An alternative explanation for biphasic behavior in protein solution studies has been advanced which involves a transfer of magnetization between two proton populations such as the protein protons and the water protons.[13] The values of T_1 and T_2 measured for the two regions of the relaxation data are also consistent with this approach. The values of T_1 and T_2 obtained in these crystalline systems indicate that a major fraction of the water molecules in the crystal are essentially liquid as suggested by several other types of measurement.

These results show quite clearly that line width measurements in such heterogeneous systems as tissue or suspensions must be interpreted with care since the line width and its saturation behavior may not necessarily be interpreted in terms of a single relaxation time or be related in a simple way to molecular motion.

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Congestion. A Conformation-Dependent Measure of Steric Environment. Derivation and Application in Stereoselective Addition to Unsaturated Carbon[1]

Sir:

Although steric effects play an important role in determining the course of many chemical reactions,[2] in general it has proved difficult to evaluate them in a quantitative manner. Taft has achieved some success in quantitatively accounting for steric effects in terms of substituent constants, E_s, in cases where conformational changes in the parent structure are not important.[3] However no generally applicable method appeared to exist which would allow automatic prediction of reaction stereoselectivity for computer analysis of synthesis.[4,5]

Stereochemistry may be conveniently divided into effects which are conformation independent (sym-

(1) This research was supported by the National Institutes of Health, Grant RR-00578, and in part by Hoffmann-La Roche and Merck Foundation.

(2) M. S. Newman, Ed., "Steric Effects in Organic Chemistry," Wiley, New York. N. Y., 1956.

(3) R. W. Taft, Jr., in ref 2, p 587.

(4) E. J. Corey and W. T. Wipke, Science, 166, 178 (1969); E. J. Corey, W. T. Wipke, R. D. Cramer III, and W. J. Howe, J. Amer. Chem. Soc., 94, 421 (1972), and following papers.

(5) Princeton Simulation and Evaluation of Chemical Synthesis (SECS) program: W. T. Wipke, T. M. Dyott, and J. G. Verbalis, Abstracts 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, CHLT-22; W. T. Wipke, P. Gund, J. G. Verbalis, and T. M. Dyott, Abstracts, 162nd National Meeting of the American Chemical Society, Washington D. C., Sept 1971, ORGN-17; W. T. Wipke, Proceedings on the Conference on Computers in Chemical Education and Research, No. Ill. Univ., July 1971, p 10–60; W. T. Wipke, P. Gund, T. M. Dyott, and J. Verbalis, Abstracts, 7th Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1972, p 42; W. T. Wipke, T. M. Dyott, P. Gund, and C. Still, Abstracts, 164th National Meeting of the American Chemical Society, New York, Sept 1972, CHED-39; W. T. Wipke in "Computer Representation and Manipulation of Chemical Information," Wiley, New York, N. Y., 1974.
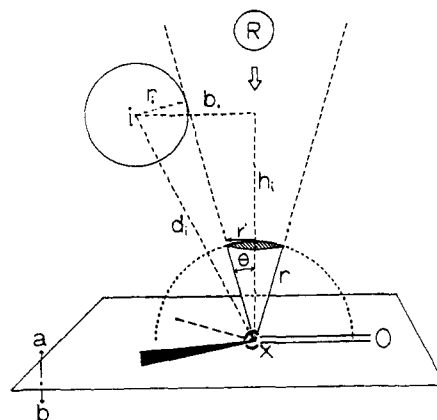

Figure 1. Cone of preferred approach of R to x allowed by atom i. The *accessibility* of x on side *a* with respect to i is defined by this solid angle and numerically equals the area on a unit sphere cut by this cone (shaded area).

bolically perceivable relationships, e.g., cis–trans), and conformation dependent (spatial relationships: axial-equatorial, proximity, steric environment). Symbolic stereochemical relationships may be treated algebraically without recourse to atomic coordinates,[6] but treatment of spatial relationships for the general case requires evaluation of a three-dimensional model.[7] We report here a function which affords a semiquantitative estimate of congestion about a reaction center of a molecular structure and which appears to correlate with preferred direction of addition to congested ketones.

We wish to define *steric congestion* at a reaction center as *a property of the substrate molecule in its ground state*—independent of reaction partners or transition-state structure.[9a] To develop a function reflecting this definition, consider the specific case of nucleophilic attack on a ketone[9b] (Figure 1). Let us assume that a nucleophile R of negligibly small radius preferentially approaches the carbon, x, along a line perpendicular to the plane of the carbonyl group. For each hindering atom, i, we may define a cone of preferred approach, centered on the perpendicular and tangent to the sphere of van der Waals radius r_i surrounding atom i. Intersection of this cone with a sphere of unit radius centered on x defines a spherical cross section of preferred approach. We equate this solid angle[10] with A_{xa} (i), the *accessibility* of x on side a with respect to i (Figure 1). Angle θ is easily derived from r_i, d_i (the distance from x to i), and h_i (the height of i above the plane).

$$A_{xa}(i) = 2\pi r^2(1 - \cos \theta) \tag{1}$$

We further define C_{xa} (i), the *congestion* at x on side a caused by i, as the reciprocal of the accessibility; then

(6) W. T. Wipke and T. M. Dyott, J. Amer. Chem. Soc., in press.

(7) Models built by SYMIN,[5] an interactive Westheimer type molecular mechanics[8] program: W. T. Wipke, P. Gund, T. M. Dyott, and J. G. Verbalis, to be submitted for publication.

(8) Review: J. E. Williams, P. J. Stang, and P. v. R. Schleyer, Annu. Rev. Phys. Chem., 19, 531 (1968).

(9) (a) Thus steric congestion is only one part of the total effect called steric hindrance. (b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, Chapter 3.

(10) The demensionless unit of solid angle is the steradian, that solid angle which encloses a surface on the sphere equivalent to the square of the radius.
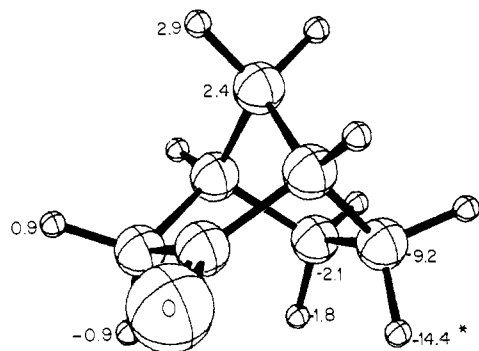
Figure 2. Significant individual congestion contributions for 2-norbornanone (1). Negative values are below the plane; starred value contains a displacement term.

the total congestion for each side is the sum of the contributions from each atom on that side.

$$C_{xa} = \sum_i C_{xa}(i) = \sum_i (1/A_{xa}(i)) \tag{2}$$

As accessibility approaches zero, i.e., when atom i starts to overlap the perpendicular pathway, nonperpendicular pathways apparently become significant. In such cases, C is set to the congestion from (1) at the arbitrary changeover point ($\theta = 14°$, $r' = 0.25$ Å) and a corrective displacement term is added

$$C_{xa}(i) = 5.32 + \exp(12(0.25 - r')) \tag{3}$$

when $r' < 0.25$ Å and where $r' = (b_i - r_i)/h_i$. While the displacement term is strictly empirical in nature, it may be envisioned as reflecting the nonbonded repulsive interaction of incoming reagent and hindering atom. Nonbonded repulsive energy is often represented as an exponential function of distance.[11]

van der Waals radii of Bondi[12] were used except for unsaturated carbon (1.8 Å) and methyl (treated as a spherical superatom of 2.2 Å radius[13]); except on methyl groups, hydrogens were considered explicitly.

Significant individual congestion contributions for atoms in 2-norbornanone (1) are given in Figure 2. Congestion for olefins may be calculated similarly, except the middle of the π bond is taken as the reaction center.

This simple model of steric environment should not be able to explain real reactions in which reagent size and transition-state effects are important. However it might be expected to correlate well with those reactions in which steric effects are dominant. Table I compares calculated exo and endo congestions and normalized congestion ratios for some sterically hindered ketones to the observed stereoselectivity for reduction. The calculated congestions do reflect observed stereospecificity in a semiquantitative manner. However, we find that congestion does not correlate as well with absolute rates of reaction, which depend strongly on transition-state effects. Furthermore not all stereoselective reactions are dominated by ground-state con-

Table I. Computed Ground-State Congestion and Observed Reduction Stereoselectivity for Some Congested Ketones

Compound	Exo	Endo	Ratio	% exo attack	Ref
1	7.4	30.3	20:80	92[a]	d
2	6.6	23.8	22:78	91[a]	d
3	574.8	32.4	95:5	10[a]	e
4	6.4	45.6	12:88	91[b]	j
5	5.6	200.9	3:97	89[b]	f
6	6.6	1747.9	0:100	100[a]	g
7	4.9	356.0	1:99	100[c]	h
8	5.1	75.9	6:94	100[c]	i

[a] LiAlH₄–Et₂O. [b] LiAlH₄–THF. [c] NaBH₄–MeOH. [d] C. H. DePuy and P. R. Story, *J. Amer. Chem. Soc.*, **83**, 627 (1960). [e] R. Howe, E. C. Friedrich, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 379 (1965). [f] H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965). [g] L. A. Spurlock and K. P. Clark, *J. Amer. Chem. Soc.*, **94**, 5349 (1972). [h] M. Sakai, R. F. Childs, and S. Winstein, *J. Org. Chem.*, **37**, 2517 (1972); T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press, and H. Schechter, *J. Amer. Chem. Soc.*, **94**, 5366 (1972). [i] M. Gates, *J. Amer. Chem. Soc.*, **75**, 4340 (1953).

gestion; for example, 3-cholestanone (congestion 20.9 α, 3.4 β or 86:14 ratio) exhibits steric control with bulky reagents (e.g, H₂–Pt–H⁺, 75% β attack) but not with hydride ion (e.g., LiAlH₄–Et₂O, 90% β or axial attack).[16] In the full paper we will discuss a method for accommodating the latter cases by correcting congestion for a torsional effect.[17] In other cases inductive effects[18] or transition-state conformational effects[19] may invalidate the congestion-derived stereoselectivity. However, steric control appears to dominate when the difference in congestion of the two sides is large and the larger of the two values is greater than ca. 30.

This congestion function has proven useful in the SECS computer program for generation of stereoselective

(11) J. O. Hirschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids," Wiley, New York, N. Y., 1954, p 31.

(12) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

(13) This gave better results than Pauling's recommended[14] value of 2.0 Å, and is still less than the maximum van der Waals radius of 2.23 Å along the C–H axis.[15]

(14) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 260.

(15) M. Charton, *Progr. Phys. Org. Chem.*, **8**, 247 (1971).

(16) "Steric approach control" vs. "product development control": W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli, *J. Amer. Chem. Soc.*, **78**, 3752 (1956), and references therein. See also ref 9.

(17) M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968); M. Chérest, H. Felkin, and C. Frajerman, *ibid.*, 379 (1971); M. Chérest and H. Felkin, *ibid.*, 383 (1971).

(18) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, **84**, 2833 (1962); A. Calvet and J. Levisalles, *Tetrahedron Lett.*, 2157 (1972); and review: A. V. Kamernitzky and A. A. Akhrem., *Tetrahedron*, **18**, 705 (1962).

(19) S. R. Landor and J. P. Regan, *J. Chem. Soc. C*, 1159 (1967).

syntheses.[5] We have also found that congestion correlates well with observed stereospecificities in epoxidation and hydroboration of congested olefins[20] and expect that it will be applicable to other stereoselective reactions and perhaps to steric hindrance of ionization,[21] and structure–activity correlations.[22]

(20) W. T. Wipke, T. F. Brownscombe, and P. Gund, in preparation.
(21) H. C. Brown, ref 2, p 181.
(22) C. Hansch, *J. Med. Chem.*, **13**, 964 (1970).

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Synthesis of Bimetallocarboranes by Thermal Metal Transfer

Sir:

In the course of our investigation of the thermal rearrangements of metallocarboranes,[1,2] we have discovered a new preparative route to bimetallocarboranes of the formula $(C_5H_5)_2Co_2C_2B_8H_{10}$ based upon thermally induced intermolecular metal transfer (eq 1).

$$C_5H_5CoC_2B_8H_{10} \xrightarrow{\Delta} (C_5H_5)_2Co_2C_2B_8H_{10} \qquad (1)$$

(six isomers)
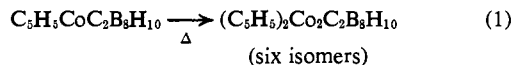
More surprisingly, similar products were obtained upon pyrolysis of the cobalticinium salt of the related commo metallocarborane, $[(C_5H_5)_2Co]^+[Co(C_2B_8H_{10})_2]^-$ (eq 2).

$$[(C_5H_5)_2Co]^+[Co(C_2B_8H_{10})_2]^- \xrightarrow{\Delta} (C_5H_5)_2Co_2C_2B_8H_{10} \qquad (2)$$

(five isomers)
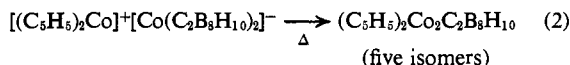
This discovery provides a new, experimentally convenient route to icosahedral bimetallocarboranes.

Rearrangement of $1\text{-}(\eta\text{-}C_5H_5)\text{-}1\text{-}Co\text{-}2,4\text{-}C_2B_8H_{10}^{3,4}$ to $1\text{-}(\eta\text{-}C_5H_5)\text{-}1\text{-}Co\text{-}2,3\text{-}C_2B_8H_{10}^5$ occurs at 350° under high vacuum in a hot tube[1] or at 145° in solution. Attempts to further rearrange $1\text{-}(\eta\text{-}C_5H_5)\text{-}1\text{-}Co\text{-}2,3\text{-}C_2\text{-}B_8H_{10}$ at 525° in a hot tube containing ceramic saddles resulted in an orange sublimate containing a mixture of products. Several species with mass spectral cutoffs at m/e 370 corresponding to the $^{11}B_8{}^{12}C_{12}{}^1H_{20}{}^{59}Co_2{}^+$ ion and isotopic distributions consistent with the formula $(C_5H_5)_2Co_2C_2B_8H_{10}$ were isolated. Increased yields resulted when the reaction was carried out in solution. After heating $1\text{-}(\eta\text{-}C_5H_5)\text{-}1\text{-}Co\text{-}2,3\text{-}C_2B_8H_{10}$ for 7 hr at 235° in hexadecane, five new red isomers and a green isomer of $(C_5H_5)_2Co_2C_2B_8H_{10}$ were produced in a total yield of 32% based on starting material consumed. Column and preparative thick-layer chromatography were used to purify the isomers which eluted in the order I–VI.[6] Three isomers were characterized by elemental analysis, while the formulas of the other

(1) M. K. Kaloustian, R. J. Wiersema, and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **94**, 6679 (1972).
(2) D. F. Dustin, W. J. Evans, C. J. Jones, R. J. Wiersema, H. Gong, S. Chan, and M. F. Hawthorne, manuscript in preparation.
(3) C. J. Jones, J. N. Francis, and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **94**, 8391 (1972).
(4) Formulas are numbered according to the guidelines outlined in R. M. Adams, *Pure Appl. Chem.*, **30**, 683 (1972).
(5) W. J. Evans, G. B. Dunks, and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **95**, 4565 (1973).
(6) Melting points (deg): I, 132–135°; II, 225–227°; III, >310°; IV, 255–258°; V, 239–240°; VI (green), 275–277°.
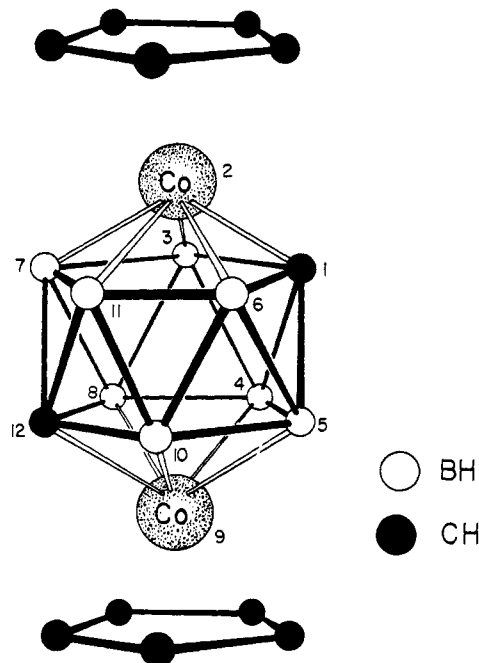

Figure 1. The structure of $2,9\text{-}(\eta\text{-}C_5H_5)_2\text{-}2,9\text{-}Co_2\text{-}1,12\text{-}C_2B_8H_{10}$.

Table I. 60-MHz ^{1}H and 80.5-MHz ^{11}B Nmr Spectra

Compound[a]	^{1}H C_5H_5, τ	^{11}B[b] chemical shift (rel intensity)
I	4.78, 4.96	−15.9 (2), −6.0 (1), −2.6 (1), +3.0 (1), +5.4 (1), +8.1 (1), +20.1 (1)
II	4.49, 4.92	−21.0 (2), −15.2 (1), −7.2 (1), −3.1 (2), +13.9 (2)
III	4.44	−1.4 (1), +6.4 (1)
IV	4.46, 4.98	−15.5 (1), −6.9 (1), +0.6 (1), +5.0 (1), +5.8 (1), +9.9 (1), +17.1 (1), +20.5 (1)
V	4.48, 4.71	−14.0 (1), −9.5 (1), −4.0 (1), −1.0 (1), +1.6 (1), +2.8 (1), +11.5 (1), +15.9 (1)
VI	4.08	−4.7 (1), +4.3 (2), +13.3 (1)

[a] In acetone-d_6. [b] Ppm *vs.* $BF_3 \cdot O(C_2H_5)_2$; all signals doublets with $J_{B-H} = 140 \pm 20$ Hz.

three were confirmed by exact mass measurement.[7] The ^{11}B nmr spectra and cyclopentadienyl proton resonances are listed in Table I.

The synthesis of I–V was also accomplished by heating $[(\eta\text{-}C_5H_5)_2Co]^+[1,1'\text{-}Co\text{-}(2,3\text{-}C_2B_8H_{10})_2]^-$ [5] interspersed on ceramic saddles at 525° under high vacuum or by heating in hexadecane at 270°. Comparable yields were obtained from both neutral and ionic substrates. Higher molecular weight products including species believed to be alkylated bimetallics (based on mass spectral and electrochemical data) were also produced using the hexadecane method but not examined further.

Of the six isomers, the structure of III is specified uniquely by the nmr data as $2,9\text{-}(\eta\text{-}C_5H_5)_2\text{-}2,9\text{-}Co_2\text{-}1,12\text{-}C_2B_8H_{10}$ (Figure 1). This is the first example of an icosahedral metallocarborane containing metal atoms in the "para" positions.

Compound VI has been previously reported as a

(7) For example, Calcd for $(C_5H_5)_2Co_2C_2B_8H_{10}$: C, 39.10; H, 5.47; B, 23.46; Co, 31.97. Found: C, 39.40; H, 5.56; B, 22.42; Co, 31.54. Calcd m/e 370.0973. Found 370.0978 ± 0.0007.