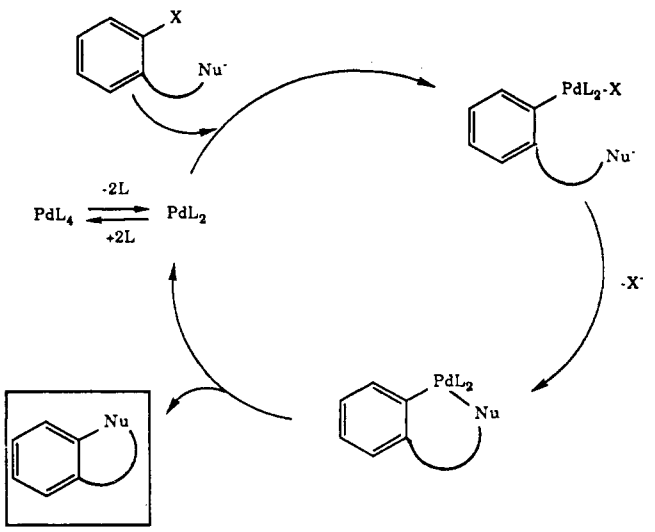
Scheme I



Cyclization of **1i** to the Cava–Nicolaou-type sulfone[10] **2i**, a precursor to an orthoquinodimethane, suggests that one of the carbanion-stabilizing groups may be located at the endocyclic position of the incipient ring. This theme is underscored in the conversion of **1i** to indolone **2i**. Interestingly, in the course of the latter reaction, decarbethoxylation took place.[11] However, yields of such endo-type arylations are 30–40%. Moreover, cyclization of substrates of the type **1k** was unsuccessful under a number of conditions. Thus, although one of the carbanion-stabilizing groups may be tolerated at an endocyclic position, the reaction appears to prefer a regime in which both such groups emerge exocyclic relative to the new ring.

An additional alkyl group ortho to the halogen appears to facilitate the reaction. For instance, cyclization of **1h** was complete in 40 min, and it afforded the expected **2h** in 75% chromatographed yield. The effect of an ortho oxygenated substituent was addressed by using substrate **4**, which was synthesized from aldehyde **3** (Figure 1).[5] Examination of the chemistry of **4** constituted a crucial test, since similar system would be used in our planned Fredericamycin synthesis. We were delighted to discover that compound **4** cyclized smoothly in just 30 min and in 76% chromatographed yield. The major byproducts obtained from most of these reactions were the dehalogenated substrates (10–15% yield). Significantly, no products derived from *bimolecular* arylations were detected.

Modification of experimental parameters (solvents, temperatures, mode of addition, nature of the catalyst, etc.) did not seem to have significant effects on the course of the reaction, provided that a good donor solvent is used (DMF, *N*-methyl-2-pyrrolidinone) and that the catalyst is introduced as a Pd(0) complex. The course of the reaction may be understood based on the catalytic cycle in Scheme I.

It is recognized that the new chemistry permits relatively facile arylation of tertiary centers, leading to quaternary carbons. The creation of such highly substituted carbons is often a major problem in many synthetic endeavors.[12] One limitation of our method is apparent at this point. The relatively high temperature required for the reaction *in its current format* precludes the use of hard enolates, which would probably not survive elevated temperatures. However, excellent methods for intramolecular arylations of those structures are known.[13] Therefore, our chemistry serves as a useful complement to existing techniques in that it offers unique advantages for the arylation of soft enolates. A number of applications of the new technology are under investigation, and progress in these areas will be the subject of future reports.

Acknowledgment. Financial support from the Research Corporation, the Robert A. Welch Foundation (Grant C-1007), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and partial support from the National Science Foundation (Grant CHE-8708130) are gratefully acknowledged.

Supplementary Material Available: Flowcharts for the preparation of the various substrates and detailed experimental procedure for the cyclization reaction (4 pages). Ordering information is given on any current masthead page.

(10) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463 and references cited therein.

(11) We presume that a Krapcho-type decarbethoxylation occurred, since iodide ion is generated in the course of the reaction and since the enolate of the resulting indolone is strongly stabilized by its aromatic character. Krapcho, A. P. *Synthesis* **1982**, 805 and 893.

(12) Cf. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(13) It may be argued that the best method for intramolecular arylation of hard enolates is the Semmelhack photochemical reaction (ref 1 d,e). Regrettably, we could only confirm Semmelhack's observation that soft enolates do not participate in this reaction. The reasons for this failure are not clear. Perhaps soft enolates act as internal filters, thus blocking the main photochemical pathway.

Marco A. Ciufolini,* Hong-Bo Qi
Margaret E. Browne
Department of Chemistry, Rice University
P.O. Box 1892
Houston, Texas 77251
Received June 14, 1988

Preferred Conformation of *C*-Glycosides. 4. Importance of 1,3-Diaxial-like Interactions around the Nonglycosidic Bond: Prediction and Experimental Proof

Summary: A simple but effective approach has been developed to predict the conformational preference of *C*-disaccharides and related compounds, recognizing the importance of 1,3-diaxial-like interactions. Three sets of *C*-disaccharides have been studied to demonstrate the usefulness of this approach.

Sir: Recent interest in this laboratory has focused on the preparation and conformational analysis of *C*-glycosides.[1] We have shown that (1) the conformational preference of both α(axial)- and β(equatorial)-*C*-glycosidic bonds is such that the C1′–C2′ bond is antiperiplanar to the nonglycosidic Cα–C*n* bond and (2) the conformational preference around the glycosidic bond is so overwhelming that a structural deviation from the ideal staggered conformation to avoid steric interactions takes place in rotating primarily the nonglycosidic bond over the glycosidic bond. Thus, it is possible to predict the conformational behavior around the glycosidic bond of given *C*-saccharides by placing the C1′–C2′ bond antiperiplanar to the nonglycosidic Cα–C*n* bond and then focusing principally on the steric interactions around the nonglycosidic bond, which can conveniently be performed by use of a diamond

(1) (a) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370. (b) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. (c) Goekjian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4823. (d) Babirad, S. A.; Wang, Y.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4825.

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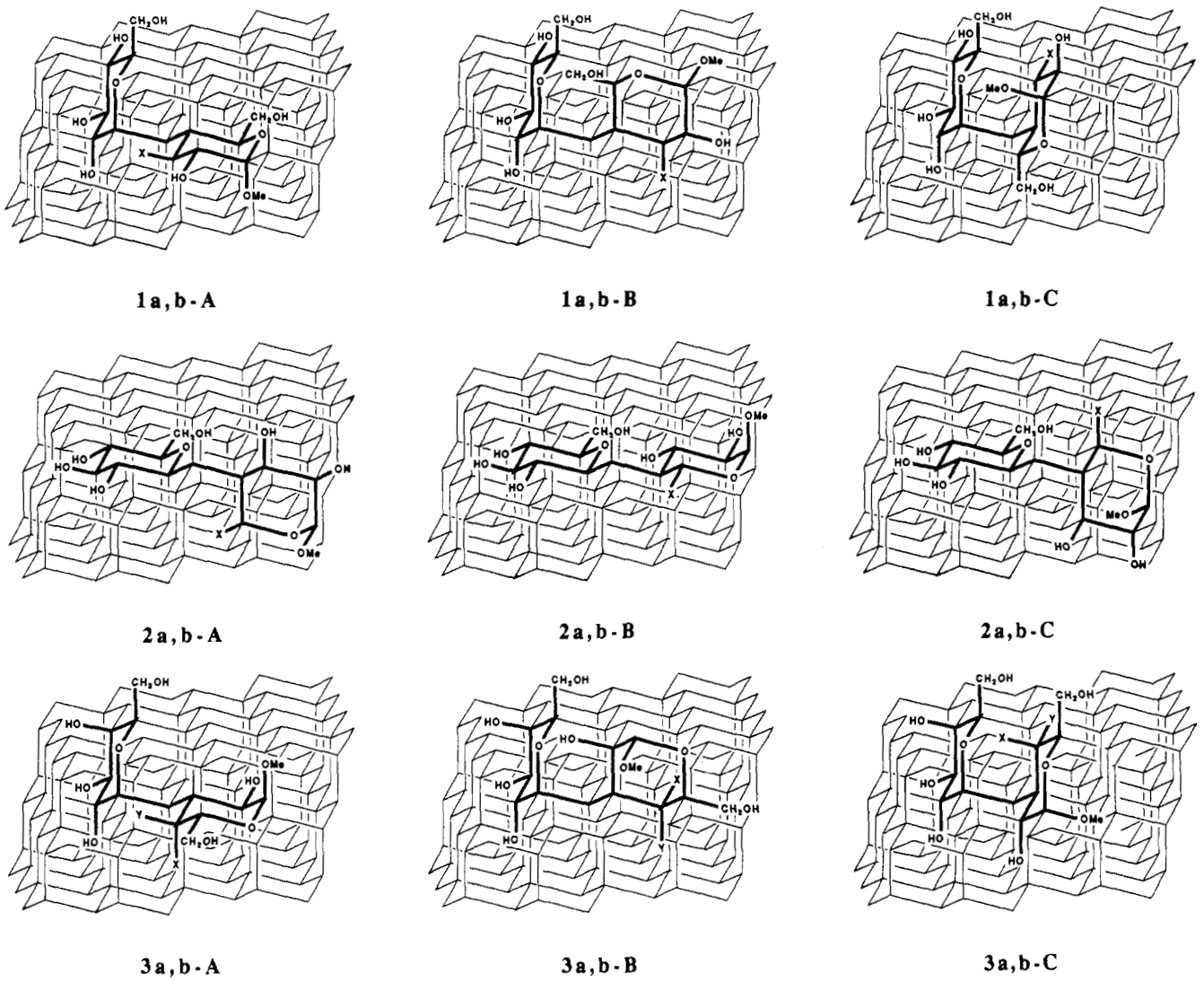
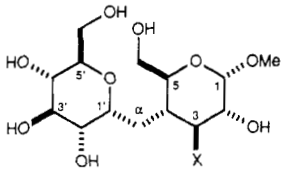
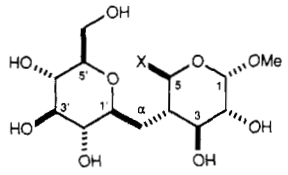


Figure 1.

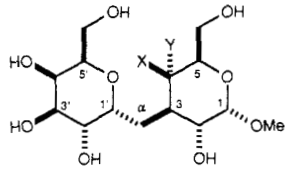
lattice. For example, none of the three ideal staggered conformers A–C available to *C*-maltose (**1a**) and *C*-cellobiose (**2a**) are free from 1,3-diaxial-like interactions (Figure 1), explaining the fact that neither **1a** nor **2a** exists preferentially in an ideal staggered conformation.[1d]



1a : X=OH (α_D +53.3°)
1b : X=H (α_D +136°)



2a : X=CH_2OH (α_D +63.2°)
2b : X=H (α_D +64.5°)



3a : X=OH, Y=H (α_D +152°)
3b : X=H, Y=OH (α_D +160°)

This analysis immediately suggests that a small structural modification on **1a** and **2a** should make them adopt an ideal staggered conformation. Namely, the 1,3-diaxial-like interaction destabilizing conformer **1a**-A would be eliminated by either removing the C3 hydroxyl group or changing its configuration. Similarly, removing the C5 hydroxymethyl group or changing its configuration should result in the same effect on the conformational balance of **2a**.

In order to confirm these predictions experimentally, we synthesized compounds **1b** and **2b**[2] by modifying our previously disclosed synthetic routes to this class of com-

Table I. ^{1}H NMR Spin–Spin Coupling Constants of Methyl Glycosides 1–3[a]

J	1a	1b	2a	2b	3a	3b
1′,α(pro-*S*)	10.3	12.1	1.7	2.0	12.1	11.0
1′,α(pro-*R*)	3.1	3.1	9.2	10.0	3.1	3.3
4,α(pro-*S*)	2.9	2.9	4.7	9.5	NA[b]	NA
4,α(pro-*R*)	5.5	11.4	3.5	3.1	NA	NA
3,α(pro-*S*)	NA	NA	NA	NA	3.3	3.6
3,α(pro-*R*)	NA	NA	NA	NA	11.3	6.1
α(pro-*S*),α(pro-*R*)	14.4	14.5	15.3	14.5	14.5	14.9

[a] Coupling constants are in hertz. The spectra were recorded on a Bruker AM-500 (500 MHz) spectrometer in CD_3OD. The spin–spin coupling constants were obtained by a first-order analysis. [b] NA = not applicable.

(2) Syntheses of **1b**, **2b**, **3a**, and **3b** are included in the supplementary material. Satisfactory spectroscopic data were obtained for all the new compounds reported in this paper.

pounds[1a] and then subjected them to ^1H NMR studies in CD_3OD (Table I).[3] An analysis of the spin–spin coupling constants reveals that both pyranose rings exist in chair-like conformations. The ^1H NMR data for the C1′ and Cα protons firmly establishes that the *C*-glycosidic bond adopts the predicted conformation for both **1b** and **2b**. Most importantly, in contrast to the reported results for **1a** and **2a**, where a mixture of conformers or a single twisted conformer around the nonglycosidic bond was detected, the vicinal spin–spin coupling constants observed for **1b** and **2b** confirm the anticipated single conformation around the C.4–Cα bond.

As previously pointed out,[1d] the carbon analogue **3a** of α-D-galactopyranosyl-D-galactopyranose, a structural unit of human blood group determinants,[4] possesses one unique conformer **3a**-A, which is free from 1,3-diaxial-like interactions around the nonglycosidic bond. Thus, we anticipate that **3a**[2] exists predominantly in the ideal staggered conformer **3a**-A. Indeed, the ^1H NMR data supports this prediction. Moreover, this analysis suggests that this conformational preference should be disturbed by changing the configuration of the C4 hydroxyl group. Indeed, the ^1H NMR data of **3b**[2] supports this prediction as well.

In summary, we have shown that an analysis of the steric factors primarily around the nonglycosidic bond, as illustrated by use of a diamond lattice, enables us to predict the conformational preference of *C*-dissacharides. The conformational similarity between *C*-disaccharides and their oxygen counterparts will be discussed in a forthcoming paper.

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged.

Supplementary Material Available: Schemes for the synthesis of **1b**, **2b**, **3a**, and **3b** and the complete table listing chemical shifts and spin–spin coupling constants (6 pages). Ordering information is given on any current masthead page.

(3) We observed a temperature effect; for example, $J_{4,\alpha(pro\text{-}R)}$ and $J_{4,\alpha(pro\text{-}S)}$ of **2b** were 3.4 and 9.2 Hz at 44 °C, 3.1 and 9.5 Hz at 23 °C, 2.8 and 10.0 Hz at −3 °C, 2.4 and 10.4 Hz at −13 °C, and 1.5 and 10.5 Hz at −35 °C.

(4) For a review, see: Lemieux, R. U. *Chem. Soc. Rev.* **1978**, *7*, 423. Lemieux, R. U. *Frontiers of Chemistry*; Laidler, K. J.; Ed.; Pergamon: New York, 1982; p 1 and references cited therein.

Yuan Wang, Peter G. Goekjian
David M. Ryckman, Yoshito Kishi*
Department of Chemistry
Harvard University
12 Oxford Street
Cambridge, Massachusetts 02138
Received March 1, 1988

Reactivity of Phosphacarbamates: Transfer of the Carbamate Group Promoted by Metal Assisted Electrophilic Attack at the Carbon Dioxide Moiety

Summary: Phosphacarbamates have been used in an unprecedented reaction as a source of carbamate group in the synthesis of organic carbamates via a metal assisted electrophilic attack at the carbon dioxide moiety.

Sir: Phosphacarbamates of of formula $Z_xP(OOCNR_2)_{2-x}$ (Z = halogen, alkyl-, dialkylamino; x = 1, 2) can be prepared via an easy carbon dioxide insertion into the P–N bond of the corresponding aminophosphines in the absence[1,2] or presence[3] of metal ions. The rate of insertion depends on the nature of substituent Z at the phosphorus atom, the solvent used, the temperature, and the metal complexes bearing the aminophosphine as ligand.[3] The reactivity of phosphacarbamates has been also studied by several authors who have shown that in the presence of amines they undergo a nucleophilic attack at the carbamic carbon[4] to afford ureas (eq 1).

$$(R_2N)_2POC(O)NR_2 \xrightarrow{H_2NR'} R'HNC(O)NR_2 + (R_2N)_2PHO \quad (1)$$

We report here an unprecedented electrophilic attack at the carboxylic function of phosphacarbamates that induces the carbamate group transfer to an organic halide (R′X) to afford carbamates of formula R_2NCOOR'.

Solutions of $P(NR_2)_3$ (1) in THF at 273 K and 0.10 MPa of CO_2 insert carbon dioxide in to the P–N bond to afford $(R_2N)_2P(OOCNR_2)$ (**2**). The dicarbamate $(R_2N)P(OOCNR_2)_2$ (**3**) can be obtained at room temperature. Attempts to insert a third molecule of carbon dioxide failed with use of aminophosphine (1) with both R = methyl (ref 1 and this work) and R = ethyl (this work). It is worth noting that we have observed CO_2 insertion neither into the P–N bond of $O{=}P(NR_2)_3$ (R = methyl and ethyl) at 300 K and 5.2 MPa of CO_2 after 24 h nor in the P–N bond of phosphonium salts $(R_2N)_3PR'X$ at 300 K and 0.10 MPa of CO_2 after 48 h.

Conversely, aminophosphines coordinated to transition metal centers[3] have been shown to be able to insert carbon dioxide into the P–N bond at a lower reaction rate than the free ligand. These results suggest that both the coordination number and the oxidation number of phosphorus can play an important role in the insertion reaction.

When phosphacarbamates (**2**) and **3**) are treated with an organic halide R′X or ArX no reaction is observed. Conversely, if a metal salt MY (M = group I metal) or $L_nM'Y$ (M′ = transition metal; L = phosphorus or nitrogen ligand; Y = F, Cl, Br, I) is added to the reaction system the synthesis of the organic carbamate is accomplished (eq 2). The yield depends on several factors: the operative

$$(R_2N)_{3-x}P(OOCNR_2)_x + xR'X \xrightarrow[\text{or } L_nMY]{MY + CE} R_2NCOOR' + (R_2N)_{3-x}PY_x \quad (2)$$

conditions, the nature of the metal salt (both M, M′, and Y play an important role; group I metal ions require crown ethers), and of the organic halide. In this paper we shall focus on the case in which aliphatic halides are used in the presence of group I metal salts. Other cases will discussed in a forthcoming paper.[5]

The first step in the reaction of phosphacarbamates with metal ions, both in the presence and absence of R′X, is the formation of metal carbamate R_2NCOOM that can be isolated from the reaction mixture when noncoordinating solvents such as benzene and toluene are used. However, this finding suggested to us that metal carbamates prepared in whatever manner might be used in the synthesis of organic carbamates under our conditions. We have, therefore, investigated the role played by the metal salt and the organic halide in the transfer reaction of the carbamate group. Among Group I metal ions investigated (Li^+, Na^+, K^+), K^+ seems to be a particularly good transfer

(1) Oertel, G.; Malz, H.; Holtschmidt, H. *Chem. Ber.* **1964**, *97*, 891.
(2) (a) The K. I.; Vande Griend, L.; Whitla, W. A.; Cavell, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 7379. (b) Light, R. W.; Hutchins, L. D.; Paine, R. T.; Campana, C. F. *Inorg. Chem.* **1980**, *19*, 3597.
(3) Aresta, M.; De Fazio, M.; Bruno, P. *Inorg. Chem.* **1982**, *21*, 441.
(4) Yamazaki, N.; Tomioka, T.; Higashi, F. *Synthesis* **1975**, 384.
(5) Aresta, M.; Quaranta, E., manuscript in preparation.

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