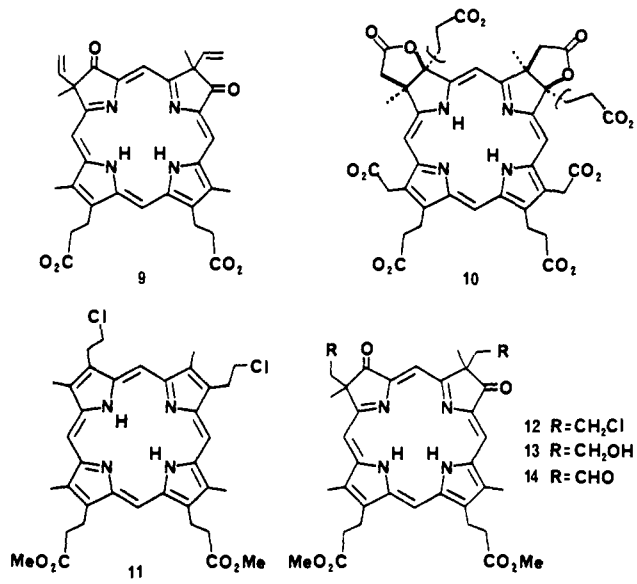
southern diols could be reduced by $HOAc/HI/H_3PO_2$ and converted[16] quantitatively back to **3**, together with recovered **3** (40%), for recycling. The yield of **4** was about 6% from **3** each time.

Porphyrinone **4** was metalated with zinc(II) acetate in $CHCl_3$/MeOH and the zinc complex[12] was oxidized with OsO_4. Following zinc removal by HCl washing, the desired diol **6** was isolated by chromatography (18% yield), with byproducts being the ring C (15%) and ring D diols (12%). We reported earlier[12] that analogous zinc(II) porphyrinones substituted with electron-rich alkyl groups exhibit a differentiation during osmate formation favoring ring B but against ring D attack; in addition, the ring C diol would not form at all. In the present case, the electronegative acetate side chain apparently has rendered the ring B attack less favorable, thereby overiding the empirical rule observed with other compounds. The presence of the acetate substituent further hindered the second pinacolic rearrangement at ring B so that the yield of **7** was a disappointing 12% under the best conditions tested.[15] In contrast, the same reaction sequence applied to the zinc complex of **5** produced overall nearly 10% yield of **8**.

The diastereomeric mixture of **7** was separated on silica gel TLC plates. The isolated cis and trans isomers each were converted by OsO_4 into a ring C diol which was then heated in benzene in the presence of HCl[8,17] to obtain the acrylate **1**. TLC and HPLC confirmed that the slower eluting, presumably cis isomer is indeed identical with the natural d_1 tetramethyl ester. The ^1H NMR of the two isomers showed recognizable differences and only the spectrum of the cis compound is in every respect identical with that of the natural pigment.[18] Absorption and mass spectra further confirmed fully what we considered to be the correct structure of d_1. Future work on resolving the racemic mixture should aid in elucidating the natural molecule's absolute configuration.

The unprecedented structure of dioneheme poses many questions. Is there a functional role of the oxo groups at the isobacteriochlorin ring? How is this structure produced biosynthetically? To the former question we have observed that the relatively positive redox potentials[19] of porphyrinone and porphyrindione distinguish them from chlorin-based heme d[20] or isobacteriochlorin-based siroheme[21] and render these keto macrocycles perhaps more like porphyrin "quinones", which may be of consequence in nitrite binding and reduction.[8] To speculate on the second question, we previously suggested pinacolic rearrangements may have been involved in the biosynthesis.[7] However, in view of the difficulties experienced in the rearrangement of porphyrin acetates,[15] a porphyrin precursor such as **3** seems less plausible. An alternative precursor could be protoporphyrin or its derivative from which a dione structure (**9**) may undergo side-chain oxidation to furnish the acetate substituents. This approach has actually been tried in one of our unsuccessful attempts to synthesize **1**. The vinyl porphyrin in the masked form of chloroethyl porphyrin **11** was processed via exactly the same steps as described above, only with much better yields, to give **12**. Substitution of the Cl by NaOH and oxidation of the diol **13** by the Swern[22] method afforded the dialdehyde **14**. Unfortunately the macrocycle did not survive the oxidants necessary for converting -CHO into $-CO_2$. This route would have been a success if milder conditions could be found. Biosynthesis without invoking



pinacolic rearrangement is also possible. Indeed, the stereochemistry and side-chain substitution patterns suggest that sirohydrochlorin or corriphyrin-4 (**10**)[23] could be the progenitor if suitable avenues exist for cleaving the two northern propionate side chains. While we are presently short of answers to these questions, it can be predicted that the striking structural features uncovered here will not fail to draw attention and to stimulate further research on this green heme.

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(16) (a) Fischer, H.; Eckoldt, H. *Justus Libigs Ann. Chem.* **1940**, *544*, 159. (b) Chang, C. K.; Sotiriou, C. *J. Org. Chem.* **1985**, *50*, 4989.
(17) Chang, C. K.; Sotiriou, C. *J. Org. Chem.* **1987**, *52*, 926.
(18) Measured at 250 MHz in $CDCl_3$ with a standard concentration of 3 mM. Prominent differences are in the α,β-meso protons (cis 8.418 (trans 8.363), 8.266 ppm (8.204)), ring B methyl (1.776 ppm (1.735)), and the acetate methyls (3.127 (3.217), 3.176 ppm (3.209)). All chemical shifts of the synthetic cis compound fall within ±0.007 ppm of the published data of Timkovich's d_1.[6,9a] Assignments were based on NOE connectivities.
(19) Chang, C. K.; Barkigia, K. M.; Hanson, L. K.; Fajer, J. *J. Am. Chem. Soc.* **1986**, *108*, 1352.
(20) Vavra, M. R.; Timkovich, R.; Yap, F.; Gennis, R. B. *Arch. Biochem. Biophys.* **1986**, *250*, 461.
(21) Chang, C. K. In *The Biological Chemistry of Iron, NATO ASI Series* Dunford, H., Ed.: D. Reidel: Dordrecht, 1982; pp 313-334.
(22) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *23*, 4148.
(23) (a) Battersby, A. R.; McDonald, E. *Bioorg. Chem.* **1978**, *7*, 161. (b) Scott, A. I.; Irwin, A. J.; Siegel, L. M.; Shoolery, J. N. *J. Am. Chem. Soc.* **1978**, *100*, 7987.

Stochastic Exploration of Molecular Mechanics Energy Surfaces. Hunting for the Global Minimum

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The use of molecular mechanics has increased in recent years as organic chemists continue to focus on important questions of stereochemistry.[1] In dealing with flexible molecules of any size or complexity, a major difficulty arises which may be described as the *local* vs. *global* minimum problem. If one enters a trial structure using any standard molecular mechanics program, optimization occurs to refine the starting structure toward one of lower steric energy, converging when a minimum energy structure is obtained. But how can one know the structure obtained is the *best* structure using that force field?

In small molecules, there are few conformations, and we can predict which are most stable. However, adding substituents or additional atoms to rings or chains rapidly takes us to situations where in the words of Allinger,[1] "The number of conformations becomes so large that a complete analysis becomes very laborious. The results depend not so much on the force-field as on the intuition of the person doing the calculation and which starting geometries were used for the energy minimizations".

(1) Burkert, O.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

0002-7863/87/1509-3150$01.50/0

In attempting to find all of the conformations (and therefore also the lowest energy conformation—the global minimum), computer programs have been written which systematically step through different values of a dihedral angle in the starting structure.[2-4] While this works for systems which are small enough, with increasing complexity, one can miss the best structure because the step size is too large or because the initial structures for some angles refine to minima which are not "global minimum" even for this dihedral angle.

One can improve the odds of finding the global minimum by stepping through all combination of values *several* dihedral angles. However, one must decide which dihedral angles to vary and by what steps. Too few angles or steps which are too large rapidly increase the chances of missing the best structure. An undesirable feature of this approach is that it must be skillfully customized for each structure examined.

"Walking" along the softest mode or modes is an attractive idea for going from one minimum to another, but, in general, this will not find all the minima. One might consider pseudorotation. For example, boat cyclohexane would go to twist-boat and then to another boat, etc., without the chair ever being found.

An automatic procedure which efficiently locates *all* of the readily accessible conformations (and therefore also the global minimum) is highly desirable. I describe here a new method which (potentially) can accomplish this through a stochastic (Monte Carlo like) approach. The incorporation of randomness has been useful in many areas of science. The Monte Carlo technique has been used[5] to accelerate the approach to Boltzmann equilibrium in proteins, but these authors did not seek all the low-energy conformations.

One might well be dismayed at the idea of a random method to attack this problem. If one chose even a few values for each of the $3N-6$ coordinates in the hyperspace of molecular structures, one finds an intimidating number of points even for a small molecule. Locating the (relatively few) important minima in this hyperspace seems impossible. However, two factors can be applied to make a stochastic method practical. First, one can start from a reasonable structure; therefore one is near a local minimum. Second, using any molecular mechanics program one can (fairly rapidly) improve an initial trial structure, obtaining a local minimum.

The new method, presented here, for attacking this problem is simple. One begins with a trial structure and refines it to a local minimum. One than applies a random "kick". One uses a random number generator to compute an independent random increment or decrement to each coordinate of each atom. One must choose points randomly within an hypersphere (not an hypercube) surrounding the starting point in structure space. Then one rerefines the perturbed structure. There are two possible results. One can return to the initial conformation, or one can obtain another conformation. One must remember all of the different (minimum energy) conformations previously found in order to be able to recognize a new one. This is conveniently done by computing the nonbonded interatomic distances and storing all of the different distance matrices. This eliminates the effect of any translation or rotation on comparison of structures.

If one uses small random kicks (a very small hypersphere), one finds no transitions. Increasing the size of the hypersphere leads to transitions to different conformations with low probability. Still larger random kicks increase the probability of conformational transitions. A topological view is useful. We can "color" a map of hyperspace with a color depending on which local minimum any structure will refine to with the particular molecular mechanics we are using. The first transitions begin to appear when we expand our random hypersphere enough to *touch* differently colored regions. As the size of the hypersphere increases, it starts to include more and more volume outside the locally colored region. The probability of transition approaches unity when *most* of the volume lies outside the local region. Still bigger hyperspheres include distant as well as adjacent regions.

A maximum step between 1.5 and 3 Å gives substantial transition probabilities (~50%). One can thus rapidly obtain the set of available conformations. When many trials yield no additional conformations, one can conclude that one has probably found all of the conformations accessible by using a particular size of random hypersphere. The central feature of this new method is that one is *not* randomly exploring structure hyperspace but is stepping, by means of random kicks followed by optimization, from one discrete (local minimum) conformation to another (mainly among ones which are adjacent). One is therefore exploring only a (finite) set of local minima in hyperspace.

It is reasonable (and also confirmed by the results) that one can rapidly obtain all of the different minima known to exist for medium-sized flexible molecules. I have used our recently reported new two-body force field[6] followed by the MM2 force field and optimization method in the above procedure to explore the previously studied cycloheptane,[7] methylcycloheptane,[8] cyclooctane,[9] cyclononane,[10] cyclodecane,[11] cycloundecane,[12] cyclododecane,[13] cyclotridecane,[12] cyclotetradecane, and cyclopentadecane[12] molecules. Beginning with planar starting structures, every previously reported low-energy conformation for each of them was obtained in a short time on a MicroVax II and many more which had not been described.

The best conformation found for cyclopentadecane I is predicted by MM2 to be 2.0 kcal more stable than the previously described structure II ([33333] by using Dale's nomenclature). In addition to all five structures previously described, 20 new conformations were found in the same energy range![12] Over 1000 distinct conformations no more than 12 kcal above the lowest energy conformation were found.

Aside from the observation that one obtains *all* previously reported conformations in all the cases studied, there is another check on the efficiency of this new method. Because of the way the structures are compared, each different conformation is obtained more than once. Therefore, a useful means of discovering whether one has allowed the process to proceed long enough is to see if one has obtained the *required set* of equivalent structures. For example, cycloundecane yielded 22 copies of the best structure in 2 days. (Since this structure has no symmetry, each different starting atom and each direction of progress around the ring are recorded separately.) Out of the possible 22 structures, 21 of the next best structures were obtained, making it seem unlikely that any still better structure was missed entirely.

This new method is not limited to rings. Starting with the extended form of heptane, the program generated conformations with different arrangements of gauche bonds. It was interesting that many conformatins with gauche+ gauche− segments were found. These are usually rejected in considering polymer structure because of nonbonded strain.[14] In most of the g+g− cases found here, one gauche dihedral angle increased to ~95° to relieve nonbonded strain, while the other was normal. In one case, two angles of 80° were found, but this conformation was 0.5 kcal higher. It is interesting that the unsymmetrical g+g− arrangement

(2) Wiberg, K. B.; Boyd, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 8426.
(3) Anet, F. A. L.; Krane, J. *Tetrahedron Lett.* **1973**, 5029.
(4) Anet, F. A. L.; Anet, R. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, A., Cotton, Eds.; Academic: New York, 1975; p 543.
(5) Noguti, T.; Go, N. *Biopolymers* **1985**, *24*, 527.
(6) Saunders, M.; Jarret, R. M. *J. Comput. Chem.* **1986**, *7*, 578.
(7) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7047. (b) Bocian, D. F.; Pickett, H. M.; Rounds, T. C.; Strauss, H. L. *J Am. Chem. Soc.* **1977**, *99*, 6652. (c) Bixson, M.; Lifson, S. *Tetrahedron* **1966**, *23*, 769.
(8) Hendrickson, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 5537.
(9) (a) Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169. (b) Allinger, N. L.; Tribble, M. T.; Miller, W.; Wertz, D. H. *J. Am. Chem .Soc.* **1971**, *93*, 1637. (c) Hendrickson, J. B. *J. Am. Chem. Soc.* **1964**, *86*, 4854. (d) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
(10) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(11) Dunitz, J. D. *Pure Appl. Chem.* **1971**, *25*, 495.
(12) (a) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115, 1130, 1149. (b) Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7810.
(13) (a) Dunitz, J. D.; Shearer, H. M. M. *Proc. Chem. Soc., London* **1958**, 348; (b) **1959**, 268. (c) Dunitz, J. D.; Shearer, H. M. M. *Helv. Chem. Acta* **1960**, *43*, 18.
(14) Abe, A.; Jernigan, R. L.; Flory, P. J. *J. Am. Chem. Soc.* **1966**, *88*, 631.

appears to be very common in the medium rings studied.

Since this method efficiently finds additional conformations from any starting geometry, it should be a valuable adjunct to *any* molecular mechanics program.

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Supplementary Material Available: A table of MM2 energies and dihedral angles for the best 7-15-membered cyclic, saturated hydrocarbons (3 pages). Ordering information is given on any current masthead page.

Convenient Routes to Vicinal Diamines. Coupling of Nitriles or *N*-(Trimethylsilyl)imines Promoted by $NbCl_4(THF)_2$

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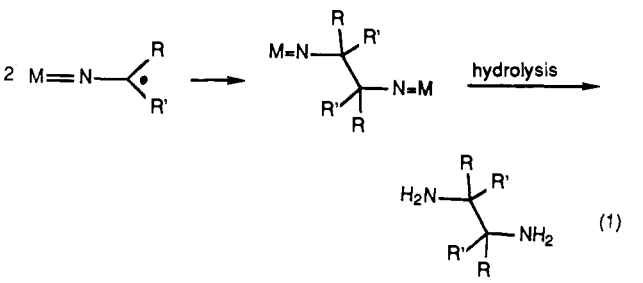
The reductive coupling of aldehydes or ketones leading to vicinal diols or olefins is promoted by a variety of reductants including low-valent early transition metals.[1] Among these, the most widely used are a series of titanium reagents derived from the reduction of titanium(III or IV) chloride.[2] Similar reactions involving carbon-nitrogen functions (e.g., imines) are less common. For example, unlike their carbonyl analogues, *N*-alkyl (or aryl) imines show little or no reactivity with low-valent titanium reagents.[3] This is an unfortunate result in view of the fact that very few general routes to vicinal diamines are known in the literature and the majority of these rely on olefin addition reactions that require several steps to arrive at the desired diamine products.[4] Carbon-carbon bond-forming routes to diamines are especially rare and are typically limited to the synthesis of N,N-disubstituted amines.[5] Herein we report a convenient one-pot synthesis of unsubstituted vicinal diamines from either *N*-(trimethylsilyl)imines or nitriles employing the d^1 niobium reagent, $NbCl_4(THF)_2$.

The approach toward vicinal diamine synthesis presented in this paper originated from considering the resonance structure one can write for a simple d^1 N-metal imine derivative (A and B). When M is an early transition metal, resonance structure

A B

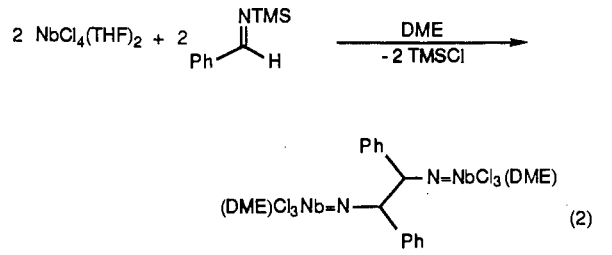
B represents a metal-imido function.[6] Dimerization of this metal-protected α-amino radical would lead to the diimido compound shown in eq 1. Hydrolysis would then give the unsubstituted vicinal diamine. Related to this reaction are examples from low-valent metal alkoxide chemistry where homolytic carbon-oxygen bond cleavage leads to metal-oxo formation and the generation of free radicals.[7]



(1)

To examine this hypothesis we chose the d^1 niobium complex $NbCl_4(THF)_2$ for two reasons, the first of which is related to its availability on large scales (>100 g) from commercially inexpensive niobium pentachloride.[8] The second reason pertains to the well-documented existence of niobium-imido complexes (the proposed product in this reaction).[6]

Reaction of $NbCl_4(THF)_2$ with the trimethylsilyl imine of benzaldehyde in dimethoxyethane (DME) (eq 2) gives a yellow



(2)

crystalline product (60% isolated yield) that has been characterized[9] as the diimido complex shown in eq 2. Hydrolysis of this material with 10% potassium hydroxide provided a quantitative yield of *d,l*-1,2-diphenylethylene-1,2-diamine, confirmed by comparison with an authentic sample.[10] Hydrolysis of the entire reaction mixture (i.e., prior to crystal isolation) afforded a 69% yield of the same diamine as a 19:1 (*d,l*/meso) mixture of diastereomers. Five other examples of *N*-(trimethylsilyl)imines that have been coupled are shown in Table I.

A limiting feature of this reaction is the lack of general methods available for synthesizing *N*-(trimethylsilyl)imines. Those in Table I were prepared by the addition of $LiN(SiMe_3)_2$ to the appropriate aldehyde followed by quenching with trimethylsilyl chloride and distillation.[11] This method is limited to nonenolizable aldehydes or ketones.

The generation of niobium imines directly from nitrile insertion into a niobium(IV) hydride would provide a practical route to diamines (eq 3). Such insertion reactions have been reported

(3)

for a few well-characterized early-transition-metal hydrides.[12] The absence of any simple d^1 niobium halo hydrides[13] in the literature

(1) For reviews, see: (a) Block, E. *Org. React.* **1984**, *30*, 457. (b) Lai, Y. H. *Org. Prep. Procd. Int.* **1980**, *112*, 361. (c) Ho, T. L. *Synthesis* **1979**, 1.

(2) (a) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (c) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

(3) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.

(4) (a) Jung, S. H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931. (b) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *Ibid.* **1984**, *106*, 7867. (c) Jung, S. H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399. (d) Gideon, L. F.; Pradip, P. *J. Org. Chem.* **1984**, *49*, 1314. (e) Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787. (f) Sharpless, K. B.; Singer, S. P. *J. Org. Chem.* **1976**, *41*, 2504.

(5) Imwinkelried, R.; Seebach, D. *Helv. Chem. Acta* **1984**, *67*, 1496.

(6) For a review of transition metal-imido chemistry, see: Nugent, W. A.; Haymore, B. A. *Coord. Chem. Rev.* **1980**, *31*, 123.

(7) (a) van Tamelen, E. E.; Akemark, B.; Sharpless, K. B. *J. Am. Chem. Soc.* **1969**, *91*, 1552. (b) Sharpless, K. B.; Hanzlik, R. P.; van Tamelen, E. E. *Ibid.* **1968**, *90*, 209. (c) van Tamelen, E. E.; Schwartz, M. *Ibid.* **1965**, *87*, 3277.

(8) Manzer, L. E. *Inorg. Chem.* **1977**, *16*, 525. For a more convenient synthesis of $NbCl_4(THF)_2$, see the supplementary material.

(9) ^1H NMR (CD_2Cl_2) δ 3.57 (s, 3 H), 3.95 (s, 3 H), 4.08 (s, 4 H), 6.49 (s, 1 H), 7.20 (m, 5 H). Anal. Calcd for $Nb_2C_{22}H_{32}Cl_6N_2O_4$: C, 33.57; H, 4.39; N, 3.56. Found: C, 33.33; H, 4.14; N, 3.52.

(10) Hawn, G. G.; Chang, C. A.; Douglas, B. E. *Inorg. Chem.* **1979**, *18*, 1266.

(11) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, *9*, 539.

(12) For example, see: (a) Churchill, M. R.; Wasserman, H. J.; Belmonte, P. A.; Schrock, R. R. *Organometallics* **1982**, *1*, 559. (b) Bercaw, J. E.; Davies, D. L.; Wolczanski, P. T. *Organometallics* **1986**, *5*, 443 and references therein.

(13) $Nb_2Cl_6H_2(PMe_3)_4$ has been mentioned but no details have been reported: Sattelberger, A. P.; Wilson, R. B., Jr.; Huffman, J. C. *Inorg. Chem.* **1982**, *21*, 4179.

0002-7863/87/1509-3152$01.50/0