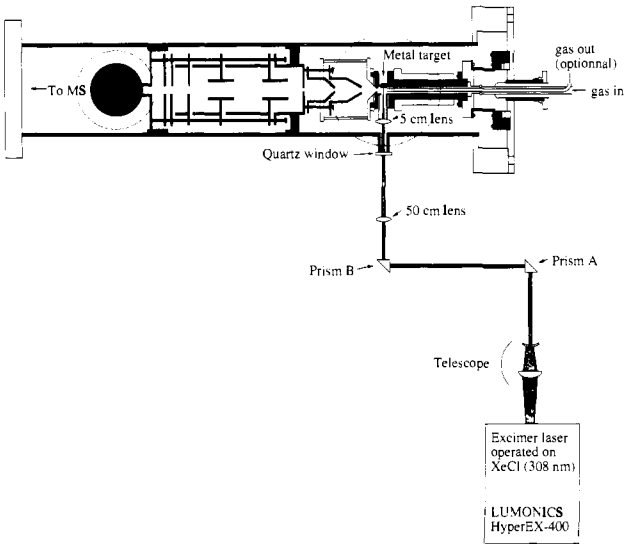


Figure 1. Schematic diagram of the laser-ablation/ionization high-pressure mass spectrometer.

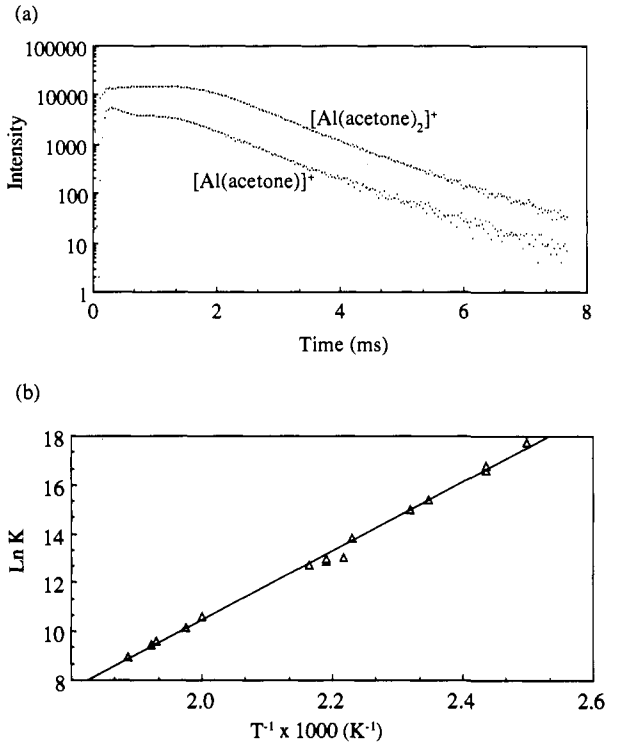
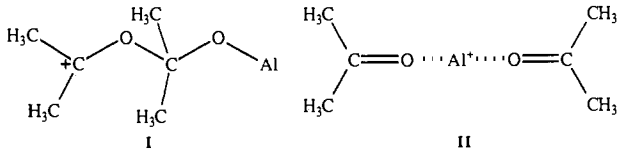


Figure 2. (a) Ion intensity profiles as a function of time after a 5-ns laser pulse. Data shown is the result of 300 laser pulses. (b) Van't Hoff plot of ln K vs $1/T$ used to obtain $\Delta H°$ and $\Delta S°$ for the clustering of Al^+ on to acetone.

since the binding of Al^+ to the first acetone is too strong to allow back dissociation to occur rapidly enough for equilibrium to be established at this temperature. However, the addition of the second acetone can be readily observed to achieve equilibrium. If this equilibrium is examined as a function of the ion source temperature, a plot of ln K_{eq} vs $1/T$ (van't Hoff plot) yields a slope of $-\Delta H°/R$ and intercept $\Delta S°/R$. In this way, the binding enthalpy of the second acetone to Al^+ is determined to be -26 ± 1 kcal/mol and the entropy of association is -45 ± 3 cal mol^{-1} K^{-1} (Figure 2b). The magnitude of this entropy change provides direct information concerning the nature of the bonding in the ion. For most simple clustering reactions, entropy changes of -25 ± 2 cal mol^{-1} K^{-1} are observed;[7] the value obtained here indicates that the cluster ion produced is of considerably lower entropy than expected. This is a result of restrictions of internal rotations of the complex. A logical conclusion is that an ion of structure I is being produced rather than one of structure II, which should have considerably greater freedom of internal rotation.[8] A similar phenomenon has been observed in the clustering of methylated acetone onto acetone. Future work will exploit the generality of metal ion production by laser ablation to carry out systematic studies of metal ion–substrate thermochemistry.



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Stereogenic (Chiral) Methyl Groups: Determination of Configuration by Direct Tritium Nuclear Magnetic Resonance Spectroscopy

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Since the original demonstration by Cornforth, Arigoni, and their co-workers,[1-3] compounds containing stereogenic[4] (so-called chiral) methyl groups, i.e., CHDT groups, have been used to study the stereochemistry of numerous biochemical (enzymatic) reactions.[5-12] The present methods for determining the configuration and enantiomeric excess of stereogenic methyl groups all involve processes in which one hydrogen is removed from the methyl group, generally by an enzymatic reaction. These methods usually depend on a kinetic isotope effect that results in the slower breaking of a C–D than a C–H bond[5,6] with the consequent formation of a tritium-labeled methylene group whose configuration can then be determined either by radioactive assays in conjunction with enzymatic or chemical techniques or, alterna-

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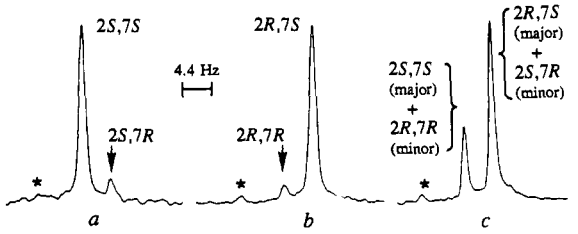
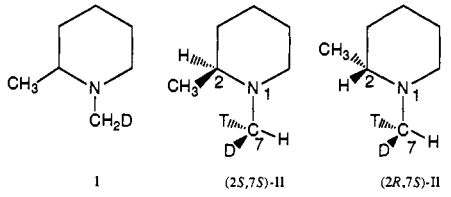


Figure 1. $^3H\{^1H,^2H\}$ NMR spectra at 320 MHz of the reaction products of (*R*)-CHDTN(Tos)$_2$ (86% enantiomeric excess, 3.4 and 6.6 mg, 0.32 mCi/mg) with (a) (*S*)-(+)- and (b) (*R*)-(−)-2-methylpiperidine having 96 and 100% enantiomeric excesses, respectively, and (c) spectrum of the mixture of the a and b samples in the ratio of 0.7:1 (note that the configuration of the methyl group inverts during the S_N2 reaction). The reactions were carried out in sealed tubes at 130 °C for 7 h, and the products were diluted with CD_2Cl_2 to give solution heights of ~2.0 cm in standard 5-mm NMR tubes. The FIDs were accumulated in an unlocked block mode, with a pulse angle of about 40°, an acquisition time of 2.8 s/FID, and total times of 112, 102, and 84 min for a, b, and c, respectively. The data were processed to give the optimum signal-to-noise (S/N) ratio with a broadening of 0.3 Hz; the smaller S/N ratio in a compared to b arises from a lower tritium concentration. The small peaks labeled with an asterisk (*) are assigned to CH_2T groups in isotopic impurities.

tively, by tritium NMR.[9,13,14] The work reported here, however, demonstrates for the first time that the configuration of stereogenic methyl groups can be assigned by direct tritium NMR analysis of a molecule containing an intact CHDT group. Although this new method is not as sensitive as the enzymatic procedure,[1-3] it allows a more accurate determination of the enantiomeric purity of the CHDT group.

A method for determining the enantiomeric excess in a CHDT group by a direct tritium NMR technique should be feasible because of the recent demonstration of diastereotopic protons with observably different ^1H chemical shifts in the CH_2D group of a chiral molecule (I) (as its racemate).[15] All that is required is



I (2S,7S)-II (2R,7S)-II

the N-methylation by a S_N2 mechanism of (*R*)- or (*S*)-2-methylpiperidine by a molecule of the type CHDTX, where X is a leaving group. The prediction is that the diastereomers (2*S*,7*S*)-II and (2*R*,7*S*)-II (and likewise their respective mirror-image forms) should have tritium chemical shifts differing by 0.015 ± 0.001 ppm, with the 2*R*,7*S* isomer containing the more shielded tritium.[15] Any compound that can be converted into CHDTX by a sequence of reactions of known stereochemistry is also a candidate for this method, and this includes chiral acetic acid, $CHDTCO_2H$. The Schmidt reaction (sodium azide and concentrated sulfuric acid, a reaction that takes place with configurational retention) on this acid gives chiral methylamine, which is converted by a two-step tosylation procedure into chiral *N*,*N*-ditosylmethylamine, CHDTN(Tos)$_2$,[7,16] where Tos_2N^- is a known leaving group in S_N2 reactions.

For demonstration purposes, we have treated (*R*)-CHDTN(Tos)$_2$ (expected to be >80% enantiomerically pure),[16] prepared from (*R*)-$CHDTCO_2H$,[17] separately with a 20-fold molar excess of (*S*)-(+)- and (*R*)-(−)-2-methylpiperidine.[18-20] The $^3H\{^1H,^2H\}$ NMR spectra of the crude reaction mixtures in CD_2Cl_2 solution were then measured, first separately and then after the samples were mixed together (Figure 1). The results clearly demonstrate that the diastereomeric [7-$^2H_1$,^3H]-1,2-dimethylpiperidines have tritium NMR chemical shifts differing by 4.4 Hz (0.014 ppm), with the tritium more shielded in the 2*R*,7*S* than in the 2*S*,7*S* diastereomer (and in their respective mirror images), in excellent agreement with predictions.[21]

The tritium NMR spectrum in Figure 1b gives an accurate estimate (86 ± 1%) of the enantiomeric excess in the (*R*)-CHDTN(Tos)$_2$ starting material. Presumably, the *S* enantiomeric impurity is the result of exchange between the protonated acetic acid or a related species with the strongly acidic solvent during the Schmidt reaction because the labeled acetic acid does not contain observable amounts of (*S*)-$CHDTCO_2H$ or of CH_2TCO_2H; this is consistent with the presence in the spectrum of a peak assignable to ~3% of the CH_2T analogue of II and an H/D kinetic isotope effect of ~5 in the exchange.

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(21) Actually, the ^1H chemical shift difference at 500 MHz in the CH_2D group of I prepared and examined as above (i.e., containing a small amount of the protonated amine) is 6.4 Hz rather than the 6.9 Hz reported[15] for the pure amine in CD_2Cl_2, and this leads to a predicted tritium chemical shift difference of 4.4 Hz at 320 MHz.

Coenzyme B_{12} Chemistry: The Crystal and Molecular Structure of Cob(II)alamin[‡,1]

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According to the available information, the homolysis of the organometallic bond of the protein-bound coenzyme B_{12} (**1**, 5′-adenosylcobalamin) induces the coenzyme B_{12} catalyzed enzymatic reactions.[2] However, the rates of these latter reactions typically exceed that of the homolysis of **1** in homogeneous solution by more than 10^{10} times at room temperature, so that the Co–C bond cleavage appears remarkably activated in the enzyme.[3,4] This is believed to result from specific interactions of the apoenzyme[4-9]

‡Dedicated to Prof. Dr. J. Schurz, on the occasion of his 65th birthday.
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