3170 *J. Org. Chem.* **1987**, *52*, 3170-3171

Calculated Optical Activity of Cyclohexanepolyols

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Received February 9, 1987

In relating the optical activity of organic molecules to their structure, there are three approaches. One, purely empirical, consists of extracting molecular fragment contributions from some set of experimental data and applying those parameters to other molecules of interest. The works of Whiffen,[1] Brewster,[2] and Lemieux[3] are representative of such an approach. Semiempirical treatments[4,5] use some form of polarizability theory, together with parameters derived from experiment. Ab initio methods are practical only for the smallest organic molecules; see, for example, recent calculations on several cyclopropane derivatives.[6]

As part of a general program of extending circular dichroism (CD) measurements into the vacuum UV region,[7] we have recently developed a semiempirical theory of optical activity[8] which meets the requirements that (a) it make explicit reference to high-energy excited states so as to be relevant to the vacuum UV CD and (b) it be sufficiently tractable to allow treatment of complex molecules. Although our main interest has been in saccharides and carbohydrates, we show here that it can successfully be applied to molecules of related structure, e.g., cyclohexanepolyols.

The details of the theory are presented elsewhere;[8] it is briefly summarized here. The method consists essentially of solving the simultaneous equations

$$\sum_{i=1}^{N} C_{ik}(V_{ij} - E_k\delta_{ij}) = 0 \qquad j = 1,2, \ldots N$$

V_{ij} is the coulombic interaction energy of transition dipole moments μ_i and μ_j representing the high-energy electronic excitations of all C–C, C–O, and C–H groups of the molecule. Solution of the secular equation yields transition energies, E_k, relative to the initial unperturbed transition energy and coefficients C_{ik}, which describe the interacted transition moments as linear combinations of the unperturbed moments.

Five of the seven independent parameters of the calculation were taken directly from the literature. Transition intensities for C–C and C–H bonds, parallel and perpendicular to the bonds, were taken from the work of Raymonda and Simpson[9] as subsequently modified by Raymonda,[10,11] and polarizability anisotropies averaged from three sets of literature values.[12-14] The fifth parameter, representing the unperturbed transition energy, was taken as the average of the transition energies of C–C and C–H bonds assigned by Raymonda.[10,11]

Table I. $[\mathrm{M}]_\mathrm{D}$ of 1-D-Cyclohexanepolyols (in deg cm^2 dmol^{-1})

	prefix[a]	form[b]	empirical[c]	ref 5[d]	present work	exptl[e]
1	1/2	1C	45	112	37	54
2	1,2/3	C1	90	244	88	92
3	1,2,3/4	1C	45	147	43	53
4	1,2,4/3	C1	45	136	49	57
5	1,3/2,4	1C	45	100	35	43
6	1,2/3,5	C1	90	186	74	90
7	1,4/2,5	C1	45	102	28	33
8	1,2,3/4,5	1C	90	219	79	102
9	1,2,3,5/4	1C	0	45	1	9
10	1,2,4/3,5	C1	90	181	72	90
11	1,2,5/3,4	1C	−135	−134	−97	−79
12	1,3,4/2,5	1C	−45	−43	−37	−42
13	1,2,4/3,5,6	C1	135	176	98	117

[a] Recommended IUPAC nomenclature.[17] [b] Conformation with the least number of axial hydroxyl groups. [c] Whiffen's empirical treatment.[1] [d] Applequist's values[5] are multiplied by 1.26 for comparison with aqueous solution data and the present calculations, similarly treated. [e] Data taken from ref 18 for all compounds except 1,[19] 6,[20] and 7.[21]

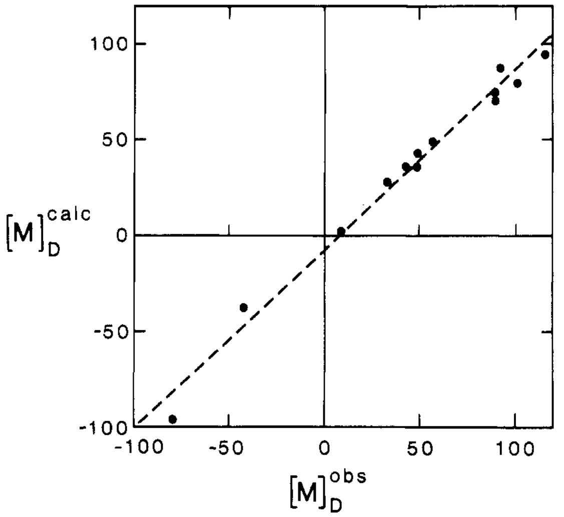

Figure 1. Correlation of calculated sodium D rotations ($[\mathrm{M}]_\mathrm{D}^{\mathrm{calcd}}$) and experimental values ($[\mathrm{M}]_\mathrm{D}^{\mathrm{obsd}}$). Units are deg cm^2 dmol^{-1}. Compounds can be identified by data in Table I. Dashed line indicates a linear least-squares fit, $[\mathrm{M}]_\mathrm{D}^{\mathrm{calcd}} = 0.95[\mathrm{M}]_\mathrm{D}^{\mathrm{obsd}} - 9$.

The C–O transition intensity was arbitrarily set at 1.5 times the C–C transition intensity, partially to reflect contributions from the hydroxyl group contributions not included explicitly. The C–O polarizability anisotopy was set equal to the C–C anisotropy.

Solution of the secular equation allows the calculation, by well-known equations, of CD rotational strengths[15] (with no additional parameters except the geometry of the molecule) and sodium D rotations[16] (with no additional parameter except the band width of an assumed Gaussian band shape). For comparison with experimental solution data, sodium D rotations were multiplied by $(n^2 + 2)/3$

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= 1.26 where *n* is the index of refraction of water at 589 nm.

The calculation was applied to 13 cyclohexanepolyols for which experimental data are available and for which the predominant chair form (${}^1C_4$ or ${}^4C_1$) can be predicted from a presumed preference for equatorial hydroxyl groups. The results are shown in Table I and Figure 1. In Table I the calculated results are compared with the results of a purely empirical treatment of the same molecules[1] and with a previous semiempirical calculation.[5]

For all of the molecules, the calculation results in one CD rotational strength at particularly low energy, well separated from higher energy rotational strengths; it typically occurs near 155 nm. It is this rotational strength that determines the sign and, to a large extent, magnitude of the sodium D rotation. This result is similar to what was observed for the more complex saccharide structures, in which case it was shown to arise from the local geometry of tetrahedral carbon atoms in a puckered-ring structure.[8]

The present model sheds light on the fact that purely empirical treatments[1-3] are rather successful even though they are based on simple group additive contributions to optical activity. In terms of the present model, the sign and order of magnitude of the sodium D rotation are determined largely by a single vacuum UV CD band, whose position and intensity are determined largely by local symmetry. Group interactions do not qualitatively change that pattern. The effect of group interactions can be seen in Table I, in that the calculated values are not exact multiples of a constant rotation; they are, however, approximately multiples of 37°. The scatter in Figure 1 arises from the approximate nature of the semiempirical model itself and also from omitting the effects of small amounts of the less favored chair form, slight variations in chair geometry, and the potential for intramolecular hydrogen bonding in some of the compounds.

Although the optical activity of cyclohexanepolyols has been treated previously, the theory described here is the first to display the connection between molecular structure and sodium D rotation explicitly in terms of high energy vacuum UV CD features which are intrinsically related. It therefore represents a conceptual advance in spite of its necessarily approximate nature.

Acknowledgment. This work was partially supported by NSF Grant CHE85-09520.

Communications

Unrecognized Benzoyl Migrations in the Lincosamine Series: Modeling of the Electrophilic Reactions of an Alkenylpyranoside

Summary: Migration of a C_4 benzoyl group to C_6 is actuated by electrophilic attack on the double bond (C_6–C_7) of an alkenylpyranoside. Upon treatment of the resultant product with DBN, the benzoyl group migrates back to C_4 and a C_6–C_7 oxirane is produced.

Sir: Recently a fully synthetic route to racemic β-methyllincosaminide (**5**) was reported.[1] An important subgoal of that synthesis was the conversion of alkenylpyranoside **1** to epoxide **4**. A two-step sequence, passing through an intermediate bromohydrin, achieved the required transformation. In the first step, involving reaction of **1** with *N*-bromosuccinimide in aqueous acetic acid, a product $C_{30}H_{29}BrO_9$, mp 206–207 °C, corresponding to the overall addition of the elements of HOBr, was obtained in 92% yield (Figure 1). Treatment of this compound with 1,5-diazabicyclo[4.3.0]non-5-ene resulted in the loss of the elements of HBr and afforded the required epoxide **4**, mp 198–199 °C, in 96% yield.

These data per se did not distinguish between the two possible vicinal bromohydrins **2** and **3**. The compound was formulated as the former structure. The preference was based on the surmise[2] that a cyclic α-face bromonium specie derived from **1** would undergo solvolytic inversion at C_7. The configuration of the bromine atom in the bromohydrin is α (in the conformation drawn), since the derived epoxide had the configuration shown in **4**.

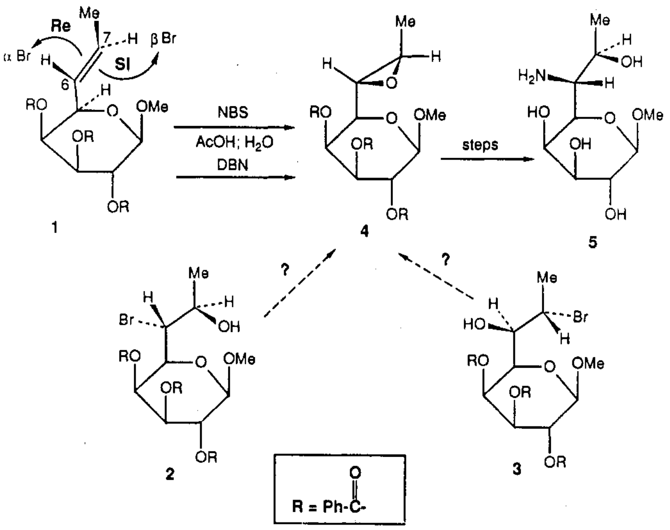

Figure 1.

By the recent arguments articulated by Chamberlin, Hehre, and co-workers,[3,4] the observed sense (α) of bromonium attack would be in accord only with that expected from a pathway where there is participation from an internal nucleophile. In the absence of such participation, these rules predict the preferred formation of the β-bro-

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[1] Danishefsky, S. J.; Larson, E.; Springer J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

[2] Our experiences in this area indicated that attack at C_7 is much less sterically encumbered than is attack at C_6. Contributing to the bias was an NMR measurement which seemed to indicate coupling between the C_7 and hydrolytic protons. This additional coupling, which is no longer seen, must have been due to some unexplained artifact.

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0022-3263/87/1952-3171$01.50/0