

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Dipole Moments of Some Sex Hormones, Sterols and Isophorone

BY W. D. KUMLER AND GEORGE M. FOHLEN

This is the second paper of a series on the dipole moments and stereostructure of the steroids. The first paper¹ dealt with the bile acids and in this communication the dipole moments of eight androstane derivatives, four sterols and isophorone are reported. Evidence is presented that some of the hydroxyl groups in the steroids do not have freedom of rotation.

Results

The symbols used in the equations and tables are those given previously.² The equations used in calculating the moments are²

$$p_{20} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta) \frac{\epsilon_1 - 1}{\epsilon_1 + 2}$$

$$P_{20} = p_{20} M_2$$

$$\mu = 0.0127 \sqrt{(P_{20} - P_{E20})T}$$

The P_{20} values are obtained by the method of

TABLE I
MEASUREMENTS IN DIOXANE AT 25°

ω_{12}	ϵ_{12}	v_{12}	ω_{12}	ϵ_{12}	v_{12}
Cholestanediol-3 β ,7 α			Δ^4 -Androstenediol-3 β ,17 β		
0.004040	2.2234	0.97395	0.003077	2.2249	0.97394
.006953	2.2283	.97405	.006400	2.2350	.97362
.009772	2.2334	.97413	.008725	2.2410	.97344
.013767	2.2403	.97425	.011763	2.2516	.97324
Cholestanediol-3 β ,7 β			Δ^4 -Androstenol-3 β -one-17		
.003955	2.2206	.97407	.002108	2.2210	.97385
.006859	2.2275	.97413	.003949	2.2263	.97372
.009771	2.2337	.97420	.005526	2.2326	.97361
.013933	2.2413	.97430	.007703	2.2395	.97346
Cholestanol-3 β -one-7			Testosterone		
.003647	2.2243	.97402	.003151	2.2350	.97382
.005122	2.2288	.97404	.005550	2.2529	.97362
.008918	2.2392	.97408	.008898	2.2762	.97333
.012527	2.2947	.97413	.011468	2.2958	.97313
Δ^4 -Cholestenol-3 β -one-7			<i>cis</i> -Testosterone		
.003917	2.2319003256	2.2503	.97375
.006736	2.2456	.97387	.006097	2.2820	.97353
.009412	2.2599008705	2.3143	.97334
.014456	2.2865	.97387	.011042	2.3413	.97316
Androsterone			Δ^4 -Androstenedione-3,17		
.003819	2.2376	.97380	.003732	2.2357	.97369
.005969	2.2508	.97367	.005789	2.2489	.97358
.007907	2.2630	.97362	.009029	2.2701	.97324
.011462	2.2841	.97340	.011112	2.2843	.97306
β -Androsterone			Isophorone		
.003065	2.2230	.97387	.003532	2.2628	.97441
.005853	2.2355	.97371	.005945	2.2988	.97468
.008778	2.2440	.97353	.009708	2.3523	.97506
.010708	2.2526	.97349	.014222	2.4157	.97562
Δ^4 -Androstenediol-3 β ,17 α			d_{20}^{25} 0.91852	n_D^{25} 1.47411	
.003323	2.2254	.97382			
.005964	2.2360	.97355			
.008967	2.2463	.97344			
.010812	2.2540	.97331			

Halverstadt and Kumler using the graphical modification.² P_{E2} values were calculated from the group refractions given by Smyth.³ In the case of isophorone P_{E2} also was obtained from the measured refractive index of the pure liquid. The data are given in Tables I and II.

Discussion

The graphs of the dielectric constant-concentration curves presented in Figs. 1, 2 and 3 are linear, indicating that no molecular association is present in these solutions at the concentrations used. There is also no evidence of lack of orientation of the large molecules at the frequency of 680 kilocycles which was employed. In both respects the behavior of the sex hormones and sterols parallels that of the bile acids.¹ In Fig. 4 the structures of the compounds are given.

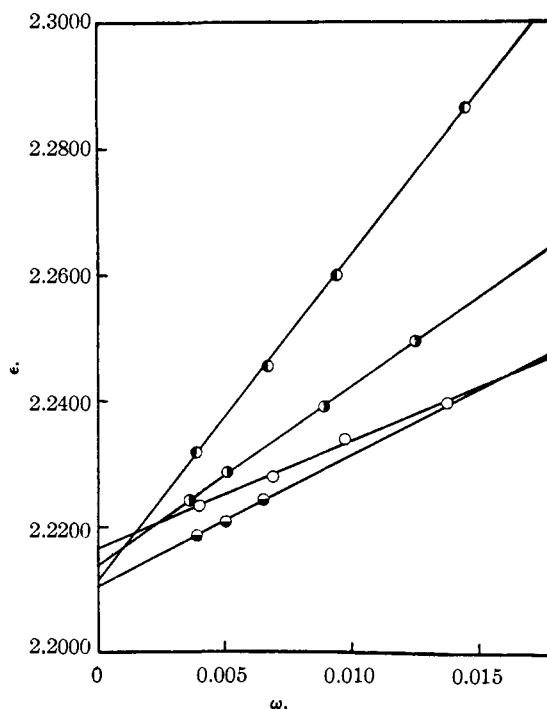


Fig. 1.—O, Cholestanediol-3 β ,7 α ; \odot , cholestanediol-3 β ,7 β ; \bullet , cholestanol-3 β -one-7; \circ , Δ^4 -cholestenol-3 β -one-7.

Restricted Rotation of the Hydroxyl Groups.—

By taking the measured moments of compounds that have only a hydroxyl group or a ketone group attached to a saturated six membered ring, we have calculated the limits within which the moments of steroids, that have two hydroxyl

(1) Kumler and Halverstadt, *This Journal*, **64**, 1941 (1942).

(2) Halverstadt and Kumler, *ibid.*, **64**, 2968 (1942).

(3) Smyth, "Dielectric Constants and Molecular Structure," Chemical Catalog Co., New York, N. Y., 1931.

TABLE II

Compound	n_D^{20} Extrap.	n_D^{25} Extrap.	α	β	P_{20}	P_{25}	μ
Cholestanediol-3 β ,7 α	2.2165	0.97385	1.728	0.0288	231.96	121.16	2.31
Cholestanediol-3 β ,7 β	2.2167	.97398	2.066	.0467	256.54	121.16	2.55
Cholestanol-3 β -one-7	2.2138	.97398	2.870	.0114	304.42	119.65	2.98
Δ^5 -Cholestanol-3 β -one-7	2.2115	.97387	4.639	.0000	418.35	119.18	3.79
Androsterone	2.2146	.97405	6.067	-.0559	366.79	81.48	3.70
β -Androsterone	2.2122	.97407	3.884	-.0570	262.17	81.48	2.95
Δ^5 -Androstenediol-3 β ,17 α	2.2132	.97405	3.774	-.0707	255.99	82.53	2.89
Δ^5 -Androstenediol-3 β ,17 β	2.2127	.97405	3.298	-.0700	233.30	82.53	2.69
Δ^5 -Androstenol-3 β -one-17	2.2136	.97400	3.377	-.0700	206.55	81.02	2.46
Testosterone	2.2127	.97408	7.273	-.0830	419.27	81.02	4.32
<i>cis</i> -Testosterone	2.2127	.97400	11.680	-.0764	637.68	81.02	5.17
Δ^4 -Androstenedione-3,17	2.2119	.97398	6.497	-.0811	380.20	80.71	3.32
Isophorone	2.2131	.97396	14.271	.1193	368.15	41.112	3.97
						42.293 ^a	3.96

^a From the measured refractive index of the pure liquid.

groups, or a hydroxyl group and a ketone group, should fall assuming free rotation—*i. e.*, equal probability for all positions as the hydroxyl group rotates about the carbon-oxygen bond. It is found that the measured moments of some steroids fall outside these limits, indicating that for such compounds the hydroxyl groups do not have freedom of rotation.

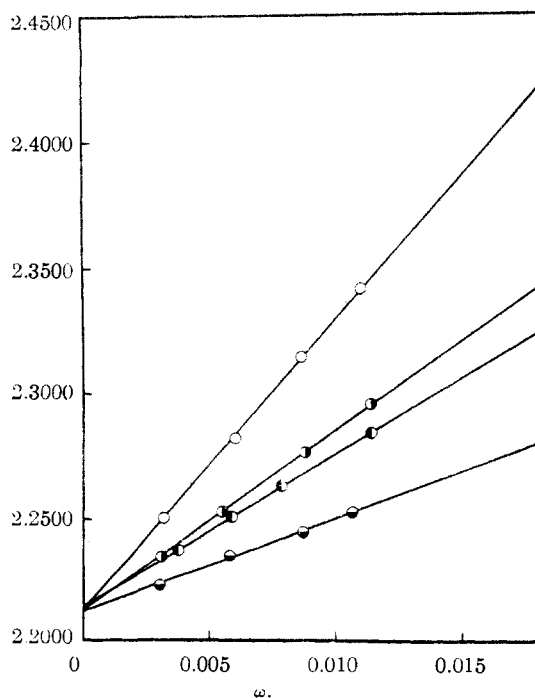


Fig. 2.— \circ , *cis*-Testosterone; \bullet , β -androsterone; \ominus , testosterone; \odot , androsterone.

In Table III are listed the measured and the calculated maximum and minimum moments. The formula⁴ used in calculating the moments is

$$\mu_{f.r.} = \sqrt{\mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cdot \cos \sigma \cos \phi_1 \cos \phi_2}$$

(4) Kumler and Halverstadt, *THIS JOURNAL*, **63**, 2182 (1941).

TABLE III
CALCULATED MOMENTS FOR FREE ROTATION

Compound	μ_{max} $\sigma = 0$	μ_{min} $\sigma = 180$	Measured moments, μ
Cholestanediol-3 β ,7 α	2.68	2.46	2.31 ^a
Cholestanediol-3 β ,7 β	2.68	2.46	2.55
Cholestanol-3 β -one-7	3.85	2.94	2.98
Δ^5 -Cholestanol-3 β -one-7	4.82	3.85	3.79 ^b
Androsterone	3.85	2.94	3.70
β -Androsterone	3.85	2.94	2.95
Δ^5 -Androstenediol-3 β ,17 α	2.68	2.46	2.89 ^a
Δ^5 -Androstenediol-3 β ,17 β	2.68	2.46	2.69
Δ^5 -Androstenol-3 β -one-17	3.85	2.94	2.46 ^a
Testosterone	4.82	3.85	4.32
<i>cis</i> -Testosterone	4.82	3.85	5.17 ^a
Δ^4 -Androstenedione-3,17	6.86	1.06	3.32

^a Measured moments outside the range for free rotation by an amount considerably greater than the experimental error. ^b Measured moments which are outside the range for free rotation.

where $\mu_{f.r.}$ is the resultant moment assuming free rotation of the polar groups, μ_1 , and μ_2 are the moments of the individual polar substituent

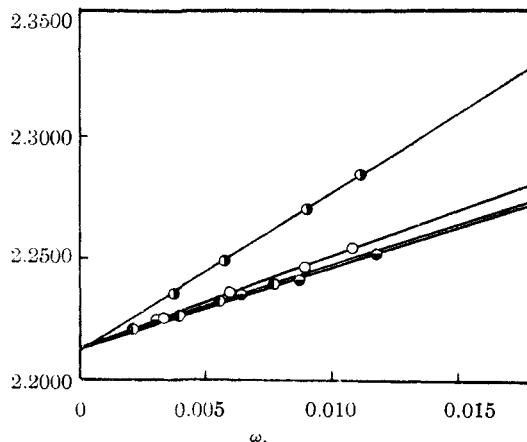
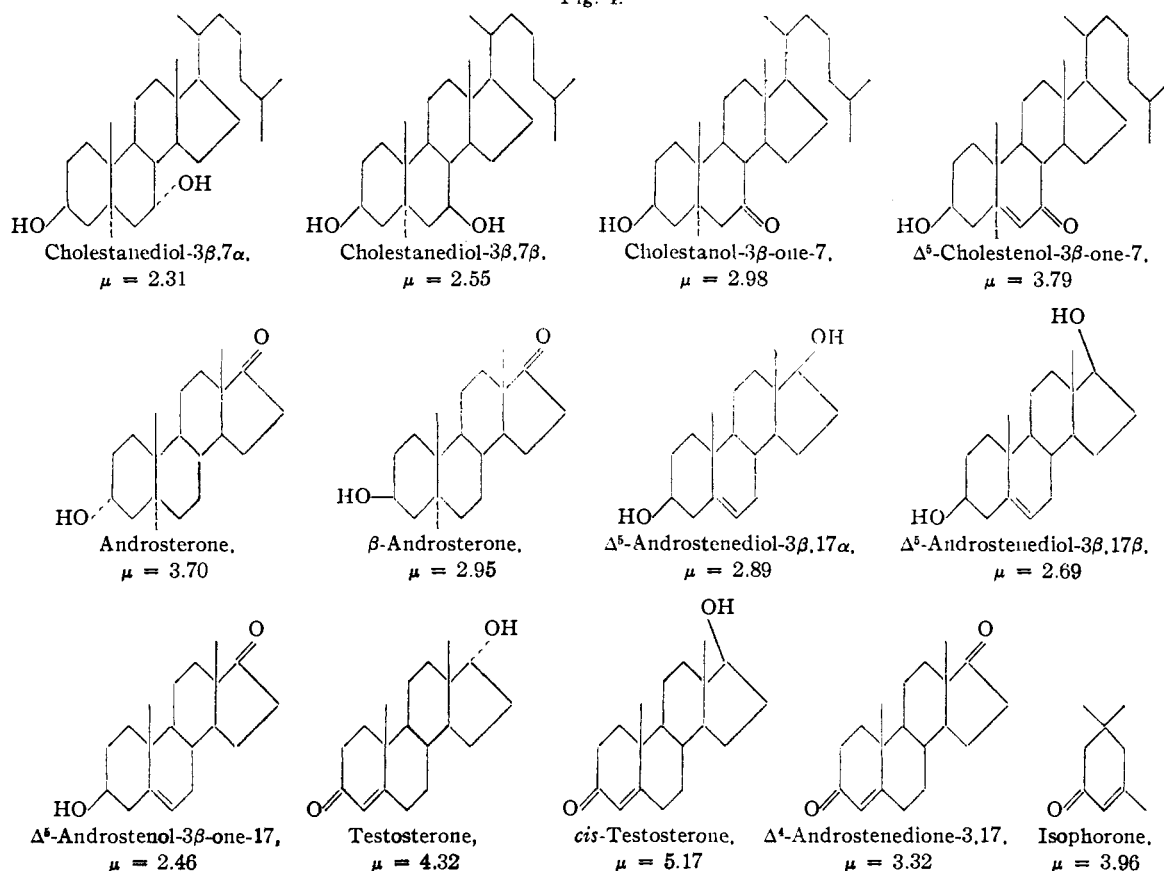


Fig. 3.— \circ , Δ^5 -Androstenediol-3 β ,17 α ; \bullet , Δ^5 -androstenediol-3 β ,17 β ; \ominus , Δ^5 -androstenol-3 β -one-17; \odot , Δ^4 -androstenedione-3,17.

Fig. 4.



groups, σ is the angle between the axes of rotation and ϕ_1 and ϕ_2 are the angles which the two moments make with their respective axes of rotation. In the calculations the moment used for the hydroxyl group was that of cyclohexanol, 1.82, and for the keto group, that of cyclohexanone, 2.90.⁵ In the case of a keto group conjugated with a double bond the moment of isophorone, 3.96, was used. The angle ϕ_{OH} which the moment of the hydroxyl group makes with its axis of rotation was taken as 73° which is the value calculated by Branch and Calvin⁶ from the moments of *p*-chloroanisole, chlorobenzene and anisole. A similar calculation from the moments of diethyl ether and ethanol gives an angle of 75° .⁷ Whether one uses an angle of 73 or 75° , one comes to the same conclusions in regard to the rotation of the hydroxyl groups.

It will be seen from Table III that the measured moments of six compounds fall outside the range of the moments calculated for free rotation. Of these, one is within the range of the experimental error and another is close but the moments of four of the compounds are greater or less than the maxi-

(5) Halverstadt and Kumer, *THIS JOURNAL*, **64**, 1982 (1942).

(6) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p. 142.

(7) Halverstadt, Ph.D. Dissertation, University of California Library, Berkeley, California, 1942.

mum or minimum moments for free rotation by amounts that are three to ten times the experimental error. (This is based on an experimental error of 0.05 unit which is a conservative estimate and is probably too large.) This indicates that some of the hydroxyl groups do not have free rotation. In the case of *cis*-testosterone where μ is greater than $\mu_{max.}$ by 0.35, the only polar group other than the 17 β -hydroxyl is the keto group which is fixed and has no possibility of rotation, hence the hydroxyl group in the 17 β -position must be restricted in its rotation. Likewise, for Δ^5 -androst-enol-3 β -one-17, where μ is less than $\mu_{min.}$ by 0.48, the hydroxyl in the 3 β -position must be restricted.

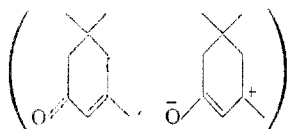
Since hydroxyl groups in the 3 β - and 17 β -positions are not freely rotating they can be considered fixed and we, therefore, calculated the maximum and minimum moments for the diols assuming the other hydroxyl is freely rotating. The values are 2.93 $_{max.}$, and 2.24 $_{min.}$ and the measured moments for the diols all fall within this range. We can thus draw no conclusions in regard to the rotation of the other hydroxyl groups in these compounds.

Whereas the observation that the measured moment falls outside the limits for free rotation indicates hindered rotation, the fact that the

measured moment falls within these limits does not prove the existence of free rotation. If the groups are hindered, the angle between them could be anywhere from 0 to 180°, so the permissible range in this case is from zero to the sum of the moments of the groups.

While our data give information only in regard to hindered rotation in the 3 β - and 17 β -positions it seems likely from an examination of models that the 3 α - and 17 α -positions are hindered also. Chemical evidence in regard to rates of reaction of substituents in the 7-position compared with the 3-position suggests that the 7-position may be hindered as well. The proof of this from dipole moment data will have to await the measurement of suitable compounds. The hindered rotation is presumed to arise from the repulsion of neighboring hydrogen atoms.

Moment of a O=C—C=C Group.—Isophorone has been measured to obtain the moment of keto groups conjugated with a carbon-carbon double bond. The moment of isophorone, 3.96, was found to be higher than that of cyclohexanone, 2.90, by about 1 unit. This is probably due to resonance between the normal form and the form with a separation of charge.



The question has been raised in regard to whether isophorone is a tautomer.⁸ Its high dipole moment, 3.96, indicates that the molecule under the conditions of measurement must be chiefly in the conjugated keto form, for the moment of the other structures suggested, namely, an enol and a molecule containing a double bond not conjugated with the keto group, would have moments considerably smaller than the observed moment. The moment of the enol would be less than 2 and that of the non-conjugated keto compound about the same as a simple keto group, 2.90.

The steroids having a conjugated keto group also have higher moments than those with an unconjugated group. Thus, Δ^5 -cholesterol-3 β -one-7 which differs from cholestanol-3 β -one-7 only in having a double bond conjugated with the keto group, has a moment that is 0.81 higher than the moment of the latter compound. The difference here is not so great as the difference between the moment of isophorone and cyclohexanone probably due to the double bond changing the shape of the nucleus thus altering the angle between the keto and hydroxyl groups and lowering the moment of Δ^5 -cholesterol-3 β -one-7.

Both of the testosterone with conjugated keto groups in the 3-position and hydroxyl groups in the 17-positions have higher moments than the androsterones with a simple keto group in the 17-positions and hydroxyl in the 3-positions.

The Effect of the Epimerism of the Hydroxyl Groups.—This series of compounds contain four epimeric pairs which differ only by the α - or β -position of the hydroxyl groups. The moment of each member of a pair is different from that of the other member by an amount which varies among the four pairs. The pairs for which the other polar group in the molecule is a hydroxyl has a smaller difference between the moment of members of the pair than pairs for which the other group is a ketone. This can be accounted for on the basis of the vector addition of two small moments compared with one small and one large moment when the angles between them are changed by an equal amount.

The lack of free rotation of some of the hydroxyl groups rules out the possibility of obtaining information from dipole moments in regard to the configuration of the nucleus from compounds containing such groups, for if the groups are fixed, there is at present no way of telling how they are oriented. Dipole studies of the nucleus will have to be confined to compounds containing only keto and halogen groups which have no possibility of rotation and the direction of whose dipole is known. The lack of free rotation also makes very dubious the possibility of telling from dipole moments whether an unknown compound is the α or β isomer.

The difference between the moment of β -androsterone, 2.95, and that of Δ^5 -androstenol-3 β -one-17, 2.46, is interesting because these compounds differ only by a double bond which is not conjugated. Furthermore, the moment of the compound with the double bond is less than that of the other compound. Two explanations appear possible. One is that the presence of a double bond changes the shape of the nucleus, thus changing the angle between the hydroxyl and ketone group by an appreciable amount. The other is that a double bond in the Δ^5 -position in the sterol nucleus alters the moment of a hydroxyl group in the 3-position. There appears to be some evidence for the latter interpretation from the chemical behavior of these compounds.⁹ The question could be settled, perhaps, by measuring the moment of a sterol that contained only a 3-hydroxyl and a Δ^5 double bond.

There appears to be no correlation between the dipole moments of the sex hormones and their physiological activity.

Experimental

The apparatus and method of measurement was the same as that previously described.¹⁰

Materials

Dioxane.—Commercial dioxane was purified as before.⁸
Isophorone.—The commercial product of Carbide and Carbon Chemicals Corporation was distilled once at atmospheric pressure. The middle fraction boiling at about

(9) Personal communication, Professor Byron Riegel, Northwestern University.

(10) Kumler and Follen, THIS JOURNAL, 64, 1944 (1942)

(8) Kharasch and Lawrey, THIS JOURNAL, 63, 2308 (1941)

215° was then distilled several times under reduced pressure. The final product had a boiling point of 69–69.5° at 7 mm.

Steroids.—

	M. p., °C.
1. Cholestanediol-3 β ,7 α	167–168
2. Cholestanediol-3 β ,7 β	152–153
3. Cholestanol-3 β -one-7	164–165
4. Δ^5 -Cholestenol-3 β -one-7	168–169
5. Testosterone = Δ^4 -androsthenol-17 α -one-3	154–155
6. <i>cis</i> -Testosterone = Δ^4 -androsthenol-17 β -one-3	220–221
7. Δ^5 -Androstenediol-3 β ,17 α	182–183
8. Δ^5 -Androstenediol-3 β ,17 β	198.0–198.5
9. Androsterone = <i>etio-allo</i> -cholanol-3 α -one-17	182.5–183.5
10. β -Androsterone = <i>etio-allo</i> -cholanol-3 β -one-17	171.4–173
11. Δ^4 -Androstenedione-3,17 = Δ^4 - <i>etio-allo</i> -cholene-dione-3,17	173–174
12. Dehydroandrosterone = Δ^5 -androsthenol-3 β -one-17	135–137

Compounds 1–4 were obtained from Dr. O. Wintersteiner of the Squibb Institute for Medical Research, compounds 5–11 from Dr. C. R. Scholz, of Ciba Pharmaceutical Products, Inc., and compound 12 from Professor Byron Riegel of Northwestern University.

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Summary

The dipole moments of eight androstane derivatives, four sterols, and isophorone have been

measured in dioxane solution. The moments of the compounds are as follows: cholestanediol-3 β ,7 α , 2.31; cholestanediol-3 β ,7 β , 2.55; cholestanol-3 β -one-7, 2.98; Δ^5 -cholestenol-3 β -one-7, 3.79; androsterone, 3.70; β -androsterone, 2.95; Δ^5 -androstenediol-3 β ,17 α , 2.89; Δ^5 -androstenediol-3 β ,17 β , 2.69; Δ^5 -androsthenol-3 β -one-17, 2.46; testosterone, 4.32; *cis*-testosterone, 5.17; Δ^4 -androstenedione-3,17, 3.32; isophorone, 3.96.

The moments of four of these compounds fall outside the range calculated for free rotation of the hydroxyl groups, from which it is concluded that the 3 β - and 17 β -hydroxyl groups do not have freedom of rotation.

A ketone group conjugated with a double bond in a six-membered ring has a moment about 1 unit higher than a simple ketone.

The dipole moment of isophorone indicates that the compound exists chiefly in a form with the double bond conjugated with the ketone group.

A double bond in the sterol nucleus that is not conjugated decreases the moment of the compound by 0.49 unit in the one case studied. Two explanations are discussed.

Sterols with two polar groups and differing only in respect to the position of a hydroxyl group on the same carbon atom have different moments. The difference in moments of the members of any epimeric pair depends somewhat on the moment of the other polar group in the molecule.

There appears to be no correlation between the dipole moments of the sex hormones and their physiological activity.

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[CONTRIBUTION FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Gel Formation in Addition Polymerization¹

BY CHEVES WALLING

When a polymerization is carried out in the presence of a polyfunctional component which permits the three-dimensional growth and cross-linking of chains, there is, at some stage in the reaction, a rather abrupt transition from the liquid to the gel state. In 1931 Carothers pointed out that such a gel is the result of the linking together of polymer molecules into a three-dimensional network of indefinitely large size.² In 1941 Flory outlined a general method for determining the extent of reaction at which such a network becomes possible, and carried out the detailed calculations for the case of polycondensation reactions.³ His results were in good agreement with experiment, and he indicated that a similar

method might be applied to addition polymerizations. Recently, Stockmayer⁴ has applied Flory's procedure to a mixture of polyfunctional components with a generalized distribution of functionality and has obtained an expression which should predict the gel-point in both vulcanization reactions and addition polymerizations in which all functions have equal reactivity.

In this paper, calculated and observed gel-points are compared for the systems methyl methacrylate-ethylene dimethacrylate and vinyl acetate-divinyl adipate. Observed extents of reaction at the gel-point are, in general, found to be several times those calculated, particularly in experiments in which very early gel-points are anticipated. This discrepancy is discussed from the point of view of the discontinuous nature of dilute polymer solutions.

(1) Presented before the Physical and Inorganic Section at the New York meeting of the American Chemical Society, September 12, 1944.

(2) W. H. Carothers, *Chem. Rev.*, **8**, 402 (1931).

(3) P. I. Flory, *This Journal*, **63**, 3083 (1941).

(4) W. H. Stockmayer, *J. Chem. Phys.*, **12**, 125 (1944).