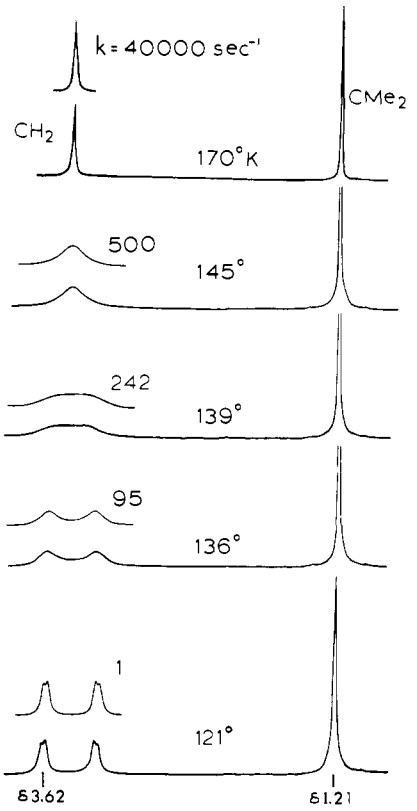

Figure 1. The ^{1}H DNMR spectra (270 MHz) of 1,3-dibromo-2,2-dimethylpropane (**1**, 2% v/v in $CBrF_3$) at various temperatures. Computed spectra using an AB to BA exchange model for the CH_2Br resonance are illustrated above the experimental spectra (k is the first-order rate constant for AB to BA exchange).

while the two methylene groups will give rise to the same AB spectrum as observed. The two protons on a given methylene group of **2** are indeed nonequivalent. Conformer **3** (C_1 symmetry) will show a doublet for CMe_2 and two different AB spectra for CH_2Br; **4** (C_{2v} symmetry) will give singlets for both CMe_2 and CH_2Br groups; **5** (C_s symmetry) will give a doublet for CMe_2 and one AB spectrum for the CH_2Br groups. Based on the observed ^{1}H NMR chemical-shift difference between the different methyl groups of neopentyl bromide at 105 K (0.10 ppm),[6] it would be anticipated that various methyl protons signals due to conformers **3**, **4**, or **5** would indeed be sufficiently shifted from that due to **2** to be detectable. In addition, the width at half-height of the methyl protons signal for **1** at 121 K (7.0 Hz; see Figure 1) is essentially identical with that for the tetramethylsilane reference signal. This speaks for no DNMR effect for the methyl groups of **1** and for magnetic equivalence of the methyl protons of **1** which is of course consistent with the symmetry of **2**.

It is interesting to note that, within the limits of NMR detection, **2** is the *only* conformer observed. Conformers **3** and **4** are more or less reasonable on steric grounds but are not observed. The geometry **5** is intuitively less stable than **2**, **3**, and **4**. The essentially parallel C–Br bonds in **5** lead to a significant dipole moment and substantial repulsions between the two proximate bromine atoms. The increased stability of **2** compared with that of **3** or **4** may result from optimized electrostatic *attractions*[5] between the respective oppositely charged monopoles of the two C–Br bond moments. These results for **1** are qualitatively consistent with IR data for 1,3-dibromopropane which indicate a preference in the *crystal* for a geometry which is analogous to **2**.[4a] However, the IR data for 1,3-dibromopropane in *solution* reveal the presence of geometries which are analogous to **2**, **3**, and **4** but not **5**.[4a] The strong preference for conformer **2** is also analogous to the preference for the gauche–gauche conformation in dimethoxymethane.[7]

The DNMR behavior observed for the CH_2Br groups of **1** can be simulated using a simple AB to BA exchange model (Figure 1). The preliminary activation parameters for exchange are $\Delta H^{\ddagger} = 6.2 \pm 0.6$ kcal/mol, $\Delta S^{\ddagger} = -1 \pm 3$ eu, and $\Delta G^{\ddagger} = 6.4 \pm 0.2$ kcal/mol at 139 K. The process detected by the DNMR method involves conversion of **2** into its enantiomeric form which of course involves rotation about two carbon–carbon bonds. The nature of the DNMR data in Figure 1 does not allow a distinction between a concerted double rotation or stepwise separate rotations.

Thus, it is apparent that the ^{1}H DNMR method will be useful in probing the effects of 1,3 interactions in relatively simple molecular systems and a systematic evaluation of steric, electronic, and solvent effects is planned.

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Nuclear Magnetic Resonance Studies of the Effects of Pressure on the Heme Environmental Structure of Hemoproteins

Sir:

The effect of pressure on the physicochemical properties of hemoproteins has been the subject of considerable investigation in recent years.[1] These studies have been dealt with changes in the functional properties, the thermodynamic properties associated with the binding of ligands, and the denaturation of the protein. Visible and Soret spectra were used to follow the changes of the heme crevice structure of hemoproteins when these molecules were subjected to high hydrostatic pressures.[1-5] We report here the effect of pressure on the ^{1}H, NMR spectra of metmyoglobin, methemoglobin, and their

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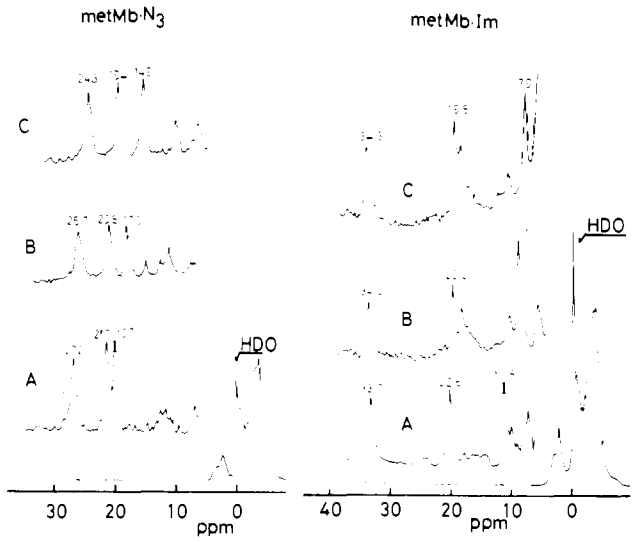

Figure 1. ^{1}H NMR spectra of azide and imidazole complexes of horse metmyoglobin at various pressures, and at pH 7.0 and 30 °C. Chemical shifts for the heme methyl signals were indicated in parts per million from the HDO resonance. Spectra of metMb·N_3^- at 1 atm (A), 1400 atm (B), and 1900 atm (C) are shown on the left side. The spectra of metMb·Im at 1 atm (A), 700 atm (B), and 1900 atm (C) are illustrated on the right side.

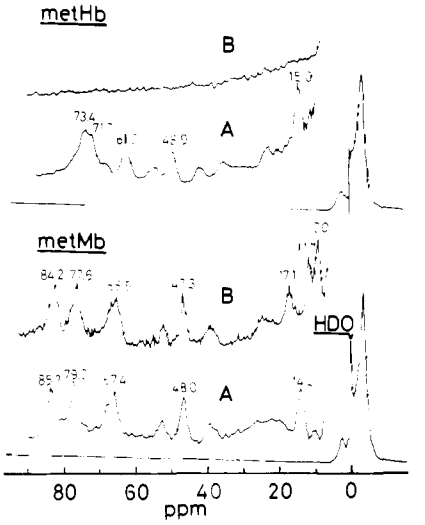

Figure 2. ^{1}H NMR spectra of aquometmyoglobin (below) and aquomethemoglobin (above) at 1 atm (A) and 2000 atm (B). The spectra were obtained at 30 °C and pH 7.0. For metHb, the gated decoupling mode was employed to saturate the residual HDO signal. The figure at each signal denotes the chemical shift in parts per million from the HDO resonance position.

derivatives. We are particularly concerned here with pressure-induced high-spin–low-spin conversion of the hemoproteins, by using the hyperfine shifted heme methyl resonances as a probe.[6]

We used a simple device for high pressure and high resolution NMR performance which allows sample spinning and temperature variation.[7-9]

Some typical results are illustrated in Figure 1.[10] The spectrum of azide complex of horse metmyoglobin (metMb·N_3^-) at 1 atm shows three of the four heme methyl proton signals at 19.7, 21.7, and 27.2 ppm downfield from HDO resonance. Upon pressurization, all of these resonances shifted upfield in proportion to the applied pressure. A similar result was obtained for methemoglobin azide complex. However, the spectrum of metmyoglobin cyanide, the heme methyl signals being at 8.0, 13.5, and 21.9 ppm, was insensitive to change in pressure up to 2000 atm. In Figure 1 is also shown the spectra of metmyoglobin imidazole (metMb·Im) at various pressures. The heme methyl signal at 11.6 ppm preferentially shifted upfield upon pressurization.

It has been well established[11] that azide and imidazole complexes of metmyoglobin are in thermal equilibrium between a high- and a low-spin ferric state, while the cyanide complex is in a 100% low-spin state. The optical absorption spectra were also obtained at high pressures for these metmyoglobin derivatives. The visible spectra showed that, as the pressure is increased, the low-spin band at 540 nm for metMb·N_3^- increased in its intensity, while no change was observed for the cyanide complex.[12] This shift of the spin equilibrium with pressure in favor of the low-spin state for metMb·N_3^- may be caused either by a conformational change accompanying a compression of the ligand–iron bond or by replacement of the sixth iron ligand by a distal base such as E-7 histidyl imidazole. The NMR spectral changes in Figure 1 suggest that what we observed for metMb·N_3^- and metMb·Im with varying pressure may be due to the compression effect on the ligand–iron bond, which is responsible for the displacement of high-spin and low-spin equilibrium.[13] The upfield bias of the heme methyl signals upon pressurization indicates that the primary effect of pressure on metMb·N_3^- and metMb·Im is to shift their spin equilibrium in favor of the low-spin state, because the heme methyl hyperfine shifts of the low-spin hemoprotein are small compared with those of the high-spin one.[6] The spin equilibrium of hemoprotein is known to be also modulated by temperature variations as studied by magnetic susceptibility,[14] IR,[15] optical absorption,[11] NMR,[16] and many other methods. In our earlier work,[16] we separated the observed hyperfine shifts of each heme methyl proton resonance for metMb·N_3^- and metMb·Im into the limiting shifts in purely high- and low-spin states by analyzing the temperature-dependent shifts. With these limiting shifts at 30 °C, the three methyl resonance positions for metMb·N_3^- at 1900 atm are plausibly reproduced when we assumed that the low-spin content is increased from 80% at 1 atm to 93% at this pressure.[17]

We have also examined the high pressure NMR spectra of aquometmyoglobin (metMb) and aquomethemoglobin (metHb) as shown in Figure 2. With increasing pressure, the hyperfine shifted heme methyl resonances at 48.0, 67.4, 79.0, and 85.7 ppm for metMb at 1 atm decreased in intensity with a concomitant appearance and increase in intensity of new low-spin signals at 17.1 and 9.0 ppm. Thus, the pressure-induced high-spin–low-spin transition of metMb is slow on the NMR time scale. We observed a more drastic NMR spectral change for metHb upon pressurization; the heme methyl signals at 48.9, 61.9, 71.7, and 73.4 ppm at 1 atm disappeared from the hyperfine shifted spectral region above 2000 atm. The above spectral change for metMb and metHb were reversible upon reducing the pressure. These findings are in accord with the results of visible spectroscopic studies[1] of metMb and metHb which show that at high pressure the distal histidyl imidazole displaces the H_2O ligand to form the so-called hemichrome, the pressure required to cause this conversion being much higher for metMb than for metHb.[1] At 2000 atm metMb appears to be partly converted into hemichrome while metHb is fully changed to ferric low-spin hemichrome. Therefore, the signals at 9.0 and 17.1 ppm for metMb at 2000 atm are likely due to the heme methyl protons of the hemichrome in ferric low-spin state, and the corresponding signals for metHb may be hidden under the envelope of the protein resonances in the diamagnetic region. Some of the hyperfine shifted resonances of metMb shifted upfield upon pressurization as shown in Figure 2A, which is possibly because of the contraction of the iron–axial ligand bond.

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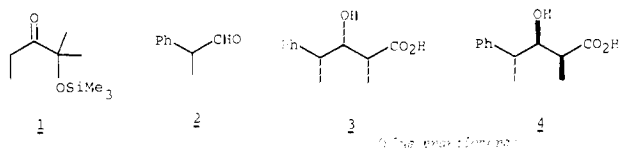
Acyclic Stereoselection. 5. Use of Double Stereodifferentiation to Enhance 1,2 Diastereoselection in Aldol Condensations of Chiral Aldehydes[1]

Sir:

As we have previously demonstrated, successive aldol condensations can be used to synthesize complex polyketides such as the macrolide antibiotics, provided that sufficient stereochemical control can be achieved in the various steps.[2] The reagent that we have developed for this purpose (**1**) provides a highly stereoselective route to *erythro*-3-hydroxy-2-methylcarboxylic acids as long as the aldehyde substrate is achiral. However, when **1** is condensed with a chiral aldehyde such as

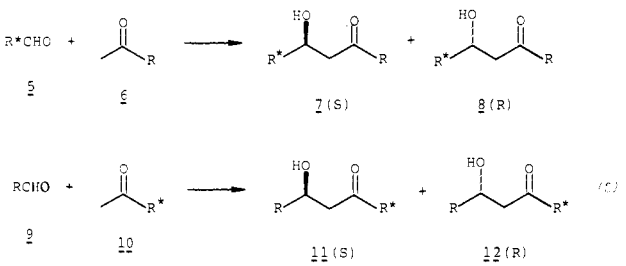


1 **2** **3** **4**

2, two erythro products, resulting from attack of the reagent on the two diastereotopic faces of the aldehyde, are produced. After oxidation, erythro acids **3** and **4** are obtained in a ratio of 6:1. The 1,2 diastereoselectivity in the condensation of **1** with other α-chiral aldehydes is in the range of 3:1 to 8:1, the major product being that predicted by Cram's empirical rule for 1,2 diastereoselection.[3] Although this particular erythro diastereomer is often the desired isomer for polyketide synthesis, the stereoselectivity is too low for a consecutive aldol strategy to be viable, since the overall stereochemical yield from such an approach is an exponential function of the average stereoselectivity of the various steps.

In principle, 1,2 diastereoselectivity can be enhanced by the use of "double stereodifferentiation".[4] We have examined the use of this little-appreciated strategy of stereoselective synthesis as a means of influencing the "Cram's rule selectivity" in aldol condensations of chiral aldehydes such as **2**. In this communication, we present the results of experiments which demonstrate the power of this method, and in the accompanying communication we report the synthesis of a new reagent (an analogue of **1**) which can be used for the stereoselective synthesis of β-hydroxy acids from chiral aldehydes.

The principle of double stereodifferentiation, as applied to the aldol condensation, may be illustrated as follows. In the reaction of a chiral aldehyde **5** with an achiral ketone **6**, diastereomers **7** and **8** are produced in unequal amounts (eq 1).

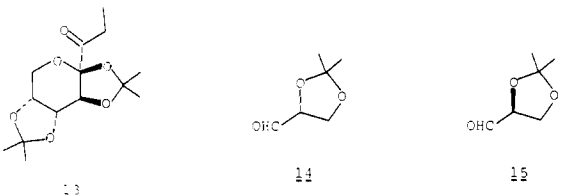


5 **6** **7**(S) **8**(R)

9 **10** **11**(S) **12**(R) (1)

As illustrated in eq 1, one enantiomer of **5** will yield **7** as the major product, and the other enantiomer will lead predominantly to **8**. Likewise, in the reaction of an achiral aldehyde **9** with a chiral ketone **10**, one enantiomer of **10** will yield primarily diastereomer **11**, while the other will afford diastereomer **12** as the major product (eq 2). Thus, we may visualize "*S*-selective" and "*R*-selective" enantiomers of both **5** and **10**, with regard to the chirality of the carbinol center created in an aldol condensation of either chiral reagent with an achiral partner. If we allow chiral aldehyde **5** to react with chiral ketone **10**, the *S*:*R* ratio will depend upon which pair of enantiomers are employed. It is intuitive that the relative amount of *S* configuration at the newly formed center will be greater when the two "*S*-selective" reactants combine than when *S*-selective **5** reacts with *R*-selective **10** or vice versa.

To examine this question, and to determine how much enhancement may be realized using such a ploy, we have utilized the enantiomerically homogeneous, chiral ketone **13** and the acetonides of the two enantiomers of glyceraldehyde (**14** and



13 **14** **15**

15). Ketone **13** was prepared by a straightforward four-step route from (*R*)-fructose.[6] Aldehydes **14** and **15** were prepared by literature procedures.[7-9] Ketone **13** was converted into its lithium enolate by reaction with lithium diisopropylamide in THF at −78 °C. One equivalent of either **14** or **15** was added at the same temperature and the reaction mixture was quenched after a reaction time of 20 min. Stereoisomeric mixtures were obtained in each case and were analyzed by ^{13}C NMR and by high pressure liquid chromatography. In several runs with both aldehydes, the condensation yield was uniformly good (85–94%). Reaction of **13** with **14** affords a mixture of

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