

the platinum center.³ (ii) The reduction of (1,5-cyclooctadiene)Pt(C₆H₅)₂ ((COD)PtPh₂)—a complex in which transfer with inversion at carbon is not possible—proceeds at a rate comparable to that of the reductions of (COD)PtR₂ (R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu), complexes in which transfer with inversion at carbon is possible.² (iii) The reduction of (COD)PtNp₂—a complex that generates neopentyl moieties¹⁷—also proceeds at a rate comparable to that of the reductions of the (COD)PtR₂ complexes.²

We conclude that the reduction of *exo*-2-norbornyl and *endo*-2-norbornyl moieties occurs with predominant retention of stereochemistry. The result from the reduction of *exo*-2-norbornyl appears to be stereochemically straightforward, with the only competing reaction being activation of ca. 20% of the *cis* C(3)-H (*exo*) bonds (probably by β -hydride elimination). The reduction of *endo*-2-norbornyl is more complicated. The observed results are accounted for by a model involving ca. 35% isomerization of *endo*-2-norbornyl to *exo*-2-norbornyl, but with the conversion of C to CD again occurring with retention of stereochemistry.

We have confirmed the structures of **1** and **2** using X-ray crystallography and have characterized (by MS and ¹H NMR) the alkane products of the reductions of **1** and **2**. These details, and their interpretations, will be described separately.

(17) Displacement with inversion at neopentyl centers is typically much slower than at other alkyl centers. See, for example: Ingold, C. K. *Q. Rev., Chem. Soc.* 1977, 11, 1-14.

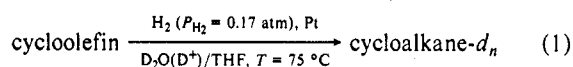
The Extent of Incorporation of Excess Deuterium in the Platinum-Catalyzed Reduction of Unsubstituted Cycloolefins by H₂ in D₂O/THF Increases with the Strain Energy of the Product Cycloalkanes¹

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Received August 9, 1990

This paper describes the isotopic compositions of cycloalkanes produced by the catalytic reduction of cycloolefins (C_nH_{2n-2}) using H₂ and platinum black in 1:1 v:v THF/D₂O_{pD=1} (eq 1).² We



conducted the reductions under conditions in which the rate of mass transport of H₂ to the surface of the catalyst limited the rate of reaction.^{3,4} Under these conditions, H₂ on the surface equilibrates essentially completely with D₂O in solution. Figure 1 summarizes the isotopic compositions of the cycloalkanes.⁵ The

(1) The National Science Foundation (Grant CHE-88-12709), the Office of Naval Research, and the Defense Advanced Research Projects Agency supported this work.

(2) We chose D₂O/THF (1:1 v:v; pD_{D₂O} = 1) because a survey of solvent systems indicated that this system yielded cyclooctanes having the highest content of deuterium in reductions of cyclooctene.

(3) We performed the reductions in a specially designed round-bottomed flask (volume = 225 mL): a small teat (volume ca. 10 mL) protruded from the bottom of the flask; a Swagelok valve and a rubber septum capped the flask. After charging the teat with a stir bar (3/8 × 3/16 in.) and 40 mg of Pt black, we purged the flask with Ar and added 0.5 mL of dry THF and 0.5 mL of D₂O (adjusted to pD = 1 with D₂SO₄). The apparatus was purged with a mixture of 10% H₂ in Ar for 1 min with stirring; the rate of rotation of the stir bar was 1400 rpm. We pressurized the vessel to 10 psi (P_{H₂} = 0.17 atm), stirred for 4 min, placed the flask in an oil bath (75 ± 3 °C), and stirred for 5 min. We removed the solvent via cannula and added the substrate (15–20 mg in 3 mL of D₂O/THF) via syringe. Stirring was started and continued for 1 h. Analysis by GC/MS indicated that all reductions were complete.

(4) Miller, T. M.; Izumi, A. N.; Shih, Y.-S.; Whitesides, G. M. *J. Am. Chem. Soc.* 1988, 110, 3146–3156.

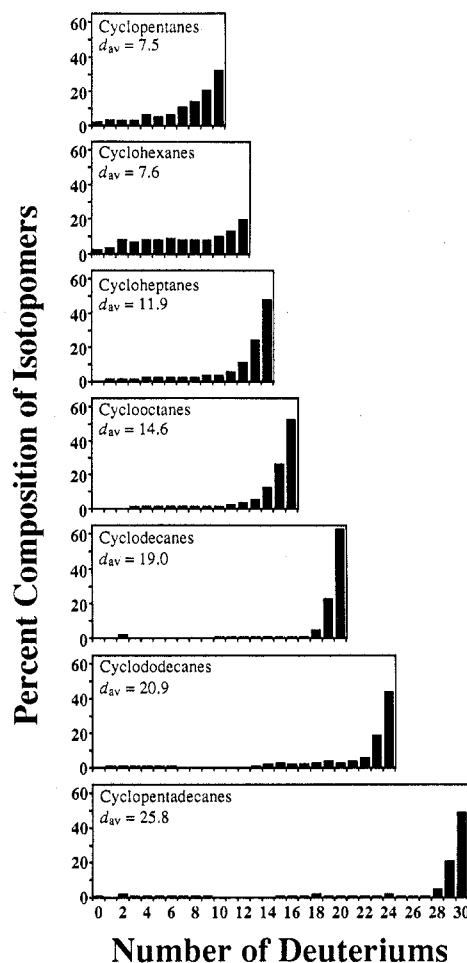


Figure 1. Isotopic distributions and values of d_{av} for the cycloalkanes from the reductions of the corresponding cycloolefins by H₂ and D₂O/THF (1:1 v:v; pD_{D₂O} = 1) over platinum black.⁵ The difference in values of d_{av} from duplicate runs was, in all cases, ≤ 0.2 .

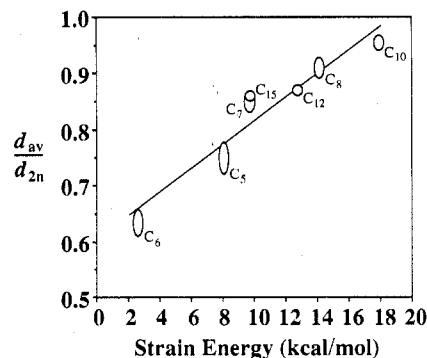


Figure 2. Values of d_{av}/d_{2n} vs strain energies of cycloalkanes (C_nH_{2n}).^{5,17} For consistency, the strain energies are all calculated values, obtained using Macromodel V2.0.^{18,19} The line drawn through the points was determined by linear regression.

important observations are as follows: (1) the isotope of hydrogen found in the cycloalkanes was predominantly that present in D₂O rather than that present in H₂; (2) the cycloalkanes contained deuterium in large excess of that required for stoichiometric

(5) Isotopic compositions were determined by GC/MS.⁶ The average content of deuterium, d_{av} , describes the extent of incorporation of deuterium. Isotopic abundances were corrected for natural abundance of ¹³C. Values of d_{av} are probably accurate to ± 0.3 D.

$$d_{av} = \sum_{n=1}^m n(\% \text{ alkane-}d_n)$$

(6) Miller, T. M.; McCarthy, T. J.; Whitesides, G. M. *J. Am. Chem. Soc.* 1988, 110, 3156–3163.

reduction of the double bond (approaching complete exchange of D for H in some cases); and (3) each substrate gave the per-deuterated isotopomer as the major product.

The observation that extensively polydeuterated cycloalkanes can be produced from cycloolefins with H₂ as the reductant is remarkable and potentially useful in the synthesis of isotopically labeled compounds. The ability to incorporate deuterium into organic compounds by the metal-catalyzed reduction of olefins with H₂ and D₂O/THF avoids the need for D₂. In addition, this technique should be applicable to the incorporation of tritium into organic compounds.

Previous studies of the hydrogenation of olefins in protic solvents showed that surface alkyls on platinum rapidly undergo isotopic exchange of hydrogen with H• (D•) and that the product alkanes contain the isotope from the solvent (ROH or ROD).⁷⁻¹³ Our results demonstrate that by working under mass-transport-limited conditions, isotopic exchange can be made more extensive than in these earlier reports. The exchange undoubtedly requires exchange between H• (D•) and the OH (OD) group of the solvent (eq 2). The mechanism of the exchange shown in eq 2 is not well established, although several mechanisms have been proposed.¹⁰⁻¹⁶



Because the exchange of H/D between the surface of platinum and the protic solvent is, under the conditions used here, faster than the conversion of surface alkyls to alkanes, the content of deuterium in the product alkanes provides a valuable mechanistic tool: a measure of the rate of exchange (and thus of C-H bond activation) of the surface alkyls relative to the rate of their reductive elimination as alkanes. Comparison of the ratio d_{av}/d_{2n} from the reduction of a series of cycloalkenes demonstrates the utility of this approach (Figure 2). These data indicate that the rates of C-H activation (relative to the rates of reductive elimination) of surface cycloalkyls decrease from cyclodecyl- to cyclohexyl.

The value of d_{av}/d_{2n} correlates with the strain energy of the product cycloalkanes ($r = 0.95$).¹⁷⁻¹⁹ Thus, as the cycloalkane is varied from one having low strain energy to one having high strain energy, the transition state for reductive elimination increases in energy relative to that for isotopic exchange. The two simple limiting hypotheses rationalizing this inference are that strain is *relieved* in the transition state for isotopic exchange (C-H activation) or that strain is *concentrated* in the transition state for reductive elimination.²¹ We emphasize that ΔG^\ddagger for reductive

elimination by reaction of R• with H₂ is dominated by the free energy term describing generation of H• by a mass-transport-limited process. We therefore hypothesize that the correlation in Figure 2 reflects primarily structure-dependent differences in rates of C-H activation.

The heterogeneous polydeuteration of hydrocarbons probably involves some combination of $\alpha\alpha$ -activation, $\alpha\beta$ -activation, and π -allyl formation.²² The *differences* in strain energies between the transition states leading to these intermediates and the transition states leading to the cycloalkane products should correlate with d_{av}/d_{2n} . Calculating strain energies for the intermediates is, however, too complicated to be approached through realistic models of surface species.²³ To date, our efforts to obtain a correlation between the experimental values of d_{av}/d_{2n} and relative strain energies calculated for simple models of surface intermediates have not been successful.

Acknowledgment. We thank our colleagues John Burns and Watson Lees for assistance with the force field calculations.

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Four-Dimensional [¹³C, ¹H, ¹³C, ¹H] HMQC-NOE-HMQC NMR Spectroscopy: Resolving Tertiary NOE Distance Constraints in the Spectra of Larger Proteins

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Received September 27, 1990

Three-dimensional (3D) heteronuclear-resolved nuclear Overhauser effect (NOE) NMR spectroscopy is a powerful tool to improve the resolution of NOE spectra of medium-sized proteins (MW <25 kDa) that are isotopically labeled.¹ However, even with 3D NMR methods it is difficult to resolve and unambiguously identify many of the NOE cross peaks. Therefore, a further increase in dimensionality of the NMR experiments is necessary. Recently, the first four-dimensional (4D) NMR spectrum appeared,² where amide-aliphatic proton NOEs of interleukin 1- β were edited with respect to two different heteronuclei.

Here we demonstrate a four-dimensional NMR experiment (4D [¹³C, ¹H, ¹³C, ¹H] HMQC-NOE-HMQC, see panel A of Figure 1), carried out with ¹³C-labeled T4-lysozyme (MW 19.7 kDa), in which both dimensions of ¹H-¹H NOE cross peaks between aliphatic and/or aromatic protons are edited by the frequencies of both attached ¹³C nuclei.³ The resulting four-dimensional

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(18) We calculated strain energies for the lowest energy conformations of the cycloalkanes given in the following: Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC 1982; pp 89-108 (for C₇-C₁₂). Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7810-7814 (for C₁₅). The strain energies for these conformations were calculated with MacroModel V2.0 using the MM2(85) parameter set: Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Cauffield, C.; Chang, G.; Hendrickson, T. *MacroModel V2.0*; Dept. of Chemistry, Columbia University: New York, NY.

(19) The strain energies shown in Figure 2 were obtained by standard modification of the values given by force field calculations ($SE = SE_{MM2} - SE_{strainless}$).²⁰ The values for $SE_{strainless}$ were empirically determined to be $n \times 0.65$ kcal/mol for a given cycloalkane (C_nH_{2n}).

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(3) The 4D spectrum appears as a series (f_1) of 3D spectra ($f_2/f_3/f_4$). Each 3D spectrum corresponds to a subset of the 4D data set in which only those f_2 protons appear that are attached to carbons resonating at a particular frequency range of f_1 . Every 3D spectrum contains a set (f_3) of (f_2/f_4) ¹H-¹H NOESY planes. These planes correspond to a subset of the 3D data in which only those f_4 protons appear that are attached to carbons resonating at a particular frequency range of f_3 (see also Figure 1 of ref 2).