p-CNB, with a high energy n,π* triplet, like that of benzophenone, and a more favorable reduction potential, due to its electronegative substituent, shows a similar reduction pattern, Table V. Photoreduction is most efficient with the tertiary amine, and similar to benzophenone, while primary and secondary amines lead to lower ϕ_{red}, lower than with the unsubstituted ketone. This may indicate greater initial abstraction of H from N. These reductions are catalyzed by thiol, but less efficiently than those of benzophenone, possibly indicating more rapid disproportionation reactions of the more acidic ketyl radical. Aniline does not enhance catalysis, indicating predominant trapping of this reactive triplet by the higher concentration of aliphatic amine.

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The ^{18}O Isotope Shift in ^{13}C Nuclear Magnetic Resonance Spectroscopy. 14. Kinetics of Oxygen Exchange at the Anomeric Carbon of D-Ribose and D-2-Deoxyribose[1]

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The kinetics of the oxygen-exchange reaction at the anomeric carbon atoms of D-ribose and D-2-deoxyribose (2-deoxy-D-*erythro*-pentose) were compared using the ^{18}O isotope induced shift in ^{13}C NMR spectroscopy. Measurements were made at a number of temperature and pH values. The oxygen-exchange reaction for these sugars is strongly pH-dependent, displaying regions of acid, water, and base catalysis. At 25 °C the oxygen-exchange rate of D-ribose was found to be approximately 20-fold greater than the rate for D-glucose between pH 2 and 9. In turn, the oxygen-exchange rate for D-2-deoxyribose was greater than the rate for D-ribose by approximately 5-fold above pH 4 and by greater than 10-fold below pH 4. The results are analyzed in terms of steric and inductive effects on the hydration kinetics of the open-chain forms and by comparison with the hydration reaction of simple aldehydes. The study also includes quantitative data, based upon ^{13}C NMR line intensities, for the various anomeric forms that exist in solutions of these sugars at the different temperature and pH values used in the kinetic measurements reported here. In each case, the oxygen-exchange reactions of the anomers are slow relative to the rate of anomerization, so that the anomers appear to exchange oxygen at the same rate.

Introduction

The mutarotation of monosaccharides in aqueous solution involves the reversible, intramolecular attack of a sugar hydroxyl group upon the carbonyl carbon of the open-chain species to form the various anomers.[2] The carbonyl carbon of the open-chain form can also be hydrated upon attack by water. In fact, at room temperature the ratio of hydrate to aldehyde in solutions of common aldoses[3] is approximately 10:1. While the hydration reactions of simple aldehydes and ketones have received extensive study,4 the corresponding reactions of the open-chain forms of sugars have received little attention.[5] A major hindrance to direct studies of monosaccharide hydration is the extremely small percentages of the reactive carbonyl species that are present in solution.[6] However, the hydration reaction can be studied indirectly by observing the oxygen-exchange process that accompanies it.[7] Furthermore, since the oxygen-exchange rate is proportional to the (low) mole fraction of open-chain species present in solution,[8] the kinetics of the rapid hydration process can be studied at slower, more convenient rates.

Oxygen exchange at carbon is readily assayed using the ^{18}O isotope shift in ^{13}C NMR spectroscopy.[9,10] We have applied this technique to study the oxygen-exchange kinetics of D-erythrose, glucose, mannose, and fructose.[1,11] These data are valuable not only because they more fully characterize the solution chemistry of carbohydrates, but also because they are critical in the interpretation of mechanistic investigations involving bond breakage or bond formation at the anomeric carbon atom.[12] Consequently, it appeared useful to extend our oxygen-exchange studies to the biologically important monosaccharides D-ribose and D-2-deoxyribose (2-deoxy-D-*erythro*-pentose). Comparison of these sugars also allows one to assess the influence of the hydroxyl group adjacent to the carbonyl function with respect to its effect on the hydration of an aldose.

Experimental Section

Materials. D-[1-^{13}C]Ribose was obtained from Omicron Biochemicals and D-2-deoxyribose (natural abundance) was purchased from Aldrich and Sigma. [^{18}O]Water (98 atom % ^{18}O) was purchased from Merck, and deuterium oxide (99.8 atom %

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Table I. Relative Proportions of the Anomeric Forms of D-Ribose and D-2-Deoxyribose[a]

sugar	temp (°C)	pH[b]	pyranose α	pyranose β	furanose α	furanose β
D-ribose[c]	21	4.8	20	61.5	6.1	12
		7.0	20	62	6.4	11.5
	36	4.8	23	57	7.8	12
		7.0	22	58	7.0	13.5
	48	5.0	22	54	8.8	15
		7.0	23	55	7.5	15
D-2-deoxyribose[d]	21	4.5	39	40.5	12	8.7
		7.0	40	40.5	11	8.6
	28	7.0	41	39	10	9.8
	36	4.5	41	37.5	11	10.5
		7.0	40	39.5	10	10.1

[a] For solutions in 20% D_2O. [b] pH values represent direct pH meter readings. [c] 68 mM ribose. [d] 0.51 M 2-deoxyribose.

D) was purchased from Aldrich. Glass-distilled deionized water and analytical-grade reagents were used in the preparation of the solutions.

The ^{18}O-labeled sugars for the out-exchange[1] measurements were prepared by placing the sugars in a minimum of [^{18}O]water containing 5 mM sodium phosphate and adjusting the pH to approximately 9 using solid sodium hydroxide. These solutions were then allowed to react at 37 °C for several days.

Solution Preparation. In studies of ribose, 68 mM solutions in 4 mL of 20% D_2O were used for the quantitative analysis. For the out-exchange measurements enough ^{18}O-labeled sugar was dissolved in 4 mL of 20% D_2O to make a 30 mM ribose solution. For the in-exchange[1] measurements 68 mM ribose solutions in 1 mL of 60% [^{18}O]water (60% $H_2{}^{18}O$, 20% D_2O, 20% H_2O) were used.

For studies of 2-deoxyribose, 0.51 M solutions were used in all experiments. For the quantitative analysis and out-exchange measurements 4-mL solutions in 20% D_2O were used. For the in-exchange measurements the sugar was dissolved in 4 mL of 60% [^{18}O]water (60% $H_2{}^{18}O$, 20% D_2O, 20% H_2O).

All solutions were prepared in sodium phosphate buffer (≤5 mM). The solution pH was adjusted using concentrated HCl or NaOH solutions. pH measurements were made using a Corning Model 130 pH meter calibrated with buffer standards containing normal water.

NMR Measurements. Spectra were obtained using an NTC-200 spectrometer fitted with a 12-mm probe operating at 50.3 MHz or a QE-300 spectrometer fitted with a 5-mm probe operating at 75.6 MHz. The instrumental parameters that were used have been described in detail.[1] Probe temperatures were measured using a chemical thermometer as previously described.[1]

Quantitative Analysis. Gated ^1H decoupling was used to suppress the nuclear Overhauser enhancement.[13] For ribose, 150 pulses spaced 25 s apart were acquired using a 55° pulse angle, an 8K block size, and an 800-Hz sweep width. For 2-deoxyribose, spectra were acquired using 400–1000 pulses spaced 24 s apart with a 55° pulse angle, 16K block size, and a 2000-Hz sweep width.

Oxygen Exchange. The in-exchange measurements were made using the same parameters as for the quantitative analysis. The out-exchange measurements were made using the parameters previously described.[1]

Data Analysis. The quantitation of the anomeric forms and the determination of the oxygen-exchange rate constants were as previously described.[1] For quantitative analysis of 2-deoxyribose the following signals (as assigned by Bock and Pedersen[14]) were used: α- and β-pyranose, C-1, α- and β-furanose, both C-3 and C-4 (averaged).

Results

Figure 1 illustrates the course of a typical oxygen-exchange reaction for D-ribose as assayed using ^{13}C NMR spectroscopy. The presence of an ^{18}O directly attached to the anomeric carbon atom causes a small upfield shift in its ^{13}C NMR signal relative to the signal for the ^{16}O species. When the ^{18}O-labeled sugar is placed into normal water the exchange reaction may be monitored by observing the change in the relative intensities of the ^{13}C signals for the ^{18}O and ^{16}O forms of each anomer with time. In this study the following isotope shifts were measured: α-ribofuranose, 0.017 ppm; β-ribofuranose, 0.016 ppm; α-ribopyranose, 0.015 ppm; β-ribopyranose, 0.019 ppm; α- and β-2-deoxyribofuranose, 0.017 ppm; α-2-deoxyribopyranose, 0.020 ppm; β-2-deoxyribopyranose, 0.017 ppm. The error in these measurements was less than 0.002 ppm. Within experimental error no difference was found in the magnitude of the isotope shift at the various temperature and pH values used in this study.

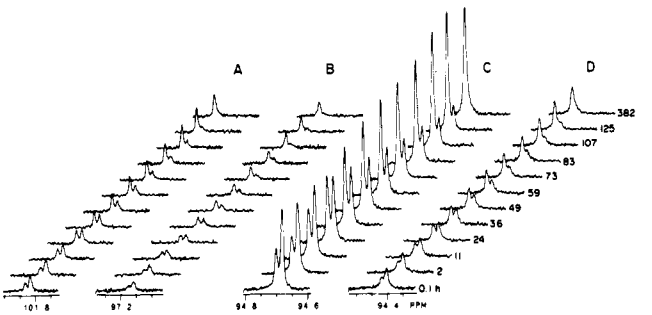

Figure 1. Oxygen exchange (out-exchange) at the anomeric carbon atom of (A) β-D-ribofuranose, (B) α-D-ribofuranose, (C) β-D-ribopyranose, and (D) α-D-ribopyranose at 25 °C and pH 5.9 followed using ^{13}C NMR spectroscopy. Signals corresponding to the ^{18}O isotopomers are shifted upfield relative to the ^{16}O species by (A) 0.016 ppm, (B) 0.017 ppm, (C) 0.019 ppm, and (D) 0.015 ppm.

For a given sugar all anomers were found to exchange oxygen at the same rate within experimental error. This can be seen qualitatively for D-ribose in Figure 1. A unique feature of the sugars used in this study is that all four anomers can be readily observed in the ^{13}C NMR spectrum. However, because over 75% of each of these sugars is in the pyranose form[3] (Table I), satisfactory kinetic data could generally not be obtained from the furanose signals. This was particularly true for D-2-deoxyribose since it was not ^{13}C-enriched and the exchange rate for this sugar is relatively fast.

The relative proportions of the anomeric forms of D-ribose and D-2-deoxyribose observed using ^{13}C NMR line intensities and measured under the solvent and temperature conditions used in these studies are listed in Table I. The values for ribose differ somewhat from some recently reported results,[15] but are in good agreement with

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Table II. Oxygen-Exchange Rates for D-Ribose and D-2-Deoxyribose[a]

sugar	temp (°C)	pH[b]	$10^6 k_{ex}$ (s^{-1})
D-ribose[c]	25	2.0	47
		2.8	7.1
		3.6	3.0
		5.0	2.6
		5.9	2.8
		7.0	6.1
		7.8	14
		8.5	33
		8.7	44
	37	7.0	14[d,e]
	48	5.0	30[d,e]
		7.0	65[d,e]
	60	7.0	290
D-2-deoxyribose[f]	25	2.7	110
		3.6	30
		4.7	8.6
		7.0	20
		7.8	53
	28	7.0	26[d]
	36	7.0	68[d]

[a] Unless otherwise noted, the rate constants are for out-exchange measured using ^{18}O-labeled sugar and solutions containing 20% D_2O (as an NMR lock) and sodium phosphate buffer (≤5 mM). The kinetic plots typically gave correlation coefficients better than 0.98. [b] pH values are direct pH meter readings. [c] 30 mM D-ribose solutions unless otherwise noted. [d] In-exchange measurement. [e] 68 mM ribose solutions. [f] 0.51 M D-2-deoxyribose solutions.

the earlier results that are cited therein. It can be seen from the data in Table I that there are no significant differences in the anomeric compositions at the different pH values employed. There are, however, small changes in the anomeric compositions over the temperature range studied. The proportions of the α-pyranose and furanose forms appear to increase slightly with temperature at the expense of the β-pyranose forms.

The effect of temperature and pH on the oxygen exchange kinetics for these two sugars is shown in Table II. Arrhenius plots of the data at pH 7.0 give energies of activation (E_a) of 22 kcal/mol for D-ribose and 21 kcal/mol for D-2-deoxyribose. As pointed out previously, extrapolations based upon these data should be used with caution since the apparent energy of activation for the oxygen-exchange reaction may change with temperature as a consequence of uncompensated changes in N_c, the mole fraction of the sugar present in the carbonyl form.[1]

The pH dependence of the oxygen exchange reaction for D-ribose and D-2-deoxyribose at 25 °C is illustrated in Figure 2. The pH profile for the oxygen exchange of D-glucose at 26 °C is included for comparison.[1] The exchange data were fitted to eq 1 where k_{EX} is the observed

$$k_{ex} = k_{H_2O} + k_H[H^+] + k_{OH}[OH^-] \quad (1)$$

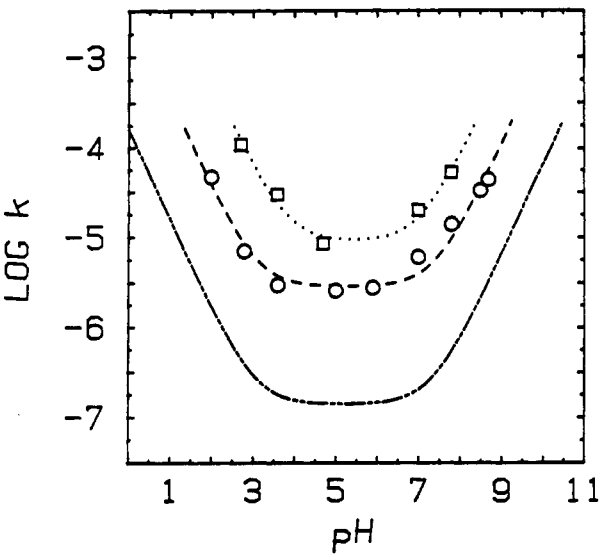


Figure 2. pH dependence for the oxygen-exchange reaction of (○) D-ribose (---) and (□) D-2-deoxyribose (···) at 25 °C, and D-glucose (—) at 26 °C. The curves drawn through the data points are based upon a nonlinear least-squares fit of the data to eq 1 (Table III).

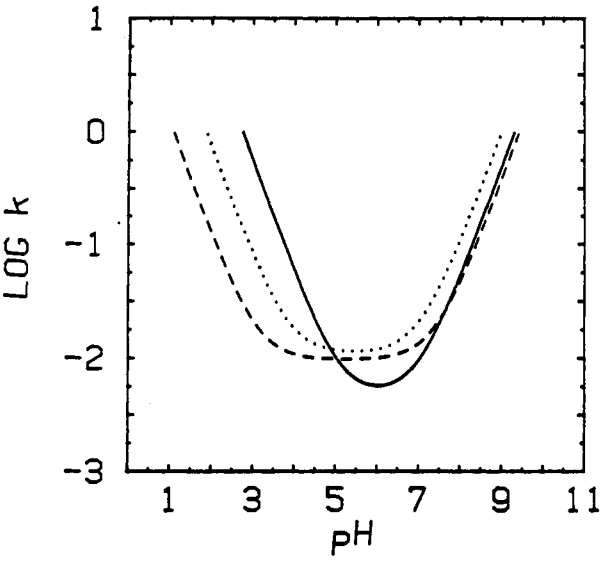


Figure 3. pH-rate profiles for the hydration reaction of D-ribose (---), D-2-deoxyribose (···), and acetaldehyde (—) at 25 °C. The hydration rate profile for D-glucose (not shown) nearly coincides with that shown for D-ribose (Table III).

exchange rate and k_{H_2O}, k_H, and k_{OH} are terms corresponding to the pH-independent reaction, the hydronium ion dependent reaction, and the hydroxide ion dependent reaction, respectively. The program KINFIT[16] was used to

Table III. Estimated Rate Parameters for the Oxygen Exchange and Hydration Reactions of Various Compounds

		oxygen exchange[a]			hydration[b]		
compound	temp (°C)	$10^4 k_H$ (M^{-1} s^{-1})	$10^7 k_{H_2O}$ (s^{-1})	k_{OH} (M^{-1} s^{-1})	k_H (M^{-1} s^{-1})	$10^3 k_{H_2O}$ (s^{-1})	$10^{-4} k_{OH}$ (M^{-1} s^{-1})
D-glucose[c]	26	1.6 (0.3)[d]	1.4 (0.2)	0.65 (0.1)	11 (2)	10 (1)	4.6 (0.9)
D-ribose[e]	25	36 (10)	29 (5)	11 (2.2)	12 (3)	9.7 (2)	3.7 (0.7)
D-2-deoxyribose[f]	25	590 (150)	91 (25)	78 (20)	74 (20)	11 (3.0)	9.8 (3)
acetaldehyde[g]	25				560	4.7	4.8

[a] Exchange rate parameters were obtained by a nonlinear least-squares fit of the exchange data to eq 1 by the KINFIT program.[16] [b] Hydration rate parameters for the open-chain forms of the sugars were obtained using eq 2, assuming that the mol % of the open-chain forms remained constant over the pH range studied and were as follows: D-glucose (26 °C), 0.0028%; D-ribose (25 °C), 0.060%; D-2-deoxyribose (25 °C), 0.16%. The value of N_c reported for D-2-deoxyribose was extrapolated to 25 °C based upon the temperature dependence of N_c for D-ribose.[1,6,17] [c] 30 mM glucose in 20% D_2O.[1] [d] Values in parentheses represent the standard deviations of the parameter estimates generated by the KINFIT program.[1,16] [e] 30 mM ribose in 20% D_2O. [f] 0.51 M 2-deoxyribose in 20% D_2O. [g] 0.1–0.2 M acetaldehyde.[7]

fit the data to eq 1 using a nonlinear regression routine assuming that $[H^+] = 10^{-pH}$ and that the dissociation constant for water $K_W = 10^{-14}$. The resulting parameters, listed in Table III, were used to draw the smooth curves in Figure 2.

The hydration rates for the open-chain forms of the sugars were calculated[8] from the exchange data using eq 2, where k_{hy} is the pseudo-first-order rate constant for the

$$k_{hy} = 2k_{ex}/N_c \quad (2)$$

hydration reaction and N_c is the mole fraction of the sugar present as the carbonyl species. The resulting hydration rate parameters (Table III) were used to draw the smooth curves in Figure 3. The pH profile for the hydration reaction of acetaldehyde[7] is included for comparison.

Discussion

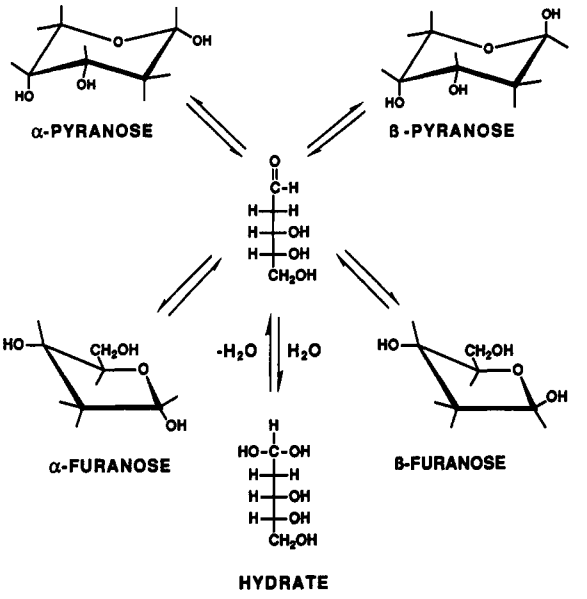
The tautomeric equilibria of D-ribose and D-2-deoxyribose involve significant proportions of both pyranose and furanose ring forms[3] (Table I). Solutions of D-ribose exhibit the same furanose:pyranose ratio (approximately 20:80) as its 2-deoxy derivative. This contrasts with the homomorphous aldohexose D-allose for which a considerable increase in the furanose content is observed when the cis-vicinal interactions between the C-2 and C-3 hydroxyl groups of the furanose form are removed in its 2-deoxy derivative.[18] Like the aldohexoses, however, the removal of the 2-hydroxyl group in D-ribose results in approximately equal amounts of the α- and β-furanose forms since a cis-vicinal interaction with the anomeric hydroxyl group has been removed in the α-anomer.[3]

The proportions of the various ring forms appear to have no influence on the relative rates of oxygen exchange for the different sugars.[1] In contrast, the proportion of the open-chain form (N_c) strongly influences the rate of oxygen exchange of one sugar relative to another (eq 2).[8] The ratio of the oxygen exchange rates for D-ribose and D-glucose[1] (approximately 20:1) is the same as the relative percentages of the open-chain forms for these two sugars.[8] For 2-deoxyribose the reported[17] value of N_c is approximately 3 times the value for ribose at the same temperature.[8] This difference explains in part the difference in oxygen-exchange rates between these two sugars. However, to more completely explain the rate increase brought about by removal of the 2-hydroxyl it is necessary to assess the factors which influence the underlying hydration reaction of the open-chain forms.

The hydration kinetics of the open-chain forms of sugars can be largely explained in terms of inductive influences on the hydration of simple aldehydes.[1] Electron-withdrawing substituents adjacent to the carbonyl carbon of aldehydes decrease the rate of hydration in the region of acid catalysis and increase the rate of hydration in the region of water catalysis.[4b] As can be seen in Figure 3 this trend is also observed in the open-chain forms of aldoses, which can be viewed as polyhydroxy derivatives of simple aldehydes.

These considerations lead to the expectation that the hydration rate of D-2-deoxyribose should be faster than the rate of D-ribose in the region of acid catalysis but slower than the rate of D-ribose in the region of water catalysis. Our data clearly demonstrate an increased efficiency of acid catalysis in the reaction of the 2-deoxy derivative.

Scheme I



However, in the water-catalyzed region, the hydration rates of the two sugars are the same within experimental error (Table III). It seems likely that, all other factors being equal, the hydration rate in 2-deoxyribose would be increased relative to the rate for ribose since the absence of the hydroxyl group adjacent to the carbonyl function removes a steric barrier to attack of the carbonyl carbon by water. Thus, the superposition of these two effects, steric and inductive, provides a reasonable explanation to the hydration and oxygen-exchange kinetics of ribose and its 2-deoxy analogue.

Aqueous solutions of monosaccharides contain at least six different species: four ring forms, the central open-chain intermediate, and its hydrate[3] (Scheme I: D-2-deoxyribose tautomerization).[19] Additional "pseudoacyclic" intermediates[20] have been proposed for some sugars,[21] including D-ribose,[21b] but there is no convincing experimental basis for their existence.[1,22] Recently, the unimolecular rate constants describing the interconversions between the ring forms and the open-chain intermediate have been reported for several sugars.[8,17,22] Oxygen-exchange studies such as the present one provide rate data about the remaining interconversion between the open-chain form and its hydrate. The available data for the hydration reaction of sugars in the region of water catalysis suggest the following trend in rates: D-erythrose > D-mannose > D-2-deoxyribose ≈ D-ribose ≈ D-glucose ≈ D-galactose > D-fructose.[1,8,11] The pH–rate profile for the hydration of the aldoses D-glucose and D-ribose are virtually identical (Table III), and the corresponding profile for D-mannose[1] differs only by a factor of approximately 2. Because the solution pH was not specified in the measurements for D-erythrose[11] and D-galactose,[8] and due to the uncertainties associated with the values used for N_c,[6]

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it is conceivable that the hydration rates of the different aldoses may be nearly identical. This is possible since the calculated hydration rate constants are critically dependent upon the value chosen for N_c (eq. 2).[8] The value of N_c is also necessary in calculations of the rate constants for the interconversions between the various ring forms.[8,17,22] The extremely small magnitude of N_c for most aldoses makes it quite difficult to obtain accurate values for this parameter.[8] In some cases it is possible that accurate measurements of N_c may be made using ultra-high-resolution NMR techniques. Such an important result has already been demonstrated for D-glucose.[23] Otherwise, the absence of precise measurements for sugars may limit the application of NMR[1,11,17,22] and other[8] techniques in the detailed elucidation of the kinetics of monosaccharide tautomerization.

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Registry No. D-Ribose, 50-69-1; D-2-deoxyribose, 533-67-5; α-D-ribopyranose, 7296-59-5; β-D-ribopyranose, 7296-60-8; α-D-ribofuranose, 32445-75-3; β-D-ribofuranose, 36468-53-8; 2-deoxy-α-D-ribopyranose, 36792-85-5; 2-deoxy-β-D-ribopyranose, 22900-10-3; 2-deoxy-α-D-ribofuranose, 36792-87-7; 2-deoxy-β-D-ribofuranose, 36792-88-8.

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Dianions of 1,4-Bis(methylene)cyclohexane. Conformational Effects in Cyclic and Acyclic Dilithiated Hydrocarbons

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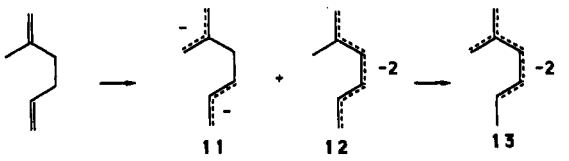
Dimetalation of 1,4-bis(methylene)cyclohexane results in formation of the *p*-xylene dianion via the linearly conjugated dianion **4**. In contrast, 2-methyl-1,5-hexadiene, an acyclic analogue of 1,4-bis(methylene)cyclohexane, undergoes isomerization via the linearly conjugated dianion **12**, rather than hydride elimination. MNDO calculations of the conformations of dilithiated **4** and **12** show that **4** is effectively planar, with a symmetrical distribution of charge. Dilithiated **12** is nonplanar, with an almost right angle bend in the π-system. The dianion can therefore be considered as two allyl anions which are orthogonal to each other. The difference in calculated conformations of **4** and **12** is advanced as the reason for the different reactivity of the two systems.

We have been interested for some time in the factors which control metalation in unsaturated hydrocarbons.[1] We have focused primarily on acyclic systems and have been particularly successful in predicting the preferential formation of "dianions"[2] in systems which allow the formation of more than one dianion by the use of REPA[3] calculations. We became interested in examining cyclic hydrocarbons to see if the same trends existed in those systems as in the acyclic systems. We chose to examine the metalation of 1,4-bis(methylene)cyclohexane (**1**) for two reasons. **1** can be considered a cyclic derivative of 2-methyl-1,5-hexadiene (**2**) whose metalation we have already examined.[1b] In addition, six-membered ring compounds with exocyclic or endocyclic double bonds in strongly basic reaction media undergo hydride elimination to yield benzene rings.[4] The observation was made that aromatization was facilitated by the incorporation of an isobutylene unit in the molecule, suggesting that a cross-conjugated dianion might be implicated. We were anxious to examine anion formation with a metalating system which would allow the opportunity to trap the anions before the formation of benzene rings from hydride elimination. We therefore report the characterization of anions from **1** by metalation with *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and their yield and behavior as a function of time.

Scheme I



Our working assumption was that the same types of anions found by metalation of **2** would be found in the metalation of **1**. That is, metalation would yield the three anions (**4**, **6**, and **8**, Figure 1) analogous to those (**11**, **12**, and **13**) shown in Scheme I from metalation of **2**. The anions formed from metalation of **1** with *n*-butyllithium/TMEDA were characterized by quenching with *n*-propyl chloride. Ten monomeric products (Figure 2) were isolated in varying amounts depending on the age of the reaction mixture, indicated by time in Table I. They were characterized by ^{1}H NMR spectroscopy and mass spectroscopy, as shown in Table II. As Table I shows, aromatic product

(1) (a) Thorstad, W. T.; Mills, N. S.; Buckelew, D. Q.; Govea, L. G. *J. Org. Chem.* **1989**, *54*, 773. (b) Mills, N. S. *J. Am. Chem. Soc.* **1982**, *104*, 5689. (c) Mills, N. S.; Rusinko, A. R. *J. Org. Chem.* **1986**, *51*, 2567. (d) Rusinko, A. R.; Mills, N. S.; Morse, P. *J. Org. Chem.* **1982**, *47*, 5198. (e) Mills, N. S.; Shapiro, J.; Hollingsworth, M. *J. Am. Chem. Soc.* **1981**, *103*, 1263.

(2) Although the species reported will often be referred to as dianions, they are dilithiated hydrocarbons, with an appreciable covalent character in the carbon-lithium bond.

(3) (a) Hess, B. A.; Schaad, L. J. *Pure Appl. Chem.* **1980**, *52*, 1471. (b) Bates, R. B.; Hess, B. A.; Ogle, C. A.; Schaad, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 5052.

(4) Wilhelm, D.; Clark, T.; Friedl, T.; Schleyer, P. von R. *Chem. Ber.* **1983**, *116*, 751.

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