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STEREOCHEMICAL EFFECTS IN THE CHEMICAL IONIZATION MASS SPECTRA OF CYCLIC DIOLS[a]

J. WINKLER and F. W. MCLAFFERTY*

Department of Chemistry, Cornell University, Ithaca, New York 14850

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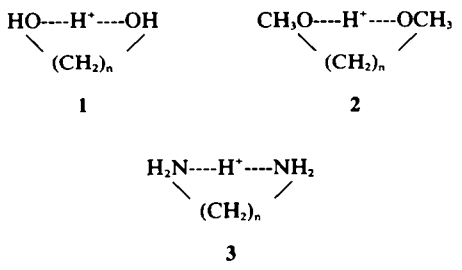
Abstract—The chemical ionization mass spectra of configurational isomers of many cyclic diols give substantial differences which are characteristic of their stereochemistry. For the *cis*-isomer of 1,3- and 1,4-cyclohexanediols, formation of a stable intramolecular proton bridge involving the OH groups gives rise to dominant MH^+ peaks, suppressing the $(M-H)^+$ peaks found in the spectra of the *trans*-isomers and monoalcohols. The stability of the proton bridge in *cis*-1,3-cyclohexanediol structures is decreased by a sterically interfering *cis*-5-methyl substituent, but increased by a *cis*-5-OH group due to additional proton solvation. *cis*-Stereochemistry also gives increased formation of the dimeric M_2H^+ ions, but decreased formation of trimers, at higher diol concentrations, for the 1,3- and 1,4-diols. The similarity of the CI spectra of *cis*- and *trans*-1,2-cyclohexanediol are explicable in terms of the similarities of the most stable proton-bridged conformers; the reduced ring flexibility in *cis*- and *trans*-1,2-cyclopentanediols makes such similar structures unfavorable, as shown by the substantial differences between their CI spectra. The substantial, but expected, variations in behavior with temperature and reagent gas are useful for maximizing stereochemical effects on CI spectra; conditions of lowest energy are usually, but not always, the most useful.

The importance of stereochemistry in natural products is well known, and has led to a substantial number of investigations on the effect of stereochemistry on mass spectra[2,3] since the pioneering work of Biemann[4] and Shannon[5] *et al.* more than a decade ago. The cyclic polyols are probably the most thoroughly studied class of compounds; stereospecific eliminations in the electron-ionization (EI) mass spectra of these compounds and their derivatives have recently been reviewed critically by Grützmacher.[1] For example, the $(M-H_2O)^+$ peaks in the spectra of *cis*- and *trans*-1,4-cyclohexanediols have relative abundances of 8% and 92%, respectively. Formation of $(M-H_2O)^+$ apparently involves elimination of OH and H through a cyclic intermediate in the boat conformer; the H eliminated for the *trans*-isomer is the tertiary hydrogen alpha to the other OH group, and for the *cis*-isomer is the OH hydrogen. Similar stereospecific eliminations are seen in the mass spectra of the *cis*- and *trans*-1,3-cyclohexanediols[3] and the corresponding methyl ethers of 1,3- and 1,4-cyclohexanediols.[3,6] Stereochemical differences are negligible, however, in some other compounds; for example the close similarity of the mass spectra of the *cis*- and *trans*-1,2-cyclopentanediols[7] and 1,2-cyclohexanediols[3,6,8] apparently arises from the ready alpha cleavage which destroys the stereochemical information.

Here we report on the utility of chemical ionization (CI) spectra to probe the stereochemistry of cyclic polyols. The isobutane and methane CI mass spectra of a number of cyclic polyhydroxy compounds have been reported, such as sugars,[9,10] steroids,[11] and prostaglandins.[12] However, no appreciable effects of the stereochemistry of the hydroxyl groups are evident in these data; for example the spectra of 5α-androstane-3α-ol and 5α-androstane-3β-ol are essentially the same.[11] After the completion of this work Longevialle *et al.* have reported[13] that the isobutane CI mass spectra of some steroidal amino alcohols are substantially dependent on their stereochemistry. However, this was not found to be true for the analogous diols.

For the isobutane CI mass spectra of monoalcohols, fragmentation is extensive,[14,15] but stable dimeric and trimeric ions containing two or three alcohol molecules bound to a proton, M_2H^+ and M_3H^+, are also observed.[15,16] It has been pointed out[17,18] that the presence of two OH or similar groups in a molecule can provide stabilization of the MH^+ ion in a similar way (1). This suggested to us that such proton bridges might be useful stereochemical probes. Studies of protonated α,ω-dimethoxyalkanes (2)[19] and α,ω-diamines (3)[20] show that the stability of this proton bridge decreases to a very low value for a five membered ring (n = 2). This appar-

[a]Chemical Ionization Mass Spectrometry, Paper III. For Paper II, see Ref 1.



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ently is a consequence of the tendency of the O–H⁺–O bond to be linear,[21] which for n = 2 would require an unfavorable trapezoidal shape for the ring.

RESULTS AND DISCUSSION

Linear diols. Stabilization by intramolecular proton bridging was first examined in the isobutane CI mass spectra of ten linear diols (Table 1). The data for 1,10-decanediol are consistent with the methane CI mass spectrum of this compound,[18] with the quantitative differences consistent with those expected from our use of a less energetic reagent gas. The reduced fragmentation of the lowest molecular weight compounds parallels the observation of Field[14] on the isobutane CI spectra of monoalcohols; unusually stable $(M + C_4H_9)^+$ and $(M_2 + C_4H_9)^+$ ions form the two largest peaks in the ethane - 1,2 - diol spectrum. The effect of the size of the proton-bridge ring[18–20] is seen clearly in a comparison of the spectra of butane - 2,3 - diol and butane - 1,4 - diol; the ratio $[MH^+]/[(M - H_2O)^+]$ increases from 0·55 to 7·0 in going from the compound in which the proton bridge would form a 5-membered ring to that in which a 7-membered ring is possible.

Cyclic diols

The effect of pressure, temperature, and reagent gas. CI spectral data for 1,2-, 1,3-, and 1,4-cyclohexanediols, triols, and 1,2-cyclopentanediols are shown in Table 2 and Figs 1 through 5. As ex-

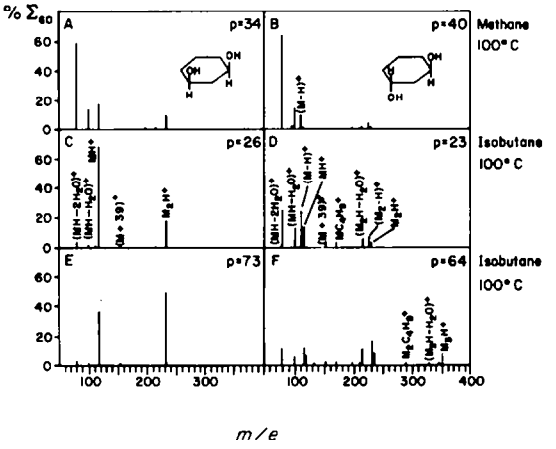


Fig 1. Chemical ionization mass spectra of *cis*- and *trans*-1,3-cyclohexanediols. The C-13 isotope peaks are omitted. The "p" values represent the % of total ionization due to the subject compound.

Table 1. Isobutane CI mass spectra of diols[a]

Compound:	C_2-1,2-diol		C_3-1,2-diol		C_3-1,3-diol		C_5-1,2,3-triol		C_4-2,3-diol	
Rel. press.:[b]	13		9		20		37		14	
Ion	m/e	%Σ60	m/e	%Σ59	m/e	%Σ59	m/e	%Σ60	m/e	%Σ60
$(MH - H_2O)^+$	45	1·4	59	12	59	3	75	6	73	60
$(M - H)^+$	61	1·8	75	2·4	75	1·0			89	1·4
MH^+	63	13	77	63	77	70	93	68	91	33
$(M + 39)^+$	101	4	115	0·9	115	0·6	131	1·3	129	2·5
$(M + C_4H_9)^+$	119	40	133	4	133	3	149	0·6	147	0·3
$(M_2 - H_2O)^+$	107	0·6	135	0·8	135	1·0			163	0·6
M_2H^+	125	16	153	7	153	11	185	23	181	1·1
$(M_2 + C_4H_9)^+$	181	18								
M_3H^+	187	7								

Compound:	C_4-1,4-diol		C_5-2,4-diol		C_5-1,5-diol		C_6-2,5-diol		C_{10}-1,10-diol	
Rel. press.:[b]	23		37		20		20		22	
Ion	m/e	%Σ60	m/e	%Σ60	m/e	%Σ60	m/e	%Σ60	m/e	%Σ60
$(M - H_2O)^+$	73	11	87	3	87	1·4	101	7	157	2·5
$(M - H)^2 +$			103	1·0	103	1·1	117	1·8	173	0·6
MH^+	91	77	105	58	105	65	119	72	175	67
$(M + 39)^+$			143	0·5	143	1·1			213	1·2
M_2H^-	181	9	209	28	209	23	237	14	349	17

[a] Temperature 80–100°C; C-13 isotope peaks and some ions with < 1%Σ60 intensity are not included in the table.

[b] Percentage of sample ions relative to total observed ionization, used as an indication of sample pressure.

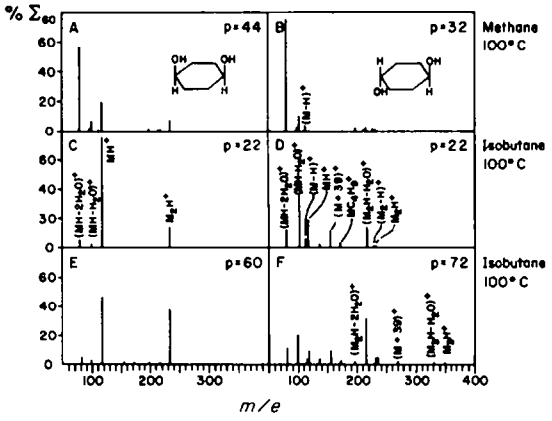


Fig 2. Chemical ionization mass spectra of *cis*- and *trans*-1,4-cyclohexanediols.

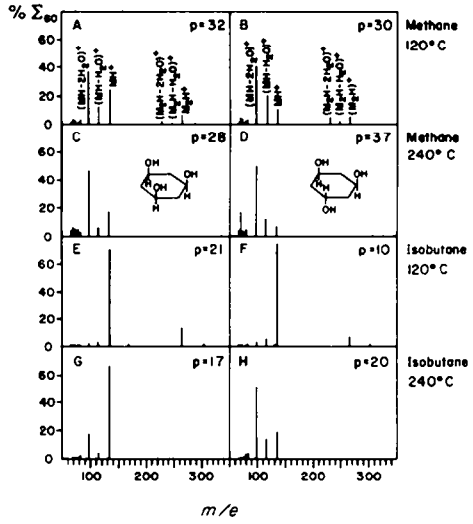


Fig 4. Chemical ionization mass spectra of (1,3,5/0)- and (1,3/5)-cyclohexanetriols.

pected from previous work, the quantitative data show a substantial dependence on experimental conditions.[15, 22] Increasing the sample pressure increases the formation of dimers, M_2H^+, and trimers, M_3H^+, and increasing the ionization temperature or the proton donor strength of the reagent ions increases the extent of fragmentation. In particular cases selection of the proper experimental conditions is necessary to optimize the stereochemical information in the spectrum. *Higher* energy conditions are sometimes necessary; as will be discussed below, much larger differences are found in the degree of fragmentation between the spectra of the *cis*- and *trans* - 5 - methyl - *cis* - 1,3 - cyclohexanediols (Figs 3A, B, D, E, G, H) and (1,3,5/0)- and (1,3/5) - cyclohexanetriols (Fig 4) with ionization at higher temperatures or using a stronger protonating agent.

1,3- *and* 1,4 - *Cyclohexanediols.* The *cis*- and *trans* - stereoisomers show dramatic differences in their spectra (Figs 1 and 2). In the methane CI spectra the MH^+ and M_2H^+ ions are approximately an order of magnitude more abundant for the *cis*-isomers. Following the reasoning advanced for the behavior of the linear diols, this stabilization of the MH^+ ions should arise from the formation of the intramolecular proton bridge. For *cis* - 1,3 - cyclohexanediol the diaxial chair conformation would lead

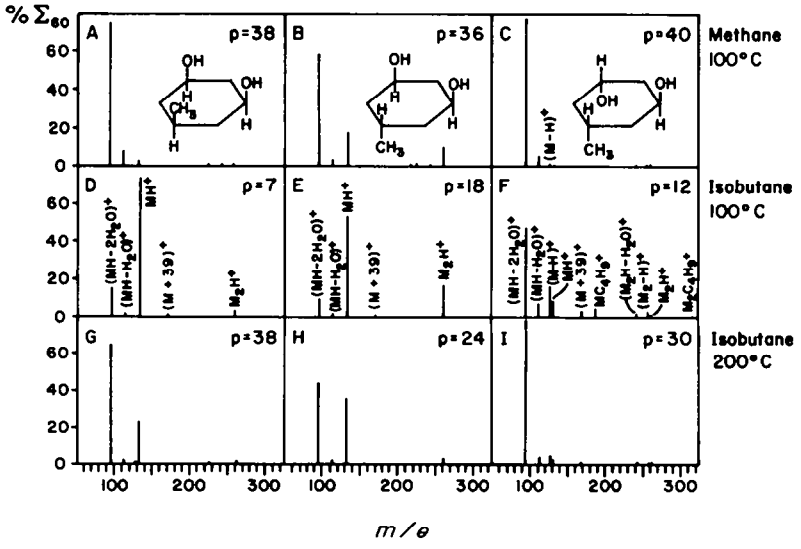


Fig 3. Chemical ionization mass spectra of (1,3,5/0)-, (1,3/5)- and (1/3,5)-5-methyl-1,3-cyclohexanediols.

Table 2. CI mass spectra of cyclic 1,2-diols[a]

Compound:	Cyclohexane-1,2-diols				cyclodecane-1,2-diol
Reagent gas:	isobutane		methane		isobutane
Rel. press.:[b]	45	38	42	37	12
Ion	*cis*	*trans*	*cis*	*trans*	
m/e					*m/e*	
$(MH-2H_2O)^+$	81	20	31	13	17	137	12
$(M-H-H_2O)^+$	97	1·1	1·7	1·6	1·3		
$(MH-H_2O)^+$	99	29	24	42	38	155	66
$(M-H)^+$	115			1·1	1·8	171	2·3
$M^{\cdot+}$	116			1·6	1·6		
MH^+	117	4	6	6	6	173	0·5
$(M_2H-2H_2O)^+$	197	1·7	2·5	3·2	2·7	309	0·5
$(M_2H-H_2O)^+$	215	6	6	11	10	327	7
M_2H^+	233	30	21	13	15	345	1·2

[a] Temperature 80–100° C; intensities in per cent Σ_{60}.
[b] See Table 1.

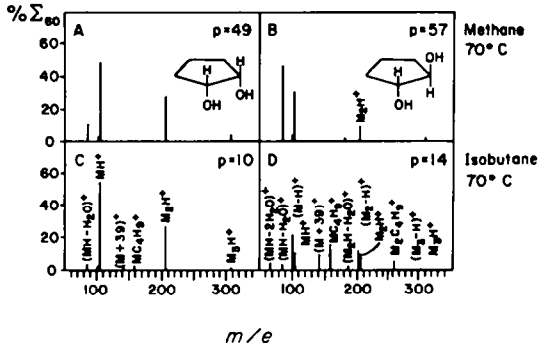
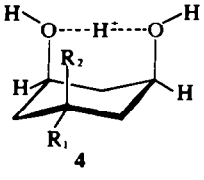


Fig 5. Chemical ionization mass spectra of *cis*- and *trans*-1,2-cyclopentanediols. Small $(M_NH+mH_2O)_+$ peaks due to occluded water are omitted from the *cis*-diol spectrum.

to a six membered ring for the proton-bridged species, **4a**, and for the *cis* - 1,4 - cyclohexanediol the OH groups would be in suitable flagpole positions in the twist-boat conformation **5**. The increased abundance of the dimeric M_2H^+ peaks in the spectra of the *cis*-isomers can be rationalized



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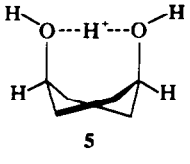

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4:	R_1	R_2
a	H	H
b	CH_3	H
c	H	CH_3
d	OH	H
e	H	OH

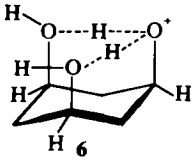
on the basis of hydrogen bonding stabilization in addition to that of the intermolecular proton bridge. Note, however, that the trimeric species M_3H^+ is only found in the higher pressure spectra of the *trans*-isomers; the much lower tendency of the *cis*-M_2H^+ ions to form a further proton bridge to a third diol is in keeping with the postulated *cis*-M_2H^+ structure in which all of the OH groups are involved in H-bonding. The isobutane CI spectra of the *trans*-isomers at 100°C also show strong association products such as $(M+C_3H_3)^+$ and $(M+C_4H_9)^+$ similar to those found in the spectra of the linear alkanols and 1,2-diols.

The type of fragmentation is also characteristic of the stereochemistry. The hydride abstraction ions, $(M-H)^+$, give strong peaks in the spectra of the *trans*-isomers, similarly to monoalcohols,[14] but are practically absent in the *cis*-diol spectra. In addition there are substantial increases for the *trans*-isomers in the common decomposition products such as $(MH-H_2O)^+$ and $(MH-2H_2O)^+$.

Steric crowding. An additional effect is shown by related 1,3 - cyclohexanediols with a third substituent in the 5-position. For the three 5 - methyl - 1,3 - cyclohenanediol isomers of Fig 3, the stereochemistry of the OH groups can be readily assigned using the MH^+ and $(M-H)^+$ intensities. In addition, there is a clear correlation between the configuration of the Me group in the two *cis* - 1,3 - diols and the abundances of the MH^+ and M_2H^+ ions. Although the methane CI spectrum of the 1,3/5-isomer **4b** (Fig 3B) is very similar to that of the corresponding *cis* - 1,3 - cyclohexanediol (Fig 1A), the 1,3 - diaxial interaction between the Me group and the two OH groups in the proton-bridged ion from the all - *cis* - isomer **4c** leads to destabilization, as shown by the substantial increase in fragmentation and reduction in MH^+ and M_2H^+. Note that the effect of the methyl group interaction is much more clearly shown by the *higher* energy ionization (CH_4

and 200° isobutane, Figs 3A and G); lowest energy conditions have been recommended previously for stereochemical studies.[13]

For the protonated 1,3/5 - cyclohexanetriol, **4d**, the addition of an OH group in the equatorial position also has little effect; this spectrum (Fig 4B) is similar to the spectra of **4a** and **4b** (Figs 1A and 3B), with the additional fragmentation being due at least in part to the higher source temperature. Note that fragmentations characteristic of the *trans*-OH group, such as that giving $(M-H)^+$ ions, are not competitive. However, the sterically crowded 1,3,5/0 - cyclohexanetriol system **4e** shows a ***higher*** stability for MH^+. The crowding must be outweighed by further stabilization through formation of a second (and possibly a third) intramolecular hydrogen bridge, **6**. The effect of additional proton solvation also becomes more apparent at higher energy conditions (Fig 4).



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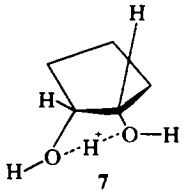
Cyclic 1,2-*diols.* The *cis*- and *trans* - 1,2 - cyclohexanediols have quite similar CI spectra (Table 2) consistent with the small amount of intramolecular proton bridging found for the linear 1,2-diols and the expected flexibility of the cyclohexane ring; stereochemical preferences for proton bridging are minimized by the ease of conformational flipping. This parallels the similarity of their EI spectra.[3,8] However, in the CI spectra of the 1,2 - cyclopentanediols (Fig 5) the MH^+ ion appears to be of substantially higher stability for the *cis*- than for the *trans*-isomer. This can be rationalized on the basis of the expected fairly rigid cyclopentane ring system which would help stabilize the five membered ring formed by proton bridging in the *cis*-diol (**7**), but destabilize the proton-bridged envelope conformation of the *trans*-isomer (**8**). Stereochemical effects in cyclopentane ring systems thus appear to be much more pronounced in CI than in EI spectra.[3,6,7]

Effect of positional isomerism on CI spectra. The CI spectra of the *cis*-1,3- and *cis* - 1,4 - cyclohexanediols are quite similar, apparently due to the high stability of the protonated bridge structures. There are significant differences in the isobutane CI spectra of the *trans*-isomers; the $(MH-H_2O)^+$ abundance is smaller for the 1,3-diol, and higher for the 1,4-diol, then either the $(MH-2H_2O)^+$ or $(M-H)^+$ peaks (the latter can also be due to H_2 loss from MH^+). The more ready loss of H_2O from the $(MH-H_2O)^+$ ion of *trans* - 1,3 - cyclohexanediol is consistent with a more stable allylic structure for the $(MH-2H_2O)^+$ product. The CI spectra of the 1,2 - cyclohexanediols show MH^+ peaks of low abundance, resembling the behavior of the *trans*-1,3- and -1,4-diols, although some intramolecular proton bridging is indicated by the reduced $(M-H)^+$ peaks. The abundant M_2H^+ ions of the 1,2-diols also suggest that additional proton bridges stabilize these dimeric ions, similar to the structure postulated for the M_2H^+ ions of the *cis*-1,3- and -1,4-diols. The isobutane CI spectrum of cyclodecane - 1,2 - diol of unknown stereochemistry indicates a lower stabilization of MH^+ than for any of the cyclohexanediols, resembling more closely the CI spectra of the higher monoalcohols.[14]

Steroidal amino alcohols and diols. A recent independent investigation[15] of the isobutane CI mass spectra of steroidal amino alcohols also reports stereochemical effects which are related to the probability of intramolecular proton bridge formation. Paralleling the behavior of the 1,2 - cyclopentanediols, the vicinal 2- or 4 - hydroxy - 3 - amino - 5α - pregnanes show highly stable MH^+ ions for all isomers except the *trans*-diaxial configuration, consistent with their reduced ring flexibility. Similarly, the 1,3-substituted compounds yield much more stable MH^+ ions for *cis*-diaxial substituents. However, in contrast to our results, the spectra of the diols 5α - androstane - 1α, 3α- and -1α,3β - diol and 5α - pregnane - 1β,3β - diol at 200° C show no appreciable MH^+ peak; it seemed surprising that the stereochemical requirements of the cyclohexane ring have been increased so greatly by the A–B ring fusion of the steroidal skeleton. This anomaly was resolved by obtaining CI spectral data at lower temperatures (Fig 6), using samples[15] kindly supplied by Dr. Fales. (The 95° data resulted from "direct chemical ionization" of the sample exposed to the ion plasma.[23]) These lower energy data are consistent with those of the 1,3 - cyclohexanediols above. The spectra of the *cis* - 1,3 - diaxial isomer (Figs 6A and D) show relatively abundant MH^+ and, at higher pressures,



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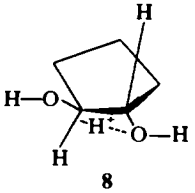

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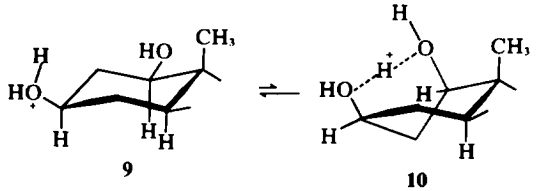

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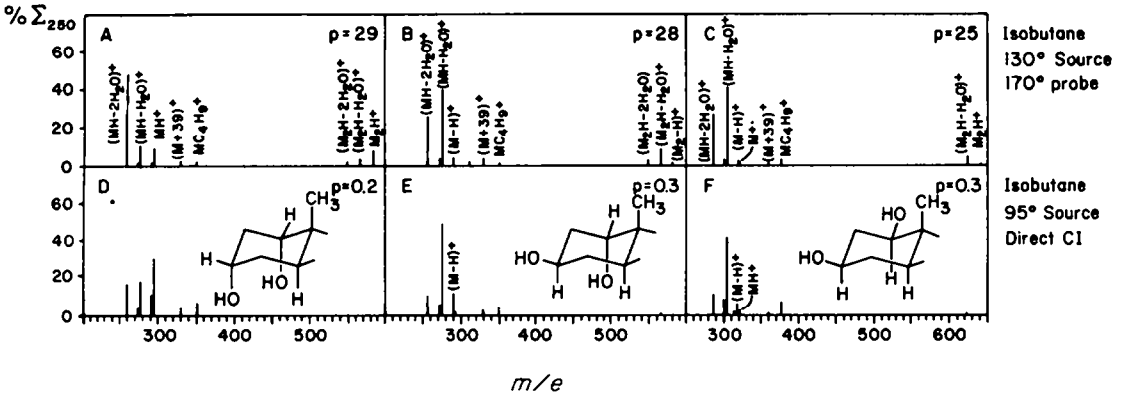

Fig 6. Chemical ionization mass spectra of 5-α-androstane-1α,3α- and -1α,3β-diol and 5α-pregnane--1β,3β-diol. In the "direct CI" runs the sample is directly exposed to the ion plasma in the CI source.[23]

M_2H^+ ions. The *cis* - 1,3 - diequatorial homolog (**9**) should have a relatively low tendency to flip to the *cis*-diaxial boat conformer (**10**) because of steric hindrance from the 19-Me group; thus its CI spectra (Figs 6C and F) are closely similar to those of the 1 - axial - 3 - equatorial homolog (Figs 6B and E). It would thus appear that the correlations found above for the CI spectra of simple cyclic diols can be extended with confidence to the elucidation of the stereochemistry of more complex systems.

EXPERIMENTAL

The spectra were recorded on an AEI MS-902 mass spectrometer fitted with a Chemspec CIS-2 source from Scientific Research Instruments. A temp controlled probe was used for the sample introduction, with the temp adjusted to achieve a sample ion yield of 10 to 40% of the total ionization. Zero repeller voltage was used. Reagent gas pressure in the source housing was 5×10^{-5} torr, corresponding to approximately 0·5 – 1 torr in the ion source. The samples of the stereoisomers were available from earlier work.[6,24] The *cis*- and *trans* - 1,2 - cyclopentanediol isomers were purified by gas chromatography on a 2 m 20% Carbowax 20 M column at 190°.

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