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A RELATION BETWEEN THE SITE-SPECIFIC NATURAL DEUTERIUM CONTENTS IN α-PINENES AND THEIR OPTICAL ACTIVITY

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SUMMARY : Correlations are observed between the optical rotation of α-pinenes and site-specific isotope ratios, $(D/H)_i$, determined by natural abundance deuterium NMR (SNIF-NMR). The optical purity can therefore be estimated by NMR without the need for spectral separation of the enantiomers.

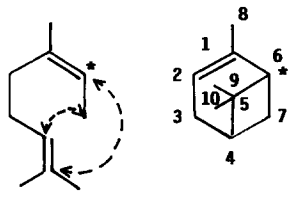
The NMR determinations of optical purity of enantiomers are mainly based on the formation of diastereotopic relationships between an enantiomeric substrate and a chiral reagent [1,2]. In order to increase the shift difference between the diastereotopic sites, lanthanide complexes can be used [2]. This technique is specially useful when the chirality arises from deuterium substitution which introduces only a weak electronic anisotropy and induces a small optical rotation. Thus the discriminating power of a camphanate moiety, towards an ester ethyl fragment can be significantly enhanced [3,4] by adding the europium complex $Eu(dpm)_3$. Chiral recognition and optical purity determinations are usually performed either by ^1H or by ^{13}C NMR spectroscopy [5]. Deuterium NMR can also be used to measure the optical purity of enriched deuterated molecules [3b] and we have shown that a natural chirality of methylene sites can be detected by applying ^2H NMR to the investigation of Site-specific Natural Isotope Fractionation (SNIF-NMR).[4]

We wish to present now experimental evidence of a correlation between the optical activity of an enantiomeric molecule and the natural abundance of some of its specific monodeuterated isotopomers. The method is founded on the investigation by SNIF-NMR [6] of the fractionation effects which are likely to occur in enzymic conversions. Indeed the kinetic and thermodynamic isotope effects intervening in the course of a biogenesis may be different for the R and S enantiomers of a natural molecule. Consequently it may be expected that the isotope ratio $(D/H)_i$ of a specific site i in enantiomer R should be different from the $(D/H)_i$ ratio of the same site in enantiomer S. For illustration the method is applied to the case of α-pinenes for which chiral recognition by NMR requires the addition of a silver (I) compound in order to transmit the splitting effect of an optically active lanthanide complex.[5]

A typical ^2H NMR spectrum of neat S(-)α-pinene at the natural abundance level is shown on the figure. Since a comprehensive assignment of all ^1H sites of α-pinene was not available we have performed a series of 2D-experiments. First the assignment of the ^{13}C

spectrum proposed by Offermann [7] was checked by a ^{13}C-^{13}C autocorrelation experiment [8a] and the proton signals were assigned from a (^{1}H-^{13}C) 2D-correlation analysis [8b] for protons 4 and 6 and from a NOESY experiment [8c] for protons 3 and 3'. The deuterium shifts were referred to the frequency of the ^{2}H TMS signal saved in the computer memory and the T_1 relaxation times were measured by the inversion-recovery method. The ^{13}C assignment used in the 2D-correlation analysis is also indicated on the scheme. Ten samples of α-pinene characterized by different optical activities have been investigated in $CHCl_3$ solutions at the same concentration. In every case the optical rotation has been determined immediately after the NMR acquisition using a polarimeter AA 10 at 291 K and 589 nm. The range of investigated optical activities is on the order of 36° (+ 20° to - 16°) The measured optical deviations, α, are not the specific angles but are directly comparable to the ^{2}H NMR results in the whole series of samples.

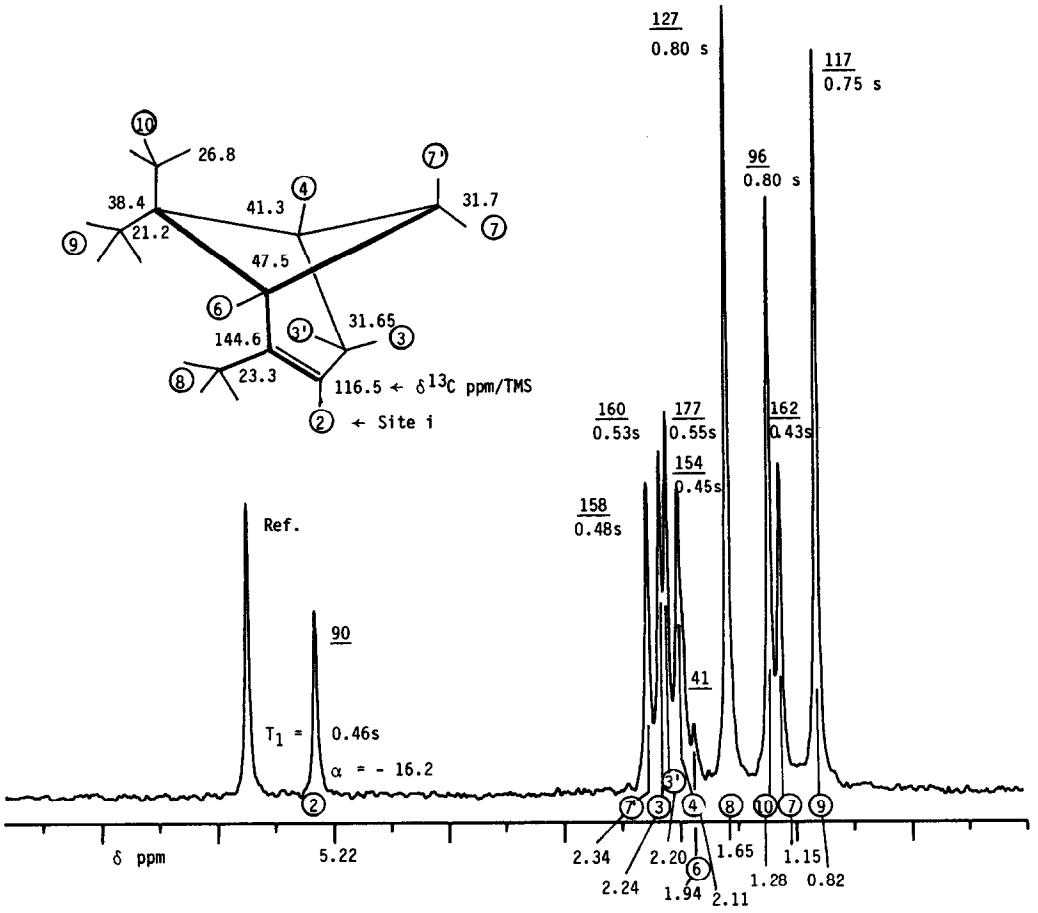
Inspection of figure 1 shows clearly that a statistical distribution of deuterium is not obeyed amongst the ten isotopomers which are nicely distinguished since even the 3,3' sites are separated. Moreover it is interesting to note that site 6, which is very depleted in deuterium is formerly the ethylenic site of the so-called "active isoprene" moiety which undergoes the cyclisation to give the bicyclic pinene skeleton.[9]



If an average value of 123 ppm is retained for the overall isotope ratio of S-α-pinene, site-specific $(D/H)_i$ values can be computed using the molar fractions of the isotopomers derived from the ^{2}H spectra. Although these ratios have only a relative significance they enable several striking features to be emphasized. Thus it is noted that sites 2 and 10 in addition to site 6 exhibit a strong ^{2}H depletion with respect to sites 3, 3', 7 and 7' in particular. If we compare now the isotope ratio of a given isotopomer arising from different α-pinene samples with the corresponding optical activity parameter α it appears that linear correlations are satisfactorily obeyed, in particular for sites 2 and 3. Thus for site 2 $(D/H)_i = 105 + 0.97\,\alpha$. It is also noted that the $(D/H)_i$ ratios of sites 3', 4 and 8 are significantly higher in enantiomer S whereas the $(D/H)_i$ ratios of sites 2 and 3 are higher in enantiomer R.

These results have two consequences. First SNIF-NMR offers an easy way of estimating the optical purity of enantiomeric mixtures without the need for addition of a chiral reagent and therefore without contamination of the sample. Secondly this kind of relationship involving specific natural labelling may be the source of information on the biogenesis of terpenes and other natural compounds since it relates the concept of configuration of a chiral centre to that of isotope effect. Thus the results obtained for site 2 of α-pinene indicate that the mechanisms which lead to a cyclisation towards the S configuration involve significantly higher isotope effects than those which give the R enantiomer.

FIGURE 1 : ^{2}H NMR spectrum of S(-)α-pinene obtained in the experimental conditions of SNIF-NMR [6c] taking into account the values of the longitudinal relaxation times (in secondes) reported for all signals. The ^{13}C chemical shifts are given on the scheme. The underlined numbers are the D/H values computed on the basis of an hypothetical average value of 123 ppm. The following $(D/H)_i$ values in ppm are determined for the various isotopomers of R(+)α-pinene : 125 (2) 170 (7') 184 (3) 162 (3') 138 (4) 35 (6) 117 (8) 99 (10) 151 (7) 122 (9)



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