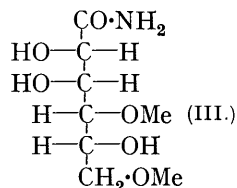
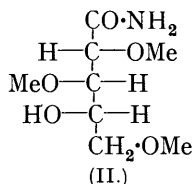
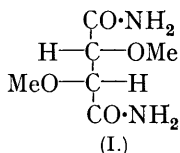


396. *Optical Rotatory Dispersion in the Carbohydrate Group.*
Part VI. The Amide Rotation Rule.

By T. L. HARRIS, E. L. HIRST, and C. E. WOOD.

WE have previously examined in detail the rotatory dispersion of two sharply contrasted lactones of the sugar acids (J., 1934, 1825; this vol., p. 295). One of these (tetramethyl γ -gluconolactone) has a strong positive rotation in all solvents and for all wave-lengths, the rotation being controlled by an absorption band which is identifiable with the carbonyl group of the lactone. Tetramethyl γ -mannonolactone differs in that the term $+k_2/(\lambda^2 - 0.06)$ representing induced activity of the carbonyl group does not in all circumstances control the sign of the rotation. The remaining dissymmetric centres now contribute a partial rotation of opposite sign $-k_1/(\lambda^2 - 0.02)$, which in some solvents is sufficiently large numerically to give a negative total rotation in the visible region. The points we desire to emphasise in connexion with these lactones are that the induced activity is dextro-rotatory irrespective of the configuration of the second carbon atom, and that the sign of the induced activity appears to be controlled by the configuration of the fourth carbon atom. There is therefore a correlation, comparable with Hudson's rule, between the configuration of the carbon atom involved in the lactone formation and the sign of the induced activity.



We wished to extend our observations to the amides of α -hydroxy- and α -methoxyaliphatic acids in order to find out whether the amide rotation rule depends in an analogous way upon control of the sign of the induced activity by the configuration of the second carbon atom. This might be anticipated by analogy with the results outlined above, in view of the large number of amides which have positive rotations in aqueous solution when the hydroxy- (or methoxy-) group attached to the second carbon atom is on the right in the Fischer conventional formula and negative rotations when it is on the left. Accordingly, we have examined the rotatory dispersion of *d*-dimethoxysuccinamide (I), which follows the amide rule, and we find that its rotation is definitely controlled by the induced dissymmetry and can be represented by a one-term equation of the Drude-Natanson type. The absorption band giving rise to the rotation is situated at λ 2300. Exactly similar considerations apply to the corresponding methylamide (*d*-dimethoxysuccinomethylamide) and to *l*-2 : 3 : 5-trimethyl arbonamide (II).

We proceeded therefore to investigate a case where the amide rule does not apply in the visible region in aqueous solution but is followed in alcoholic solution. Here two possibilities are open. On the one hand, the behaviour might be similar to that of tetramethyl γ -mannonolactone, and in that case we should expect to find that the total rotation is composed of two opposite partial rotations, $k_1/(\lambda^2 - \lambda_1^2)$ and $k_2/(\lambda^2 - \lambda_2^2)$. When the hydroxyl group attached to C₂ is on the left the negative partial rotation $-k_2/(\lambda^2 - \lambda_2^2)$ (low-frequency term) is the one which on this view would be associated with the induced dissymmetry. In these circumstances the rotation could be positive or negative in the visible region according to the numerical values of the rotational constants k_1 and k_2 but must tend to become negative in the ultra-violet because the low-frequency term is negative. On the other hand, these exceptional amides may differ from tetramethyl γ -mannonolactone in the sense that special stereochemical arrangements of the substituent groups may give rise to an induced activity opposite in sign to that which would be found if the amides behaved normally. The rotation of such a substance (the hydroxyl group being on the left) would therefore contain a positive partial rotation associated with the induced dissymmetry. It is evident that examination of the rotatory dispersion would enable

a decision to be made between the two alternatives, and we were fortunate in having at our disposal a small quantity of a suitable amide (4 : 6-dimethyl mannonamide, III) which had been prepared in the course of other work (Ault, Haworth, and Hirst, this vol., p. 1012). We had noticed that this substance failed to obey the amide rule in water but followed it in alcohol, and examination of its rotatory dispersion in these solvents has shown clearly that the second of the above two hypotheses is correct. In water, the observed rotation is governed by the induced dissymmetry, the sign of the induced term is positive, and the rotation therefore fails to obey the amide rule at any wave-length. The observations on the alcoholic solution confirm this view. The rotatory dispersion is now visually anomalous, and it is clear that the positive term which governs the sign of the rotation in the ultra-violet is associated with the induced dissymmetry.

In this amide, therefore, the normal action of the α -hydroxy-group has been altered by the influence of the neighbouring groups to such a degree that the total effect produced by coupling with the carbonyl group gives a positive partial rotation in place of the expected negative term. The case is thus comparable with that observed with other derivatives of mannose; for example, the α - and β -forms of mannose and the corresponding methyl-mannosides display marked deviations from Hudson's iso-rotation rules by reason of complications arising from the mutual influence of the *cis*-hydroxy-groups attached to the second and the third carbon atom.

In view of the similarity in the visible region between the rotations of *d*-dimethoxy-succinamide and methyl *d*-dimethoxysuccinate, we examined also the rotatory dispersion of the ester. This investigation had additional interest because of the results we had obtained with tetramethyl γ -gluconolactone, the dispersion of which could be expressed by a two-term equation containing a small second term for which λ_2^2 has the inexplicably large value 0.075 (see below). We wished to see whether the rotation of methyl *d*-dimethoxysuccinate demanded a similar term, more especially since a term of this type has been proposed for tartaric acid (Lowry and Austin, *Phil. Trans.*, 1922, **222**, A, 249; compare Bruhat, *Trans. Faraday Soc.*, 1930, **26**, 400). We find that between λ 6708 and λ 2613 the rotation of the ester in water is given by the equation $\alpha_\lambda = 4.5288/(\lambda^2 - 0.03) - 2.0129/(\lambda^2 - 0.05)$, in which the two frequency constants are identical with those used by Bruhat for tartaric acid (*loc. cit.*). The low-frequency constant ($\lambda_2^2 = 0.05$) is almost the same as the corresponding constant calculated for each of the amides referred to above, and is apparently associated with the induced dissymmetry of the carbonyl groups. It is noteworthy that in methyl *d*-dimethoxysuccinate the sign of this induced term is negative and is opposite to that of the corresponding term in *d*-dimethoxysuccinamide. Here the rotation of the amide has the same sign as that of the ester in the visual region. On the other hand, the rotations of methyl α -chloropropionate and the corresponding dimethyl amide (Kuhn, Freudenberg, and Wolf, *Ber.*, 1930, **63**, 2367) are opposite in sign in the visible region. Fundamentally, however, the phenomena are similar, since in both sets of substances there occurs (on passage from an ester to the corresponding amide) a reversal of sign of the low-frequency term associated with the absorption band of the carbonyl group. Such changes in sign are not uncommon, but their origin is imperfectly understood and at present they add yet a further difficulty to the problem of correlating structure with rotatory power. Additional instances which may be cited are ascorbic acid and iminoglucoascorbic acid, where a low-frequency term changes sign on transformation of the un-ionised acid into a salt (Herbert, Hirst, and Wood, J., 1933, 1564; 1934, 1196).

The Interpretation of Dispersion Equations.

The substances referred to in this and previous papers possess absorption spectra in which the expected bands are obscured by heavy end-absorption, and for this reason it is not possible to make rotation measurements in the vicinity of the bands. The equations of Lowry and Hudson (*Phil. Trans.*, 1933, **232**, A, 117) and of Kuhn and Braun (*Z. physikal. Chem.*, 1930, **8**, B, 281) cannot therefore be utilised, and the distance from the band is such that in most cases the simplest form of the Drude equation should be applicable. In many instances this is true. Nevertheless, this form of the equation cannot apply in the

immediate neighbourhood of a narrow band or at a greater distance from a wide band. The Drude-Natanson equation, $\alpha_\lambda = (\lambda^2 - \lambda_0^2)k_1/[(\lambda^2 - \lambda_0^2)^2 + \lambda^2\lambda_1^2]$, although it does not accurately express rotation values throughout the region of absorption, is a closer approximation to the real form of the dispersion. Sörenson and Trumpy (*ibid.*, 1935, **28**, B, 135) have recently expressed the rotation of certain methylglycosides and their derivatives by single-term Drude-Natanson equations. We were interested therefore to discover whether the data for sucrose could be represented by an equation of this type, in view of the fact that down to a very short wave-length ($\lambda 2356$) the observations can be expressed by a single-term Drude equation. Calculation has shown that within the limit of experimental error the equation used in our previous work $\alpha_\lambda = 7.4645/(\lambda^2 - 0.0213)$ can be replaced by $\alpha_\lambda = 7.4645/[\lambda^2 - 0.0212 + 0.0001\lambda^2/(\lambda^2 - 0.0212)]$, the half-width of the band (λ_1) having the reasonable value 100 Å.

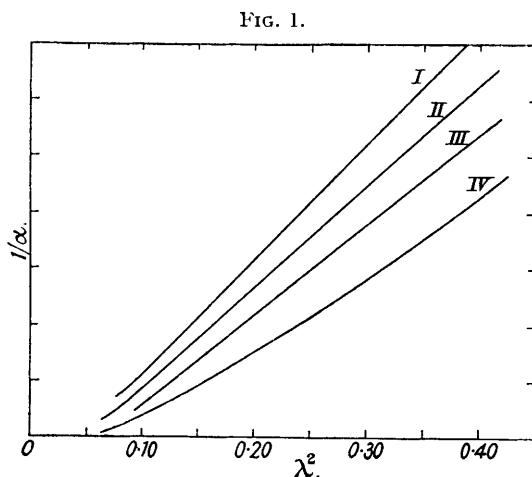
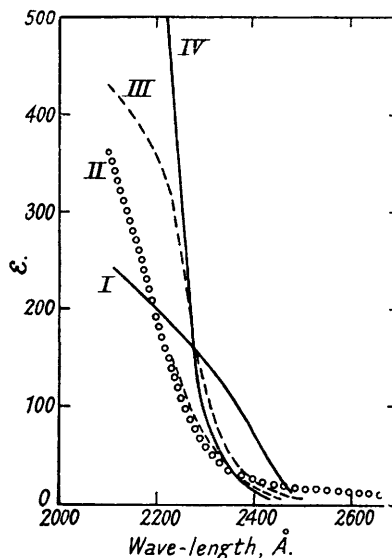


FIG. 1.
I. d-Dimethoxysuccinomethylamide; II. d-dimethoxysuccinamide; III. 4:6-dimethyl mannonamide; IV. 2:3:5-trimethyl arabonamide in alcohol. Aqueous solutions except IV. The graphs are plotted directly from the figures given in the text, but for convenience of representation the scale of $1/\alpha$ is arbitrary and not the same for each.

All the above-mentioned rotatory dispersion curves to which the Natanson equation has been applied are alike in that they deviate only slightly from the curves given by the nearest one-term Drude equations, and always in such a direction that in the ultraviolet the observed rotation is less than that calculated from the single-term Drude equation. We have shown (J., 1934, 1151; this vol., p. 295) that such deviations can be accommodated by the use of a two-term Drude equation in which λ_1^2 is slightly less than λ_0^2 of the simple equation and λ_2^2 is considerably greater. When the data for tetramethyl α -methylglucoside and tetramethyl γ -gluconolactone are analysed in this way, the resulting equations contain small terms with a frequency constant (λ_2^2 ca. 0.07) the origin of which (as was pointed out in the papers cited) is inexplicable on ordinary grounds. In all probability the constant thus calculated is devoid of physical meaning. In such circumstances, the Natanson equation, which requires a frequency constant slightly greater than λ_0^2 of the single-term Drude equation, is obviously to be preferred, and we have used it in the present work on dimethoxysuccinamide and the corresponding methylamide. It should be pointed out, however, that the equation must be used with circumspection when the observations do not cover a wide spectral range. For example, down to $\lambda 3200$ it is possible

FIG. 2.
Absorption spectra in aqueous solution.



I. 1-2:3:5-Trimethyl arabonamide; II. (a) (circles) 4:6-dimethyl mannonamide; (b) (broken lines) methyl d-methoxysuccinate; III. d-dimethoxysuccinamide; IV. d-dimethoxysuccinomethylamide.

to express the rotation of methyl *d*-dimethoxysuccinate by a single-term Drude-Natanson equation, but observations at shorter wave-lengths show that this mode of representation is of little value and a two-term equation is necessary. Instances may arise, therefore, in which the rotatory dispersion, throughout the range open to investigation, can be accurately expressed by more than one equation, with corresponding variations in the constants. In the absence of observable absorption bands, selection of the true frequency constants may then depend on the use of additional data which may not always be available. Nevertheless, approximate values of the frequency constants are almost invariably obtainable. The general character of the rotatory dispersion is then abundantly clear, and arguments such as those developed in the present paper can be based securely on interpretations of the dispersion data.

EXPERIMENTAL.

Methyl d-Dimethoxysuccinate.—Prepared by methylation of methyl *d*-tartrate by methyl iodide and silver oxide (compare Purdie and Barbour, J., 1901, **79**, 973), this was a colourless liquid, b. p. 120°/12 mm., n_D^{25} 1.4318, which rapidly crystallised. The material used in the following experiments was recrystallised from light petroleum.

(a) In water: *c*, 4.68; *l*, 2 dm.; *t*, 20°. [α_λ^{20} = 10.45 α_λ ; α_λ^{20} = 4.5288/(λ^2 - 0.030) - 2.0129/(λ^2 - 0.050)].

λ .	<i>a</i> , obs.	<i>a</i> , calc.	Diff.	λ .	<i>a</i> , obs.	<i>a</i> , calc.	Diff.
6708	+5.70°	+5.75°	-0.05°	3280	+23.44°	+23.42°	+0.02°
5893	7.43	7.50	-0.07	3161	24.44	24.45	-0.01
5515	8.56	8.59	-0.03	3090	24.94	24.89	+0.05
5225	9.62	9.61	+0.01	2930	24.93	24.95	-0.02
4887	10.99	11.03	-0.04	2877	24.42	24.40	+0.02
4789	11.45	11.49	-0.04	2829	23.42	23.49	-0.07
4422	13.45	13.52	-0.07	2787	22.40	22.26	+0.14
4005	16.45	16.50	-0.05	2742	20.39	20.31	+0.08
3780	18.45	18.45	±0	2720	19.39	19.04	+0.35
3685	19.45	19.34	-0.11	2682	16.38	16.22	+0.16
3576	20.45	20.42	+0.03	2655	13.38	13.51	-0.13
3392	22.44	22.30	+0.14	2613	8.36	8.19	+0.17

$\lambda_{\max.}$ = 3000 Å. (obs. and calc.); $\alpha_{\max.}$ = 25.20° (obs.), 25.18° (calc.).

(b) In alcohol: *c*, 6.544; *l*, 1 dm.; *t*, 20°. [α_λ^{20} = 15.28 α_λ ; α_λ^{20} = 3.1068/(λ^2 - 0.03) - 1.3808/(λ^2 - 0.05) (i.e., α_λ^{20} = 0.686 × value of α_λ^{20} for the above aqueous solution)].

6708	+4.00	+3.95	+0.05	3420	+15.45	+15.11	+0.34
5893	5.10	5.14	-0.04	3255	16.45	16.23	+0.22
5515	5.85	5.88	-0.03	3144	16.95	16.86	+0.09
5225	6.53	6.58	-0.05	2855	16.42	16.49	-0.07
4887	7.50	7.58	-0.08	2802	15.42	15.61	-0.19
4370	9.45	9.44	+0.01	2734	13.41	13.63	-0.22
4025	11.45	11.21	+0.24	2692	11.39	11.70	-0.31
3827	12.45	12.36	+0.09	2650	8.38	8.97	-0.59

$\lambda_{\max.}$ (by interpolation) = 3040 Å. (calc. 3000).

The absorption spectrum is shown on Fig. 2. At λ^2 = 0.05, ϵ = 130.

d-Dimethoxysuccinamide.—This was prepared from crystalline methyl *d*-dimethoxysuccinate by the action of methyl-alcoholic ammonia, and was recrystallised from aqueous alcohol. Owing to its limited solubility in water and organic solvents, only a dilute aqueous solution could be used for polarimetric work.

In water: *c*, 0.8168; *l*, 2 dm.; *t*, 20°; [α_λ^{20} = 61.2 α_λ ; α_λ^{20} = 0.4692/(λ^2 - 0.053 + 0.00065 λ^2 /(λ^2 - 0.053))].

λ .	<i>a</i> , obs.	<i>a</i> , calc.	Diff.	λ .	<i>a</i> , obs.	<i>a</i> , calc.	Diff.
6708	+1.14°	+1.18°	-0.04°	3298	+8.44°	+8.23°	+0.21°
5893	1.59	1.59	±0	3110	10.44	10.40	+0.04
5515	1.87	1.86	+0.01	2888	14.42	14.58	-0.16
5225	2.17	2.13	+0.04	2759	18.39	18.57	-0.18
4887	2.52	2.51	+0.01	2631	24.37	24.69	-0.32
4625	2.95	2.90	+0.05	2576	28.34	28.23	+0.11
4000	4.45	4.34	+0.11	2525	32.33	32.15	+0.18
3558	6.45	6.28	+0.17	2550	30.34	30.27	+0.07

The absorption spectrum is shown on Fig. 2. At λ^2 = 0.053, ϵ = 120.

1662 *Optical Rotatory Dispersion in the Carbohydrate Group. Part VI.*

d-Dimethoxysuccinomethylamide.—Prepared from crystalline methyl *d*-dimethoxysuccinate by Haworth and Jones's method (J., 1927, 2349), the material was recrystallised from light petroleum before use; m. p. 205°.

In water: *c*, 1.935; *l*, 2 dm.; *t*, 20°; $[\alpha]_{\lambda}^{20} = 25.8\alpha_{\lambda}$; $\alpha_{\lambda}^{20} = 1.500/[\lambda^2 - 0.050 + 0.00135\lambda^2/(\lambda^2 - 0.050)]$.

λ .	α , obs.	α , calc.	Diff.	λ .	α , obs.	α , calc.	Diff.
6708	+3.77°	+3.74°	+0.03°	3380	+22.44°	+22.50°	-0.06°
5893	5.02	5.02	±0	3200	27.44	27.25	+0.19
5515	5.88	5.86	+0.02	3050	32.43	32.65°	-0.22
5225	6.71	6.68	+0.03	2947	37.42	37.47	-0.05
4887	7.85	7.87	-0.02	2858	42.41	42.64	-0.23
4750	8.45	8.46	-0.01	2794	47.40	47.14	+0.26
4096	12.45	12.53	-0.08	2730	52.44	52.39	-0.05
3665	17.45	17.35	+0.10				

The absorption spectrum is shown in Fig. 2. At $\lambda^2 = 0.05$, $\epsilon = 450$.

l-2 : 3 : 5-Trimethyl Arabonamide.—A specimen of this amide prepared by Haworth, Hirst, and Oliver (J., 1934, 1922; compare Humphreys, Pryde, and Waters, J., 1931, 1298) was used.

In alcohol: 0.1494 g. in 6 c.c.; *l*, 1 dm.; *t*, 20°. $[\alpha]_{\lambda}^{20} = 40.2\alpha_{\lambda}$.

λ	6294	5893	5515	5225	4920	3754	3277
α_{λ}^{20}	+0.46°	0.59°	0.68°	0.82°	0.94°	2.44°	4.43°
λ	3058	2928	2834	2744	2685	2583 *	2498 *
α_{λ}^{20}	+6.42°	8.42°	10.39°	13.38°	16.37°	23.5°	37.4°

* Measurements with tube *l* = 0.25 dm.

The absorption spectrum is shown in Fig. 2. At $\lambda^2 = 0.05$, $\epsilon = 190$.

The above figures disclose an unusually rapid rise of rotation with decrease of wave-length in the visible and the near ultra-violet region. Their representation by an equation will be considered later. The graph in Fig. 1 shows that the rotation is controlled by an absorption band the position (λ^2 ca. 0.05) of which is the same as that of the bands associated with the other amides referred to in this paper.

d-4 : 6-Dimethyl Mannonamide.—The sample used in these experiments was the one prepared by Ault, Haworth, and Hirst (*loc. cit.*).

(a) In water: *c*, 0.734; *l*, 2 dm.; *t*, 20°. $[\alpha]_{\lambda}^{20} = 68.1\alpha_{\lambda}$; $\alpha_{\lambda}^{20} = 0.060263/(\lambda^2 - 0.068)$.

λ .	α , obs.	α , calc.	Diff.	λ .	α , obs.	α , calc.	Diff.
6294	+0.18°	+0.18°	±0°	3874	+0.74°	+0.73°	+0.01°
5515	0.25	0.26	-0.01	3560	1.00	1.03	-0.03
5225	0.30	0.29	+0.01	3406	1.24	1.25	-0.01
4887	0.34	0.35	-0.01	3272	1.50	1.54	-0.04
4780	0.40	0.38	+0.02	3130	1.99	2.01	-0.02
4243	0.54	0.54	±0	3060	2.48	2.35	+0.13

The observed rotations are small and the above equation is regarded only as an approximation.

(b) In alcohol: *c*, 1.613; *l*, 1 dm.; *t*, 20°. $[\alpha]_{\lambda}^{20} = 62\alpha_{\lambda}$.

λ	5893	5515	5225	4887	4600	4400
α_{λ}^{20}	-0.04°	-0.04°	-0.04°	-0.03°	+0.01°	+0.04°
Calc. by equation (A)	-0.04	-0.04	-0.04	-0.01	+0.02	+0.05
λ	4230	4100	3950	3850	3700	
α_{λ}^{20}	+0.09°	+0.14°	+0.20°	+0.24°	+0.34°	
Calc. by equation (A)	+0.09	+0.13	+0.19	+0.23	+0.34	

The rotation is visually anomalous. The observations are accurately reproduced by the equation

$$\alpha_{\lambda} = 0.1425/(\lambda^2 - 0.06) - 0.176/(\lambda^2 - 0.02) \quad (A.)$$

but in view of the small rotations observed the constants are to be regarded as approximate only. Nevertheless, the general character of the rotatory dispersion is clear.

The authors thank the Government Grants Committee of the Royal Society for a grant.