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Empirical Model for the Molar Rotations of *syn*-2,2-Dimethyl-1,3-dioxanes

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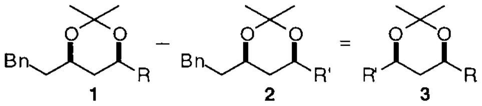
ABSTRACT



$$\lambda_R = [\Phi]_1 + \lambda_{CH_2Bn}$$
$$\lambda_{R'} = [\Phi]_2 + \lambda_{CH_2Bn}$$
$$\lambda_R - \lambda_{R'} = [\Phi]_3$$

A useful method for the prediction of molar rotation ([Φ]) of *syn*-2,2-dimethyl-1,3-dioxanes (acetonides) is described. A series of acetonides were prepared by standard methods. A simple additive relationship between the substituents (R, R′) and molar rotation was realized.

Historically, the assignment of absolute configuration to natural products has been an arduous task. Most common methods have limitations. X-ray crystallography requires a crystalline compound or derivative. Circular dichroism requires a thorough understanding of conformation and often requires the synthesis of derivatives.[1] Mosher ester analysis requires derivatization of a suitable functional group in the compound of interest.[2] Kishi's recently introduced NMR method for the determination of absolute configuration is currently limited to a narrow set of compounds.[3] Optical rotation (polarimetry) is one of the simplest physical methods for assaying chirality, but traditionally it has required direct comparison with a synthetic sample (or known compound) to assign absolute configuration.[4] Recently, Wipf and Beratan have demonstrated that optical rotations can be predicted with reasonable accuracy using modern computational methods.[5] This strategy holds great promise but is still limited by the size of the molecule and the number of low-lying conformations. We describe herein an empirical strategy for predicting the optical rotation of substituted *syn*-2,2-dimethyl-1,3-dioxanes.

Various empirical models have been developed to predict the sign and magnitude of optical rotation.[6] The primary goal of these methods has been to use the sign of the experimentally determined optical rotation at a single wavelength to assign the absolute stereochemistry of a molecule. Most methods are based on van't Hoff's principle of optical superposition. This principle states that the optical rotation of a molecule is equal to the sum of the rotation of the individual noninteracting asymmetric carbon atoms contained in a molecule.[7,8] Thus each isolated segment of the molecule

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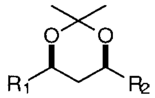
can be treated independently and summed to give the predicted rotation for the complete molecule. Brewster's empirical model has been one of the most successful.[6d−i] In the Brewster model, the contribution of each carbon−carbon bond is calculated and the components are summed. Since each conformation contributes to the observed rotation, application of Brewster's model to conformationally flexible molecules requires the contribution of each conformer in a Boltzmann-weighted average to be summed, which can be tedious. A general analysis of additivity schemes for more complex frameworks has been developed by Ruch.[9] This analysis has been applied to allenes[10] and stereogenic carbons[11] with some success. Ruch's analysis underlies our own work with *syn*-2,2-dimethyl-1,3-dioxanes.



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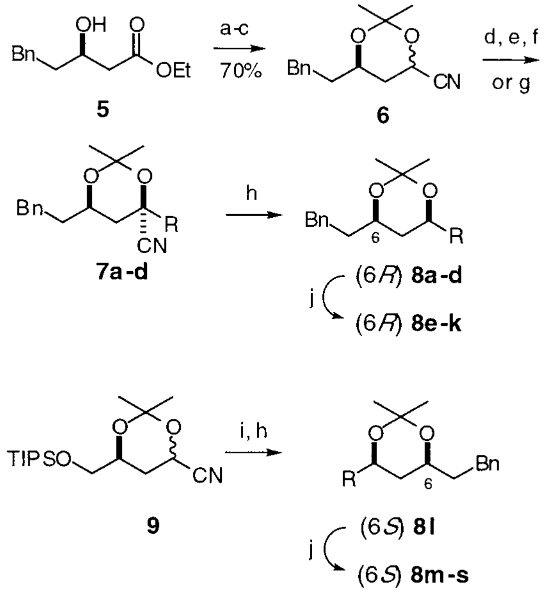
The 2,2-dimethyl-1,3-dioxane (e.g. acetonide **4**) structure is one of the most widely used protecting groups for 1,3-diols and has been used to assign relative configurations to diols as the *syn* and *anti* isomers are easily distinguished by ^{13}C NMR analysis.[12] The conformation of the *syn*- and *anti*-2,6-dialkyl-1,3-dioxanes are well defined, with the former adopting a chair conformation and the latter adopting a 2,5-twist-boat conformation.[12,13] Furthermore, the two substituents on a *syn* acetonide ring are remote in space and unlikely to interact with each other. Thus we postulate that the specific conformation of R_1 will not depend on the identity or conformation of R_2. The *syn* isomer **4** is a "category a" molecular framework as defined by Ruch, in that it has only two substituents (ligands) and these ligands are exchanged by a mirror plane.[9] Ruch has shown that the optical rotation of category a skeletons can be predicted with "chirality functions" in which each ligand has an empirically derived λ-parameter.[10,11] The range of ligands is restricted by the requirement that a molecule with exclusively identical ligands must have the symmetry of the skeleton. In the case of skeleton **4**, this restriction excludes the use of R_1 or R_2 that contain stereogenic centers. It is obvious on inspection that **4** will be achiral when R_1 is identical to R_2 and when R_1 and R_2 do not contain stereogenic centers. We set out to develop a simple, empirical additivity scheme to predict the molar rotations of *syn* acetonide structures.

Synthesis of the desired substrates began with β-hydroxy ester **5** (98% ee)[14] and with cyanohydrin **9**, which was derived from L-malic acid.[15] Ester **5** was converted to cyanohydrin acetonide **6** in 71% yield in a standard three-step sequence.[16] The lithium anion of **6** was alkylated with several electrophiles in good yield (steps d−g, Scheme 1), and the cyano group was removed in a stereoselective reduction.[15] Nitrile **9** was alkylated with 2-phenethylbromide and then treated under dissolving metal conditions to generate acetonide (6*S*)-**8l** in 42% yield over two steps. The 2,2-dimethyl-1,3-dioxanes (6*R*)-**8a** and (6*S*)-**8l** were converted to compounds (6*R*)-**8e−k** and (6*S*)-**8m−s** by standard methods.[17] Acetonide (6*R*)-**8t** (R = H) was prepared by DIBALH reduction of **5** and acetonide formation.

Scheme 1. Preparation of *syn*-2,2-Dimethyl-1,3-dioxanes **8** and **10**[a]



[a] The R substituent is defined in Table 1. (a) TMS·NEt$_2$; (b) DIBALH, Et$_2$O, −78 °C; (c) (i) TMSCN, 18-crown-6/KCN, (ii) acetone, 2,2-DMP, CSA; (71%); (d) 2-(*tert*-butyldimethylsilyloxy)-ethyl bromide, LDA, THF, −40 °C (73%); (e) LHMDS then allyl chloride, THF, −78 to −20 °C; (48%); (f) *n*-BuBr, LDA, THF, −40 °C (50%); (g) 1-bromo-3-butene, LDA, THF, −40 °C (68%); (h) Li, NH$_3$, −78 °C, THF or Et$_2$O; (i) 2-phenethylbromide, LDA, THF, −40 °C (60%); (j) see Supporting Information.

$$[\Phi] = \frac{\mathrm{MW}[\alpha]}{100} \qquad (1)$$

Optical rotation data was collected for each of the acetonides, and the molar rotation was calculated according to eq 1, where MW is molecular weight.[18] Molar rotation is

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[17] Details are provided in Supporting Information.

[18] Rotations were measured at 23−25 °C in CHCl$_3$ (*c* 0.80−1.40). Uncertainties in molar rotation derive from errors in mass, volume and rotation measurements. Estimated uncertainties for the molar rotations in Table 1 are approximately 10%.

Table 1. Acetonide Molar Rotations and Refined λ-values

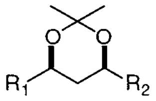
	R	molar rotation[a]	λ-value[d]		R	molar rotation[a]	λ-value[d]
8a	$CH_2CH_2OTBDMS$[c]	+23.4	−79.5	**8l**	CH_2OTIPS[b]	+67.5	−18.3
8b	$CH_2CH{=}CH_2$[c]	+43.5	−51.6	**8m**	CH_2OH[b]	+36.3	−61.0
8c	*n*Bu[c]	+41.6	−55.6	**8n**	CH_2OAc[b]	+25.4	−69.7
8d	$CH_2CH_2CH{=}CH_2$[c]	+59.1	−36.0	**8o**	CH_2OPiv[b]	+31.4	−63.7
8e	CH_2CH_2OH[c]	+28.6	−56.5	**8p**	$CH_2OTBDPS$[b]	+58.7	−36.4
8f	CH_2CH_2OAc[c]	+20.9	−74.2	**8q**	$CH_2OTBDMS$[b]	+77.3	−18.4
8g	CH_2CH_2OPiv[c]	+15.1	−73.1	**8r**	CH_2OBn[b]	+70.1	−25.0
8h	CH_2CH_2OBn[c]	+19.9	−75.2	**8s**	CH_2Cl[b]	+71.8	−34.5
8i	CH_2CH_2Cl[c]	−18.2	−113.5	**8t**	H	+95.1	0.0
8j	CH_2CH_2Br[c]	−27.7	−124.7	**8u**	CH_2Bn	0.0	−95.1
8k	CH_2CH_2I[c]	−39.3	−134.4				

[a] Molar rotations for the (6*R*) acetonides are shown. Molar rotations measured in $CHCl_3$ at concentrations of 0.80−1.40 at the sodium D line. [b] (*S*,*S*) enantiomer (6*S*)-**8** was prepared. [c] Molar rotations corrected to 100% ee. [d] The λ-value for H was arbitrarily set to zero.

proportional to the number of moles of analyte, rather than the mass of analyte as in the case of specific rotation. Presenting the data as molar rotations allows for direct comparison of the optical rotatory power between different substrates. The unrefined λ-value for each substituent is the molar rotation for the appropriate compound (6*R*)-**8** minus that for (6*R*)-**8t** (R = H). This arbitrarily defines hydrogen as the zero point for λ. The refined λ-values in Table 1 were calculated by minimizing the RMS deviation between calculated and experimentally determined molar rotations for compounds (6*R*)-**8a**−**u** and **28**−**35** (Table 2).[18] Compounds **28**−**35** were included to add redundancy and to increase the structural diversity of our dioxanes.

The λ-values from Table 1 can be used to predict the molar rotations of a range of substituted acetonides. The simple additivity relationship is defined in Figure 1. The λ-values

Table 2. Predicted Molar Rotations



$$[\Phi]_{calc} = \lambda_2 - \lambda_1$$

compound	R_1	R_2	calcd	exptl[18]	deviation	ref
10	CH_2CH_2OH	CH_2OBn	+31.5	+64.5	33.0	20a
11	CH_2OH	CH_2CH_2OBn	−14.2	−40.9	26.7	20b
12	$CH_2CH_2CH{=}CH_2$	CH_2CH_2OBn	−39.2	−48.7	9.5	20c
13	CH_2OH	CH_2OAc	−8.7	−10.1	1.4	20d
14	$CH_2CH_2OTBDMS$	CH_2OH	+18.4	+31.1	12.7	20a
15	$CH_2CH_2OTBDMS$	CH_2OBn	+54.5	+69.5	15.0	20a
16	CH_2OBn	CH_2CH_2OPiv	−48.1	−76.5	28.4	20a
17	$CH_2OTBDPS$	CH_2CH_2OH	−20.1	−57.4	37.3	20a
18	$CH_2OTBDPS$	CH_2CH_2OBn	−38.8	−65.8	27.0	20a
19	$CH_2CH{=}CH_2$	CH_2CH_2OH	−4.9	−4.4	0.5	20e
20	CH_2CH_2OH	CH_2CH_2OAc	−17.7	−31.5	13.8	20f
21	CH_2OAc	CH_2OH	+8.7	+11.1	2.4	20g
22	CH_2OPiv	$CH_2CH{=}CH_2$	+12.1	+19.9	7.8	20h
23	CH_2CH_2OH	CH_2CH_2OBn	−18.7	−26.5	7.8	20i
24	CH_2CH_2I	CH_2CH_2OBn	+59.2	+48.9	10.3	20h
25	$CH_2CH{=}CH_2$	CH_2CH_2OBn	−23.6	−36.5	12.9	20h
26	CH_2CH_2OH	$CH_2CH_2OTBDMS$	−22.9	−26.1	3.2	20j
27	CH_2CH_2OAc	$CH_2CH_2OTBDMS$	−5.3	−6.1	0.8	20i
28	CH_2OTIPS	CH_2CH_2OPiv	−54.8	−47.9	6.9	20k
29	$CH_2OTBDMS$	*n*Bu	−37.3	−36.7	0.6	17
30	CH_2OTIPS	*n*Bu	−37.3	−53.4	16.1	17
31	CH_2OH	*n*Bu	+5.4	+7.6	2.2	17
32	CH_2CH_2Br	$CH_2CH_2OTBDMS$	+45.3	+47.2	1.9	17
33	CH_2CH_2OH	$CH_2CH_2OTBDMS$	+34.1	+34.3	0.2	17
34	CH_2CH_2Cl	$CH_2CH_2OTBDMS$	−22.9	−32.9	10.0	17
35	CH_2Cl	*n*Bu	−21.1	−9.9	11.2	17

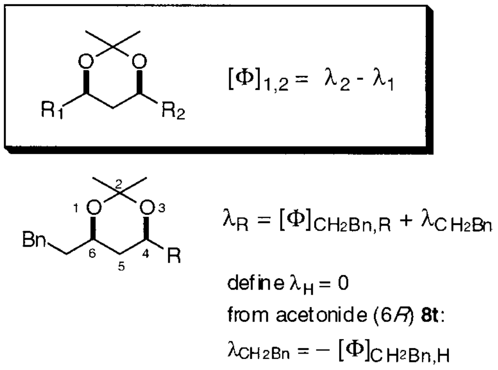


Figure 1. Predictive model for molar rotations. The unrefined λ-values for substituents **a**−**t** were calculated using the formula shown. The refined λ-values reported in Table 1 were calculated as described in the text.

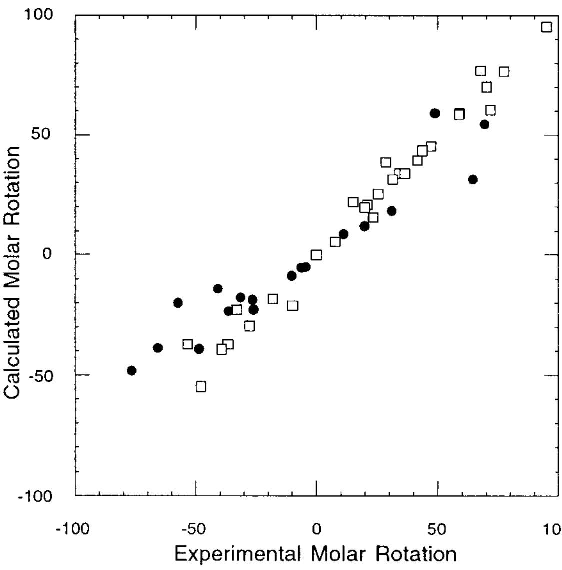


Figure 2. Graphical representation of predictive model with refined λ-values: (□) compounds **8a**−**u** and **28**−**35**; (●) test compounds **10**−**27**.

for 21 different side chains that are reported in Table 1 should be useful for predicting the molar rotations of 210 unique, chiral acetonides.

Our additivity model was evaluated by calculating the molar rotation of known compounds **10**−**27** (Table 2).[19,20] A literature search revealed 18 compounds that contained substituents in our data set. The calculated and experimental molar rotations are presented in Table 2. Unrefined λ-values worked well for most substituents but gave poor predictions for a few compounds. Large substituents are the ones most likely to violate our assumption that the two R groups will not interact with each other. Intermolecular aggregation and hydrogen bonding may also contribute to the deviations between predicted and experimental values. Our model using refined λ-values correctly predicts the sign of the molar rotation for 17 of 17 literature acetonides (**14** and **22** are enantiomers). A graphical representation of the predicted and experimental values is presented in Figure 2. The data for the test compounds (**10**−**27**) shows a good correlation ($R^2 = 0.90$) to the best-fit line.

Given the small optical rotation for members in this class, the agreement between the predicted values and the literature values is very good.[21] This method can be extended to a variety of other substituents and should be useful for assigning the configuration of *syn*-acetonides. It is important to note that concentration and solvent should be held constant to make use of these refined λ-values.[18] This work further validates Ruch's analysis and suggests a wider application of his approach is warranted.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Experimental rotations for compounds **10**−**27** were measured in $CHCl_3$, where T = 16−28 °C.

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(21) The largest $[\alpha]_D$ of a 2,2-dimethyl-1,3-dioxane reported in Table 2 is +23.0 (compound **10**).