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A Benzimidazole Rule for the Determination of Configuration of the Aldonic Acids and Related Compounds

BY NELSON K. RICHTMYER AND C. S. HUDSON

During the course of a recent investigation[1] in which several 2-[*aldo*-polyhydroxyalkyl]-benzimidazoles were prepared for the identification of aldonic acids, as recommended by Moore and Link,[2] a certain correlation was noticed between the sign of rotation and the configuration of the compound. This correlation may be stated in the form of a "benzimidazole rule" as follows: *whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is written on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive, and conversely, when the hydroxyl group is written on the left, the rotation of the benzimidazole derivative is negative.*

In Table I are recorded the specific and molecular rotations in either aqueous citric or hydrochloric acid, or both, of the known benzimidazoles derived from the optically active aldonic acids. Of these, the D-*ribo*, the D-*glucomethylo*, the L-*galacto*, and the D-*gluco*-L-*gala*-*octo* derivatives are described for the first time; the D-*arabo*, the D-*galacto* and the D-*gluco* derivatives have been prepared and recrystallized to constant rotation the better to compare the D- and L-forms of these substances. All twenty-three compounds, or all nineteen if we include only one member of a D and L pair, are in agreement with the rule stated above. From the laws of probability we should expect this rule to hold for other benzimidazoles of this class which may be prepared in the future.[2a] Consequently, this benzimidazole rule, like the well-known phenylhydrazide[3] and amide[4] rules, may be used to determine the configuration of the hydroxyl group on the carbon atom adjacent to the carboxyl group of an aldonic acid.

If the benzimidazole derivatives listed in Table I are arranged according to the configurations of the hydroxyl groups on the second and third carbon atoms, certain additional correlations will be noted. When these hydroxyl groups are in a *cis* relationship, as in compounds 1, 2, 5, 6, 9, 15, 17, 18, 19 and 20, the molecular rotations are of relatively low magnitude, the highest being +7350 in the case of the L-*mannomethylo* derivative. When the hydroxyl groups in question are in a *trans* relationship, the compounds may be separated further into two classes. The members of the one class, with the hydroxyl groups on the second, third and fourth carbon atoms in a + − − or − + + sequence (arabonic configuration), as in compounds 3, 4, 10, 11, 12, 22 and 23, have relatively high molecular rotations, between 11,750 and 14,750. The members of the other class, with the same three hydroxyl groups in a + − + or − + − sequence (xylonic configuration), seem to show no regularity in their molecular rotations, the values ranging from +1900 for the D-*glucomethylo* to +15,450 for the D-*xylo* derivative. As new benzimidazoles are prepared in the future for characterization and determination of configuration of other aldonic acids, additional regularities or irregularities in their rotations may become evident.

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Summary

1. The "benzimidazole rule" may be stated as follows: whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is written on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive and, conversely, when the hydroxyl group is written on the left, the rotation of

(1) Richtmyer and Hudson, THIS JOURNAL, **64**, 1609 (1942).

(2) Moore and Link, *J. Biol. Chem.*, **133**, 300 (1940); *J. Org. Chem.*, **5**, 637 (1940).

(2a) Note added June 10, 1942.—Dimler and Link [*J. Biol. Chem.*, **143**, 557 (1942)] have reported the rotation of the benzimidazole derivative of L-lactic acid ("sarco" lactic acid, with the configuration $CH_3-\underset{H}{\overset{OH}{C}}-COOH$) to be −33.4° in ethyl alcohol, and the rotation of the D-antipode to be +33.4° in the same solvent. Inasmuch as the L-derivative has a rotation of −14.7° in 5% aqueous citric acid [Moore, Dimler and Link, *Ind. Eng. Chem., Anal. Ed.*, **13**, 160 (1941)] the data for these derivatives of the simplest optically active α-hydroxy acid are in accord with the benzimidazole rule.

(3) Levene, *J. Biol. Chem.*, **23**, 145 (1915); Hudson, THIS JOURNAL, **39**, 462 (1917).

(4) Hudson, THIS JOURNAL, **40**, 813 (1918).

TABLE I

ROTATIONS OF 2-[*aldo*-POLYHYDROXYALKYL]-BENZIMIDAZOLES

No.	Substituent group	Configuration of the second carbon atom[a]	Rotation in 5% aqueous citric acid[b] $[\alpha]^{20}D$	$[M]^{20}D$	Rotation in *N* HCl[b] $[\alpha]^{20}D$	$[M]^{20}D$
1	D-Erythro	+	+ 9.0°[c]	+ 1,850		
2	L-Erythro	−	− 8.3°[c,d]	− 1,750		
3	D-Arabo[e]	−	−49.4	−11,750	−49.7	−11,850
4	L-Arabo	+	+49.7°[c,f]	+11,850	+49.8[g]	+11,850
5	D-Lyxo	−	−12.8°[h]	− 3,050		
6	D-Ribo[i]	+	+21.6	+ 5,150		
7	D-Xylo	+	+64.8°[h]	+15,450		
8	D-Glucomethylo[j]	+	+ 7.6	+ 1,900		
9	L-Mannomethylo[k]	+	+27.4°[h]	+ 6,900	+29.1[l]	+ 7,350
10	D-Altro	−			−48.1[l]	−12,900
11	D-Galacto	+	+44.5[m]	+11,950	+45.1[n]	+12,100
12	L-Galacto[o]	−	−44.1	−11,850	−45.0	−12,050
13	D-Gluco	+	+ 9.5[p]	+ 2,550	+ 8.7[q]	+ 2,350
14	L-Gluco	−	− 9.0°[c,d]	− 2,400	− 8.3[d]	− 2,250
15	D-Gulo	+			+16.7[l]	+ 4,500
16	D-Ido	−			−19.2[l]	− 5,150
17	D-Manno	−	−22.0°[h]	− 5,900	−23.7[l]	− 6,350
18	D-Talo	−			−23.0[l]	− 6,150
19	D-Gala-L-manno-hepto[r]	+			+18.5[l]	+ 5,500
20	D-Gluco-D-gulo-hepto[r]	+			+14.3[l]	+ 4,250
21	D-Gluco-D-ido-hepto[r]	−			−27.6[l]	− 8,250
22	D-Manno-D-gala-hepto[r]	+			+49.5[l]	+14,750
23	D-Gluco-L-gala-octo[r,s]	−			−44.7	−14,700

[a] A plus sign indicates that the hydroxyl group on the second carbon atom is on the right, and a minus sign indicates that the hydroxyl group is on the left, when the aldonic acid is written in the usual vertical projection formula. [b] The specific rotations reported by the present authors, either here or in a preceding paper (ref. *c*), were measured in a 4-dm. tube; the values are considered accurate to ±0.2°. Concentrations were 2 g. per 100 cc. of solution unless otherwise noted. The rotations reported by Moore and Link (ref. *h*) were observed at 25°. [c] Richtmyer and Hudson, THIS JOURNAL, **64,** 1609 (1942). [d] The rotations observed in the cases of the L-*erythro* and L-*gluco* benzimidazoles were slightly lower than the corresponding values in the D-series; this is due, probably, to the presence of a trace of a high dextrorotating, less soluble impurity (see ref. *c*). [e] This compound was prepared first by Moore and Link (ref. *h*, p. 307). The rotation was reported as −51°; no analysis was given. *Anal.* Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.31; H, 5.88. [f] Reported as +49.2° by Moore and Link, ref. *h*. [g] Reported as +51.96° in 5 *N* HCl (*c*, 1.6) by Ohle, *Ber.*, **67,** 162 (1934). [h] Moore and Link, *J. Biol. Chem.*, **133,** 301 (1940). [i] **2-[D-*Ribo*-tetrahydroxybutyl]-benzimidazole** was prepared from D-ribonolactone which was obtained in turn from cadmium D-ribonate, furnished through the courtesy of Dr. C. R. Addinall of the Merck Research Laboratories. The product was recrystallized from hot water, in which it is readily soluble, as prismatic needles melting about 190° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92. Found: C, 55.48; H, 5.81. [j] Also known as D-*isorhamno* (see ref. *r*). The **2-[D-*glucomethylo*-tetrahydroxyamyl]-benzimidazole** was recrystallized from hot water, in which it is readily soluble, as needles melting about 190° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39. Found: C, 57.28; H, 6.25. [k] Also known as L-*rhamno* (see ref. *r*). [l] Haskins and Hudson, THIS JOURNAL, **61,** 1267 (1939). [m] Reported as +43.3° by Moore and Link, ref. *h*. [n] Reported as +44.4° by Haskins and Hudson, ref. *l*, and also by Moore and Link, ref. *h*, p. 309. [o] **2-[L-*Galacto*-pentahydroxyamyl]-benzimidazole** was prepared from the γ-L-galactonolactone described by Richtmyer, Hann and Hudson, THIS JOURNAL, **61,** 342 (1939). The product was recrystallized four times from 50% aqueous alcohol as fine needles melting about 250° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.02. Found: C, 53.82; H, 6.18. [p] Reported as +9.6° by Moore and Link, ref. *h*. [q] Reported as +8.9° by Haskins and Hudson, ref. *l*, and +9.4° by Moore and Link, ref. *h*, p. 309. [r] For the nomenclature of the methylpentoses, heptoses and octoses, see Hudson, THIS JOURNAL, **60,** 1537 (1938). [s] The **2-[D-*gluco*-L-*gala*-*octo*-heptahydroxyheptyl]-benzimidazole** was prepared in this Laboratory by Dr. Alice T. Merrill and Dr. Raymond M. Hann, to whom we are indebted for permission to publish their data. The compound was thrice recrystallized from water as fine needles melting at 246–247° with decomposition. The rotation was observed at a concentration of 1 g. per 100 cc., in a 4-dm. tube. *Anal.* Calcd. for $C_{14}H_{20}N_2O_7$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.05; H, 5.96; N, 8.69.

the benzimidazole derivative is negative. No exceptions have been noted.

2. D-*Ribo*, D-*glucomethylo*, L-*galacto* and D-*gluco*-L-*gala*-*octo* benzimidazoles have been described.

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