faster rate of exchange than diastereoisomeric interconversion for (6) and (8) brings into question the commonly held idea that protonation on oxygen should occur, followed by rearrangement of the *aci*-nitro intermediate. It seems quite likely that the hydroxy-group plays a role in the exchange process, but the exact nature of its involvement must be clarified in future research. It is noteworthy that a recent study of nitronate salts indicated a planar structure for these salts.[35,36] If so, the dominant process must be a proton attack on one side of the planar structure, perhaps mediated by hydroxy.

In conclusion, it should be reiterated that the NO_2 and OH functions prefer a gauche orientation even in polar solvents in which external hydrogen bonding prevails (as evidenced by the strong downfield shift of OH). Certain CX_3 groups also prefer a gauche orientation to NO_2. The OH coupling constants were not indicative of a strong conformational preference, and in many cases were very similar in dilute $CDCl_3$ as in very concentrated $CDCl_3$ or in DMSO solutions, where inter-

molecular hydrogen bonding is likely. The acetate derivative of one compound exhibited similar conformational preferences as the parent alcohol. No evidence for a charge-transfer interaction of CX_3 or OH with NO_2 was found. We disagree that hydrogen bonding is a strong force that dominates the choice of conformation. The strongest alternatives appear to be either a two-electron donor–acceptor interaction of the OH and NO_2 functions, or the dominance of quantum mechanical forces associated with the gauche effect.

The failure of the nitro-group to engage to a greater degree in hydrogen bonding is surprising, but finds analogy in the case of the sulphone group.[37] Photoelectron spectra of nitroalkanes have been interpreted in terms of a strongly bonding $^2A_1$ orbital of lowest ionization potential.[38] The electrons of this bonding orbital presumably are not accessible to a hydrogen bond donor unless bonding is reduced. The next highest energy electrons occupy a π non-bonding orbital. π Orbitals have seldom been implicated in strong hydrogen bonding. The third highest energy electrons occupy a $^2B_2$ antibonding σ orbital. Although the spatial characteristics of this orbital seem favourable, these low energy electrons may simply be unavailable, much the same as non-bonded krypton electrons.

EXPERIMENTAL

The general procedure for the preparation of the nitroalcohols was the method of Henry (procedure A), or a variant thereof (procedure B).[39]

Compound (5) was prepared by procedure A by mixing nitroethane (150 g, 2.0 mol) with water (120 ml) in a flask (1 l); acetaldehyde (88 g, 2.0 mol) was added to the stirred solution in one portion, along with water (155 ml). After stirring for an additional 10 min, solid potassium carbonate was added until the solution was distinctly basic to litmus. The mixture was stirred for an additional 2 h, with intermittent addition of potassium carbonate to keep the solution basic. The final mixture was allowed to stand for 3 h. The mixture was extracted with ether, and the organic fraction washed three times with water, dried ($MgSO_4$), filtered, the solvent evaporated, and the residue distilled through a Vigreux column with the fraction distilling at 99—102 °C and 18 mmHg collected (yield 128 g, 54%) (lit.,[40] b.p. 97 °C at 17 mmHg) (Found: *M*, 120.060. Calc. for $C_4H_{10}NO_3$: *M*, 120.064); *threo*, δ (300 MHz; $CDCl_3$) 1.29 (3 H, d, CH_3), 1.56 (3 H, d, CH_3'), 2.21 (1 H, d, OH), 4.13 (1 H, sextet, C*H*OH), and 4.46 (1 H, quintet, C*H*NO_2); *erythro*, δ (300 MHz; $CDCl_3$) 1.24 (3 H, d, CH_3), 1.57 (3 H, d, CH_3'), 2.31 (1 H, d, OH), 4.37 (1 H, m, C*H*OH), and 4.52 (1 H, m dq, C*H*NO_2). Compound (6) was similarly prepared in 40% yield, b.p. 68—69 °C at 0.3 mmHg (lit.,[41] b.p. 89 °C at 2 mmHg); *m/e* 73 ($C_4H_9O^+$) and 104 ($C_3H_6NO_3$); *threo*, δ (300 MHz, $CDCl_3$) *ca.* 0.93 [3 H, d, (CH_3)$_2$CH], *ca.* 1.03 [3 H, d, (CH_3)$_2$CH], 1.53 (3 H, d, CH_3CHNO$_2$), 1.67 [1 H, m, (CH$_3$)$_2$C*H*], 2.84 (1 H, s, OH), 3.72 (1 H, dd, C*H*OH), and *ca.* 4.62 (1 H, m, C*H*NO_2); *erythro*, δ (300 MHz, $CDCl_3$) *ca.* 0.93 [3 H, dm, (CH_3)$_2$CH], *ca.* 1.03 [3 H, d, (CH$_3$)$_3$CH], 1.80 [1 H, m, (CH$_3$)$_2$CH], 2.84 (1 H, s, OH), 3.89 (1 H, dd, C*H*OH), and *ca.* 4.62 (1 H, m, C*H*NO_2).

Compound (7) was synthesized by procedure A in 8.2% yield; sodium hydroxide was used in place of sodium carbonate as the base, b.p. 75—78 °C at 15 mmHg (lit.,[42] 76° at 9 mmHg); *m/e* 127 ($M - NO_2^+$); *threo*, δ (100 MHz; $CDCl_3$) 1.70 (3 H, dq, CH_3), 3.44 (1 H, s, OH), 4.44 (1 H, dq, C*H*OH), and *ca.* 4.83 (1 H, m, CHNO$_2$); *erythro*, δ (100 MHz; $CDCl_3$) 1.69 (3 H, dq, CH_3), 3.60 (1 H, s, OH), *ca.* 4.6 (1 H, m, C*H*OH), and *ca.* 4.8 (1 H, m, C*H*NO_2).

Compound (8) was synthesized by the alternative procedure (B), by mixing of chloral (83 g, 0.50 mol), sodium hydrogensulphite (51 g, 0.50 mol), and water (150 ml) in a flask (1 l) with stirring for *ca.* 15 min. Then, nitroethane (41.5 g, 0.55 mol) and sodium hydroxide (20 g, 0.50 mol) dissolved in water (150 ml) were added in one portion. After stirring overnight, the mixture was extracted with ether (3 × 75 ml); the organic layers were combined and washed three times with similar quantities of water which had been acidified with a few drops of acetic acid, dried ($MgSO_4$), filtered, and the solvent evaporated. Vacuum distillation of the residue gave a liquid (65.5 g, 30%), b.p. 95—100 °C at 0.3 mmHg (lit.,[43] 115 °C at 2 mmHg); $\tilde{\nu}_{OH}$ (0.7% w/v CCl_4) 3 601 (s) and 3 502 (s) cm^{-1} (Found: *M*, 221.950. Calc. for $C_4H_7{}^{35}Cl_3NO_3$: *M*, 221.959); *threo*, δ (300 MHz; $CDCl_3$) 1.84 (3 H, d, CH_3), 3.9br (1 H, s, OH), 4.43 (1 H, d, C*H*OH), and *ca.* 5.2 (1 H, dq, CHNO$_2$); *erythro*, δ (300 MHz; $CDCl_3$) 1.77 (3 H, d, CH_3), 3.9br (1 H, s, OH), 5.00 (1 H, d, C*H*OH), and 5.13 (1 H, dq, CHNO$_2$).

Compound (9) was synthesized by adding bromal hydrate (10 g) and nitroethane (10 g) to an Erlenmeyer flask with stirring. A small quantity (*ca.* 100 mg) of potassium carbonate was added, whereupon the slurry became homogeneous. After stirring for *ca.* 30 min, the solution was filtered, and the filtrate acidified with a few drops of acetic acid. The excess of nitroethane was removed under vacuum. Direct distillation of the residue gave a yellow oil (1.2 g, 10%), b.p. 125—130 °C at 0.03 mmHg. This product decomposed under distillation at higher pressures, and also decomposed quite rapidly in storage under refrigeration, *m/e* 104 ($M - CBr_3^+$) and 249 (CBr_3^+); *threo*, δ (MHz; $CDCl_3$) 1.90 (3 H, d, CH_3), 4.1br (1 H, s, OH), 4.37 (1 H, d, C*H*OH), and *ca.* 5.2 (1 H, m, C*H*NO_2); *erythro*, δ (60 MHz; $CDCl_3$) 1.83 (3 H, d, CH_3), 4.1br (1 H, s, OH), 5.01 (1 H, d, C*H*OH), and *ca.* 5.2 (1 H, d, CHNO$_2$).

Compound (10) was synthesized by procedure A with the use of sodium hydrogencarbonate as base. The product was purified by fractional crystallization from ether–pentane (with difficulty, as once dissolved, crystals tended to form with extreme slowness) (16.3%), m.p. 115—117 °C; *m/e* 194 ($C_{10}H_{12}NO_3$); δ (100 MHz; $CDCl_3$) 0.90 (3 H, t, CH_3), 1.69 (2 H, m, CH_2), 3.08 (1 H, d, OH), 4.58 (1 H, ddd, CHNO$_2$), 5.18 (1 H, dd, CHOH), 7.58 (2 H, d, aromatic), and 8.24 (2 H, d, aromatic).

Compound (11) was similarly prepared, m.p. 98—99 °C; *m/e* 208 ($C_{11}H_{14}NO_3$); δ (100 MHz; $CDCl_3$) 1.02 (3 H, d, isopropyl methyl), 1.06 (3 H, d, isopropyl methyl), 2.12 (1 H, m, isopropyl methine), 3.56 (1 H, d, OH), 4.64 (1 H, dd, CHNO$_3$), 5.32 (1 H, dd, C*H*OH), 7.57 (2 H, d, aromatic), and 8.18 (2 H, d, aromatic).

Compound (12) was synthesized by procedure A using nitroethane and trifluoroacetophenone. A mixture of the two isomers resulted. The major isomer crystallized from chloroform, and was purified by fractional crystallization, m.p. 104—106 °C. The minor isomer could not be purified beyond a 1 : 1 mixture, *m/e* 249 ($C_{10}H_{10}F_3NO_3$); major isomer, δ (100 MHz; $CDCl_3$) 1.24 (3 H, d, CH_3), 4.32 (1 H, s, OH), 5.50 (1 H, q, C*H*NO_2), and 7.2—7.6 (5 H, m, aromatic); minor isomer, δ (100 MHz; $CDCl_3$) 1.82 (3 H, d,

CH_3), 4.8 (1 H, s, OH), 5.36 (1 H, m, $CHNO_2$), and 7.2—7.6 (5 H, m, aromatic).

A similar compound (13) was prepared by condensation of nitromethane with trifluoroacetophenone (film dried; not distilled), *m/e* 235 ($C_9H_8F_3NO_3$); δ (100 MHz; $CDCl_3$) 4.65 (1 H, s, OH), 5.00 (2 H, s, CH_2), and 7.25—7.67 (5 H, m, aromatic).

The acetate derivative of (5) was prepared by the usual acetyl chloride–pyridine route,[43] *threo*, δ (90 MHz; $CDCl_3$) 1.22 (3 H, d, CH_3), 1.46 (3 H, d, CH_3'), 1.98 (3 H, s, OAc), 4.56 (1 H, m, $^3J_{ab}$ 8.0 Hz, CH_bNO_2), and 5.17 (1 H, m, $^3J_{ab}$ 8.0 Hz, $CNOAc$); *erythro*, δ (90 MHz; $CDCl_3$) 1.22 (3 H, d, CH_3), 1.47 (3 H, d, CH_3'), 1.93 (3 H, s, OAc), 4.52 (1 H, m, $^3J_{ab}$ 4.4 Hz, CH_bNO_2), and 5.28 (1 H, m, $^3J_{ab}$ 4.4 Hz, CH_aOAc). The ^{13}C data are given along with the data for the parent compound (5) in parentheses. Major coupling constants are given in square brackets: *threo*-isomer, CH_3', 14.2 (15.5) [$^3J_{CH_3'-H_a}$ 2.3 (2.1)]; CH_3, 14.8 (18.7), the variance is a typical β-effect of OAc *versus* OH, [$^3J_{CH_3-H_b}$ 2.3 (2.3)]; OAc, 19.5; C_a, 69.7 (68.1); C_b, 84.6 (88.6); *erythro*-isomer, CH_3', 11.6 (12.2) [$^3J_{CH_3'-H_a}$ 3.0 (3.3)]; CH_3, 14.5 (18.4) [$^3J_{CH_3-H_b}$ 2.4 (2.2)], OAc, 19.5; C_a, 69.0 (68.1); C_b, 83.6 (86.8). The coupling constants for (5)-OAc were not simulated, and may be slightly inaccurate.

Data Acquisition.—The osmometric molecular weight of (12) was determined by Galbraith Laboratories in benzene solution. The instrument was calibrated against benzil. The extrapolated molecular weight (at infinite dilution) was calculated as 262.98 g mol^{-1} (acual molecular weight 249 g mol^{-1}).

I.r. data were taken on a Perkin-Elmer 283, or less frequently, a Beckman Acculab 4 instrument. The solvents (either CCl_4 or $CHCl_3$) were distilled from P_2O_5 into a dried receiver immediately prior to use. The compounds themselves were dried under high vacuum for at least one day before determination. Fresh 1.07 mm solution cells were used. However, the limit of dilution accessible with these cells was *ca.* 0.2% (w/v). A rough run on the mixed diastereoisomers of (5) showed a complex hydroxy spectrum with peaks evident at 3 603—3 612 and at 3 578 cm^{-1}; with considerable fine structure visible in both sets of peaks. An attempt was made to correlate the symmetric and asymmetric vibrations of the nitro-group with other data with regard to the strength of hydrogen bonding, but no correlation was evident, unlike the case of sulphones.[37]

The n.m.r. spectra were taken on a Varian XL-100 instrument for the bulk of the ^1H, ^{13}C, and ^{15}N runs. Less frequently a Varian A-60D or EM-390 instrument were used. The highfield ^1H runs were determined at the University of Utah on a Varian 300 MHz instrument. For the ^1H runs, full scale runs at 1 000 Hz were taken at various concentrations in order to establish chemical shifts. Coupling constants were determined using 100 Hz expansions of the area of interest, at several concentrations. Those spectra whose first-order nature was in doubt were simulated by the LAOCON3 program. The ^{13}C coupling constants often require LAOCON3 simulation, as instead of a ABX_nY_m pattern (in which $^3J_{ab}$ should be directly obtainable from the spectrum), a AM_3XY situation prevails in the ^{13}C spectrum, in which $^3J_{ax}$ and $^2J_{ay}$ are not directly reproduced in the observed spectrum, similar to J_{ax} and J_{bx} in the familiar ABX pattern. The gated mode of decoupler operation was used to obtain coupled ^{13}C spectra; 1 000 Hz windows were used with a tip angle of *ca.* 60°, a 4 s acquisition time, and a 1.5 s pulse delay used in order to establish the decoupling field. *Ca.* 5 000—10 000 transients were collected. The normal ^{13}C runs utilized a 5 KHz window, a *ca.* 45 ° tip angle, and a pulse repetition rate of 1 s, collecting *ca.* 5 000 transients. The error in line position given by the computer was ±1.25 Hz for an 8 K transform, which was always used. The ^{15}N spectra were usually run in nitromethane solvent (*ca.* 2 g of compound per 2 ml of nitromethane). The solvent also served as the internal standard, whose line position was taken as 380 p.p.m. from ammonia, the ultimate standard. *Ca.* 100 mg of $Cr(acac)_3$ was present to enhance relaxation. The pulse repetition rate was *ca.* 4—5 s. *Ca.* 10 000 transients were usually collected. As the present system gives a false signal in an unpredictable manner, the spectra were determined several times using different spectral widths (1 000—5 000 Hz) and at various offsets to ensure the reproducibility of the data. The tip angle used was *ca.* 30°; the spectra were run with *ca.* 2 W decoupling. The ^{17}O spectrum of (5) indicated a hydroxy chemical shift of 23 p.p.m. (L = 20 p.p.m.) at 40° for a neat solution. This is rather similar to other secondary alcohols.[44] The nitro function has not been located as yet.

The mass spectra were taken on an AEI MS-50 instrument.

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