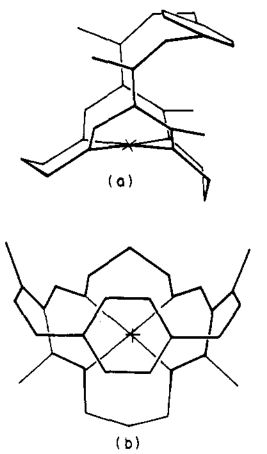


Figure 1. (a) Side view of the Ni(II) complex (I) where the bridge is a *p*-xylyl group. (b) Top view looking perpendicular to the xylyl ring at the nickel atom.

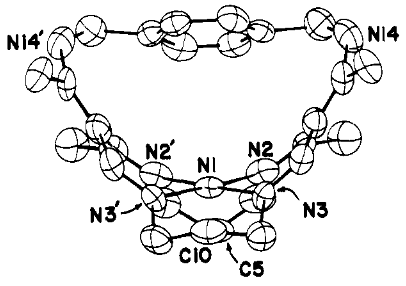
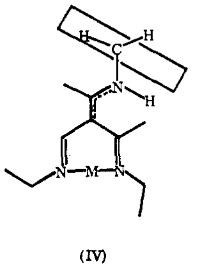


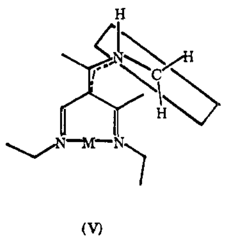
Figure 2. ORTEP diagram of the Ni(II) complex looking into the "dry cave".

conformation of the ligand (Figures 1 and 2). It clearly forms a hydrophobic cavity or "dry cave" in the vicinity of a vacant metal coordination site. The center of the *p*-xylyl group is displaced 2.6 Å to one side of the nickel and is tilted ~ 23° with respect to the coordination plane (Figure 1a), thus effectively forming both the roof and back of the cave but leaving a wide opening (~3.6 by 2.5 Å) at its mouth. The cavity is 6.78 Å wide (between nonbridghead vinyl carbons) and varies from 4.55 to 4.27 Å (rear) in height (Figure 2). The interior walls consist almost entirely of filled π orbitals, causing the cavity to be intrinsically hydrophobic—a "dry cave".

The double bonds in the parent macrocycle (N-2=C-6 and N-3=C-8) are localized so that C-6—C-7 and C-7—C-8 are essentially single bonds (Figure 3). In contrast, the bridging nitrogens are involved in delocalized π bonding, i.e., between N-14—C-12 and C-7=C-12. This causes N-14 to be planar and sp^2 hybridized and produces a form of geometrical isomerism that we have also characterized thoroughly for a number of these nickel complexes.[9] As shown in structures IV and V, the bridge may either rise directly above the N-14 atoms (lid-on isomer, structure IV) or project rearward from N-14 (lid-off isomer, structure V). The structure described here is that of a lid-off isomer.



(IV)



(V)

The characteristic saddle shape of the parent macrocycle requires the two saturated chelate rings to extend away from the dry cave. One of these has the favored chair conformation but the other adopts the boat shape (Figure 1a), presumably because of steric requirements of the bridging moiety. The coordination sphere about the nickel atom is approximately square planar with distances of the usual magnitude (Figure 3).

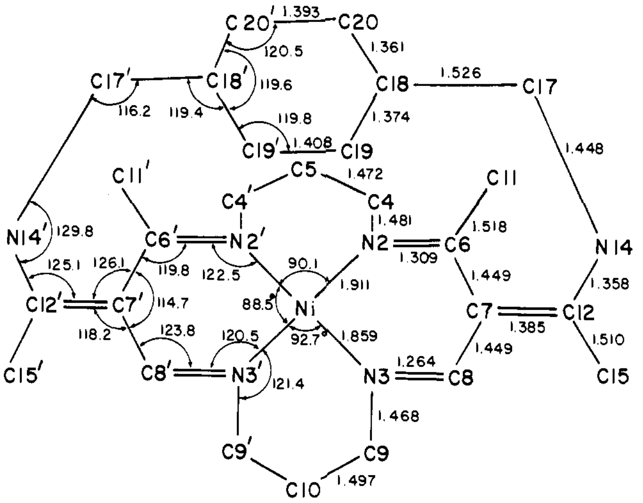


Figure 3. Bond distances and angles. The halves of the molecule are related by a crystallographic mirror plane through Ni, C-5 and C-10, bisecting the *p*-xylyl bridging group. Estimated standard errors in the metal-nitrogen distances are 0.005 Å (0.1° for the angles), while for the C-C and C-N bonds the esds average 0.007 Å (0.3°).

The complexes of these new ligands with other metal ions are under investigation. As would be expected, the dry cave site confers useful capabilities on the metal ion.[10]

References and Notes

(1) Recent synthetic developments in these and other laboratories employ the addition to ligands of components that may be viewed as serving roles analogous to the superstructures of ships; i.e., as the superstructure is altered the function of the species changes.
(2) Extracted in part from the thesis of Wayne Schammel, The Ohio State University, 1976.
(3) J. Almag, J. E. Baldwin, and J. Huff, *J. Am. Chem. Soc.*, **97**, 227 (1975); J. Almag, J. E. Baldwin, R. L. Dyer, and M. Peters, *ibid.*, **97**, 226 (1975).
(4) J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Land, and W. T. Robinson, *J. Am. Chem. Soc.*, **97**, 1427 (1975); J. P. Collman, R. R. Gagne, T. R. Halbert, J. C. Marchon, and C. A. Reed, *ibid.*, **95**, 7868 (1973).
(5) C. K. Chang and T. G. Traylor, *Proc. Natl. Acad. Sci., U.S.A.*, **70**, 2647 (1973); C. K. Chang and T. G. Traylor, *J. Am. Chem. Soc.*, **95**, 5810, 8475 8477 (1973).
(6) A. R. Battersby, D. G. Buckley, S. G. Hartley, and M. D. Turnbull, *J. Chem. Soc., Chem. Commun.*, 879 (1976).
(7) P. W. R. Corfield, J. D. Mokren, C. J. Hipp, and D. H. Busch, *J. Am. Chem. Soc.*, **95**, 4465 (1973).
(8) F. Lustig, *Ber.*, **28**, 2992 (1895).
(9) S. C. Jackels, R. Callahan, L. L. Zimmer, J. C. Stevens, A. M. Tait, and D. H. Busch, unpublished work.
(10) These studies were partially supported by the National Science Foundation.

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Palladium(0) Catalyzed Reaction of 1,3-Diene Epoxides. A Useful Method for the Site-Specific Oxygenation of 1,3-Dienes

Sir:

The site-specific oxygenation of unsaturated carbon skeletons is one of the most fundamental tasks in synthetic organic chemistry. We here describe three types of oxygenative transformations of 1,3-dienes, A–C. The type A reaction is formally viewed as an ene-type reaction caused by oxygen

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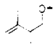
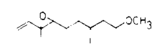
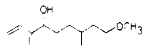
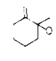
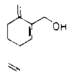
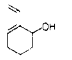
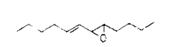
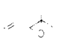
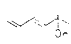
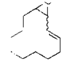
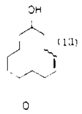
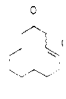
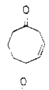
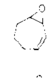
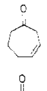
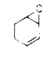
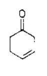
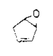
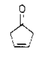
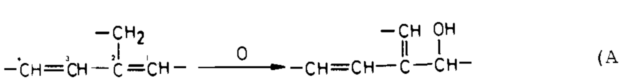
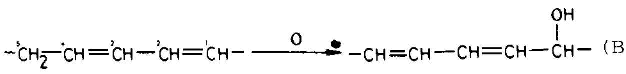
Table I. Palladium(0) Catalyzed Reaction of Diene Epoxides[a]

Entry	Epoxide	Catalyst, mol %	Solvent	Temp, °C	Time h	Product (% yield[b])
1		0.03	Ether	60	24	 (70)
2		1.4	THF	60	24	 (81)
3		0.5	THF	50	24	 (90)
4		0.1	THF	60	23	 (99)
5		0.8	THF	110	24	 (15)
6		1.2	Benzene	115	22	(57)
7		3.5	THF	150	41	 (70[c])
8		1.1	Benzene	130	16	(79, 81[c])
9		3.5	CH_2Cl_2	100	37	(68[c])
10		0.6	Benzene	120	24	 (13) and  (70)
11		1.1	THF	120	22	 (74[c])
12		0.6	Benzene	110	41	(62, 81[c])
13		0.2[d]	None[e]	120–140	1	 (36)
14		0.5	Benzene	25	21	 (61, 79[c])
15		0.4	Ether	0	1	(79[c])
16		0.4	THF	0	1	 (81[c])
17		0.4	Benzene	5	1	(82[c])
18		0.00013	CH_2Cl_2	0–10	2	(77, 88[c,f])

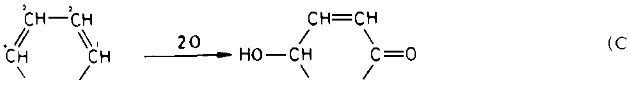
[a] All reactions were carried out under argon atmosphere. In most cases some PPh_3 (1–2 equiv to $Pd(PPh_3)_4$ catalyst) was added. All new compounds gave consistent NMR and IR characteristics and correct elemental analysis and/or mass spectral data. [b] Isolated yield (silica gel chromatography and/or distillation). [c] Determined by GLC analysis. [d] Coated on Celite 545. [e] Vapor phase reaction. [f] Obtained by NMR analysis.



$$-\overset{4}{C}H=\overset{3}{C}H-\overset{\displaystyle -CH_2}{\overset{|}{\overset{2}{C}}}=\overset{1}{C}H- \xrightarrow{O} -CH=CH-\overset{\displaystyle -CH}{\overset{\|}{C}}-\overset{\displaystyle OH}{\overset{|}{C}H}- \qquad (A)$$



$$-\overset{5}{C}H_2-\overset{4}{C}H=\overset{3}{C}H-\overset{2}{C}H=\overset{1}{C}H- \xrightarrow{O} -CH=CH-CH=CH-\overset{\displaystyle OH}{\overset{|}{C}H}- \qquad (B)$$



$$\begin{matrix} {}^{2}CH-{}^{3}CH \\ {}^{1}CH \qquad {}^{4}CH \end{matrix} \xrightarrow{2O} HO-CH\begin{matrix} CH=CH \\ \; \end{matrix}C=O \qquad (C)$$

atom, whereas the double-bond shift reaction of type B is considered as a vinylogous ene reaction. The overall 1,4-dioxygenation of dienes (type C) has long been of interest in connection with prostaglandin chemistry.[1] These oxidative modifications could be achieved by utilizing singlet oxygen molecules but, as usual, such method lacks general selectivity.[2] Reported herein is the realization of such functionalizations by way of diene 1,2-epoxides, which under the influence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)[3] undergo unique isomerizations.

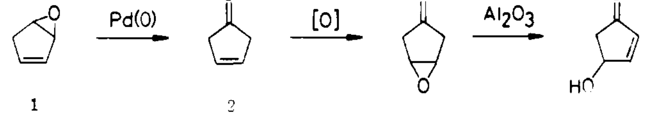
The course of the Pd(0) catalyzed reaction of the epoxides appeared to be highly dependent on the substitution pattern of the substrates as indicated in Table I.

Type A Transformation. In order that this hydrogen migration reaction be effected, the diene epoxides must have a transferable hydrogen atom in the C-2 alkyl substituent. Entries 1-4 in Table I are its typical examples.[4]

Type B Transformation. Entries 5-9 of Table I exemplify the general reaction that involves transfer of a C-5 hydrogen atom. The propensity to undergo this type of reaction is characteristic of open-chain substrates which lack alkyl substituents at C-2 position. Unfortunately, this reaction is nonstereospecific. Isomerizations A and B proceed smoothly in ethereal solvents such as THF or diethyl ether.

Type C Transformation. This dioxygenation of dienes has been achieved by stepwise introduction of oxygen atoms. The Pd(0) catalyzed reaction of the 12-membered-ring epoxide (entry 10) afforded a mixture of the dienol and enone isomer with the latter predominating. Notably, monoepoxides derived from simple cyclic 1,3-dienes possessing ordinary ring size gave the β,γ-unsaturated ketones as the sole isolable product (entries 11-18). Epoxidation of such unconjugated enones followed by epoxy-ring opening by alumina gave rise to the corresponding 4-hydroxy-2-cyclenones, accomplishing the desired overall 1,4-dioxygenation of dienes.

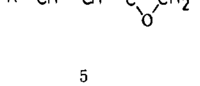
Particularly important is the synthesis of 4-hydroxy-2-cyclopentenone (**4**, a prostaglandin intermediate[5]) from cyclopentadiene. The following procedure may be illustrative.



1 2 3 4

The epoxide **1** (22.7 g, 0.27 mol) was added in a dropwise manner to a solution of $Pd(PPh_3)_4$ (40 mg, 34 µmol) in CH_2Cl_2 (70 mL) cooled in an ice bath. The reaction was highly exothermic and temperature of the reaction mixture rose to ~10 °C. After 2 h when the heat evolution had ceased, the mixture was subjected to flash distillation (bath temperature 25 °C, 7 mmHg) and then distillation through a Vigreux column to give 3-cyclopentenone (**2**, bp 59-63 °C (108 mmHg), 17.4 g, 77% yield).[6] No trace of 2-cyclopentenone was produced. Then a mixture of **2** (9.2 g, 0.11 mol), $NaHCO_3$ (30 g), and EDTA disodium salt (33 mg) in CH_2Cl_2 (70 mL) was treated with CF_3CO_3H (prepared from 90% H_2O_2 (3.9 mL, 0.14 mol) and $(CF_3CO)_2O$ (23.6 mL) in CH_2Cl_2 (70 mL)) at 0 °C for 15 min and 25 °C for 20 h, and quenched with $Na_2S_2O_3 \cdot 5H_2O$ (30 g). The CH_2Cl_2 extracts containing the keto epoxide **3** were stirred with basic alumina (Woelm, activity I, 35 g) in 1:1 CH_2Cl_2-ether (200 mL) at 25 °C for 1 h and then the alumina was removed by filtration. The filtrate was concentrated and distilled to give the hydroxy enone **4** as a colorless oil (bp 100-103 °C (4 mm Hg), 7.2 g, 66% yield based on **2**).[7]

The efficiency of the catalytic reaction of the epoxides should be ascribed to eminent nucleophilic character of the Pd(0) catalyst and hydrogen-carrying ability of Pd(II) species.[8-10] In principle the diene epoxide **5** is susceptible to Pd(0) attack at C-2 (S_N2-type reaction), C-4 (S_N2' reaction), or C-3-C-4 double bond. β,γ-Unsaturated ketone would form via the zwitterion **6** and Pd hydride intermediate, **7** or **8**. Al-



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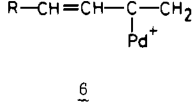

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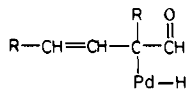

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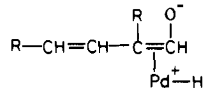

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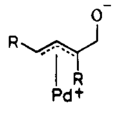

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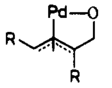

10

ternatively the epoxide could isomerize to dienols through the π-allyl complex, **9** or **10**. The detailed mechanistic study is now in progress.

Acknowledgment. This research was supported in part by the Ministry of Education, the Japanese Government (Grant-in-Aid, No. 303023).

References and Notes

(1) For example see the following. Schenck, G. O.; Dunlap, D. E. *Angew. Chem.* **1956**, *68*, 248. Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974,** 876. Adam, W.; Eggelte, H. J. *Angew. Chem., Int. Ed. Engl.* **1977,** *16*, 713.

(2) Reviews follow. Adams, W. R. "Oxidation", Augustine, R. L., Trecker, D. J., Eds.; Marcel Dekker: New York, 1971; Vol. 2, Chapter 2. Kearns, D. R. *Chem. Rev.* **1971,** *71*, 395. Denny R. W.; Nickon, A. *Org. React.* **1973,** *20*, 133.

(3) Coulson, D. R. *Inorg. Syn.* **1972,** *13*, 121. The complex was purified before use by recrystallizations from a 3:1 mixture of THF and ether at 0 °C.

(4) For conventional methods for converting epoxides to allylic alcohols, see the following. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973,** *95*, 2697. Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.* **1978,** *17*, 169, and references cited therein.

(5) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975,** *97*, 6260. Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayashi, M.; Ishimoto, S.; *Tetrahedron* **1976,** *32*, 1713.

(6) $Pd(PPh_3)_4$ was the best catalyst for the isomerization, **1** → **2**. Other catalysts examined were $Pd(acac)_2$–PPh_3 (11 mol %, benzene, 50 °C, 11 h, 53%), $PdCl_2$–PPh_3 (13 mol %, THF, 50 °C, 59 h, 35%), Pd_2(tribenzylideneacetylacetone)$_3$·$CHCl_3$ (supplied kindly by Professor K. Itoh)–PPh_3 (3.4 mol %, benzene, 50 °C, 11 h, 65%), $Pt(PPh_3)_4$–PPh_3 (3.9 mol %, 25 °C, 50 h, 39%), $MgBr_2$ (9 mol %, ether, 50 °C, 11 h, 29%), $LiClO_4 \cdot 3H_2O$ (11 mol %, ether, 50 °C, 11 h, 33%), $LiBr \cdot H_2O$ (37 mol %, ether, 50 °C, 23 h, 14%). The following compounds were inactive for the isomerization under comparable reaction conditions: Pd_2(tribenzylideneacetylacetone)$_3$·$CHCl_3$, $Pd(PhCN)_2Cl_2$, Na_2PdCl_4, Pd/C, $Rh(PPh_3)_3Cl$, $Ni(PPh_3)_2(CO)_2$–PPh_3, $Ni(acac)_2$.

(7) For a singlet oxygen route to **4,** see Schulte-Elte, K. H.; Willhalm, B.; Ohloff, G. *Angew. Chem., Int. Ed. Engl.* **1969,** *8*, 985.

(8) Trost, B. M. *Tetrahedron* **1977,** *33*, 2615. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977,** *10*, 434, and references cited therein.

(9) $Pd(acac)_2/PPh_3$ catalyzed isomerization of 3,4-epoxy-3-methyl-1-butene to 2-methyl-2-butenal was briefly noted (Nakatani, Y.; Sugiyama, M.; Honbo, C. *Agric. Biol. Chem.*, **1975,** *39*, 2431). See also Adames, G.; Bibby, C.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1972,** 491.

(10) Previous reports on the reaction of diene epoxides and transition metal complexes follow. $Fe(CO)_5$: Aumann, R.; Fröhlich, K.; Ring, H. *Angew. Chem., Int. Ed. Engl.* **1974,** *13*, 275; Chen, K. N.; Moriarty, R. M.; DeBoer, B. G.; Churchill, M. R.; Yeh, H. J. C. *J. Am. Chem. Soc.* **1975,** *97*, 5602; Annis, G. D.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1977,** 581. $Mo(CO)_6$: Alper, H.; Roches, D. D.; Durst, T.; Legault, R. *J. Org. Chem.* **1976,** *41*, 3611. Rh(I): Grigg's report given in ref 9; Aumann, R.; Ring, H. *Angew. Chem., Int. Ed. Engl.* **1977,** *16*, 50. Organocuprates: Anderson, R. J. *J. Am. Chem. Soc.* **1970,** *92*, 4978; Herr, R. W.; Johnson, C. R. *ibid.* **1970,** *92*, 4979; Staroscik, J., Rickborn, B. *ibid.* **1971,** *93*, 3046; Wieland, D. M.; Johnson, C. R. *ibid.* **1971,** *93*, 3047.

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New Nuclear Magnetic Resonance Methodology in Biosynthetic Studies of Mixtures of Statistically Enriched ^{13}C and Unlabeled Precursors

Sir:

An increasing number of analyses of biosynthetic experiments using double labeling has been reported either with two ^{13}C carbon atoms[1] or with one ^{13}C and one ^2H.[2] However, reports on experiments carried out with statistically enriched precursors are sparse, especially in the field of polysaccharides. It is clear that NMR analyses of spectra of biosynthesized compounds can give unique information on the origin of groups of coupled carbon atoms, since complex mixtures of isotopomers can be analyzed from ^{13}C experimental spectra. In some particular cases a more powerful technique, providing both structural and biochemical informations, is obtained by using a mixed precursor of unlabeled material and statistically ^{13}C-enriched material.

The basic principle can be illustrated with a very simple example: the final product has two *adjacent* carbons, C-1 and C-2 for instance, with the *same fraction* (τ) *of labeling with* ^{13}C and is supposed to be formed in 100% yield from a 1:1 mixture of unlabeled and statistically enriched ^{13}C precursor. If we define P_{12} *as the probability of both carbons in the final product coming from the same precursor molecule of either the unlabeled or statistically enriched fractions, and* $P_{1/2} = 1 - P_{12}$ *as the probability of their coming from different precursor molecules,* the four populations of isotopomers having ^{12}C or ^{13}C at C-1 or C-2 are only a function of P_{12}. In particular, if we consider the ^{13}C-1 spectrum, we see that this carbon is either coupled or noncoupled to the neighboring C-2. If we call X_{12} *the probability of* ^{13}C*-1 having a* ^{13}C*-2 as a neighbor,* we have

$$X_{12} = P_{12}[\alpha\rho_A^2 + (1 - \alpha)\rho_B^2]/\tau + [1 - P_{12}]\tau$$

The first term refers to two ^{13}C atoms coming without cleavage from the precursor of either the unlabeled or statistically enriched fractions; the second is related to two ^{13}C atoms coming from two different fragments cleaved and recombined. In this expression, ρ_A is the fraction of ^{13}C in the statistically enriched precursor; ρ_B is the fraction of ^{13}C in the "unlabeled" precursor ($\rho_B = 0.01$, but to a first approximation $\rho_B = 0$ can be used); α is the fraction of the statistically enriched precursor incorporated in the final product at positions C-1 *and* C-2—this value has to be determined experimentally by means of the relation $\tau = \alpha\rho_A + (1 - \alpha)\rho_B$ and is generally smaller than the fraction of labeled precursor used. The general derivation of the expression proceeds with consideration of the four isotopomers having ^{12}C or ^{13}C at C-1 and C-2. Experimental determination of X_{12} gives then P_{12}, which value is a number between 0 (all groups of C-1 and C-2 atoms come from different precursor molecules) and 1 (all groups of C-1 and C-2 atoms come from the same precursor molecule).

The mathematical treatment proposed here, more general than that given by Tran-Dinh et al.[3] and by London et al.,[1h] can then be used with any groups of more than two atoms. For a group of three consecutive atoms such as C-1, C-2, and C-3, the observation of the spectrum for the "middle" atom (in this case C-2) provides experimental data about the four species corresponding to ^{12}C or ^{13}C at C-1 or C-3. Thus we can define four probabilities resulting from the four possible origins of the three carbon atoms (i.e., from the same precursor molecule, from two molecules (two cases), and from three different molecules). This gives three independent parameters or *one new correlation term* C_{13} *if* P_{12} *and* P_{23} *are known. The definition* (*and sign*) *of this correlation term can be determined from one of the following equations:* $P_{123} = P_{12}P_{23} + C_{13}$ (in the case of the three atoms originating from the same precursor molecule of either the unlabeled or statistically enriched fraction); $P_{1/23} = (1 - P_{12})P_{23} - C_{13}$ (C-1 comes from one molecule, C-2 and C-3 from another); $P_{12/3} = P_{12}(1 - P_{23}) - C_{13}$ (C-1 and C-2 come from one molecule, C-3 from another); $P_{1/2/3} = (1 - P_{12})(1 - P_{23}) + C_{13}$ (three atoms from three different precursor molecules).

More detailed calculations and generalization to a group of four atoms are given elsewhere.[4] In this case two new correlation terms are necessary, but experimental data to date are perfectly described by only *P* and *C* values.

As a typical example, biosynthesis of cellulose with *Acetobacter xylinum,* as described by Hestrin,[5] has been chosen, since it is a rather complicated in vivo biosynthesis with at least three principal pathways.[6] It is also a case where many experiments of labeling with ^{14}C,[6,7] ^2H,[8] and ^{13}C[4] have been performed, particularly in our laboratory, thus giving a clear indication of the significance of the methodology proposed here.

The NMR analysis, for the starting material[9] and for the biosynthesized cellulose, has been performed with chemical

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