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How quickly do knotty molecules lose their energy as they grow?

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ABSTRACT: The results of UFF and AM1 calculations for C_NH_{2N} hydrocarbon trefoil knots are reported for the range of N from 12 to 59 and used to discuss stabilities of knots and size-dependent trends in their structural parameters. Other types of molecular knots, including figure-eight and five-crossing knots, were identified on MM3 and UFF potential energy surfaces of $C_{30}H_{60}$ and $C_{50}H_{100}$. A simple tubular model of molecular knots is discussed and used to identify the minimum size of a knot that has no excess energy due to its topology. Predictions of the tubular model are consistent with UFF and AM1 results. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: molecular knot; ideal knot; knot energy; MM3; UFF; AM1

MATHEMATICAL AND PHYSICAL KNOTS

Mathematically, non-trivial knots are defined as closed curves in three-dimensional space that cannot be transformed into a circle by a continuous deformation avoiding self-crossing. Any two knots that can be transformed into each other by such continuous deformation are considered equivalent. Closed curves equivalent to a circle are referred to as trivial knots or *unknots*. A non-closed curve, even entangled, does not form a knot since it can be transformed into a line segment by a continuous deformation avoiding self-crossings. However, if the opposite ends of such a curve are linked, it forms a knot. Therefore, these curves are often referred to as *pseudoknots*.

Graphically, knots are represented by their planar projections and can be classified by the minimum number of crossings present in these projections. Examples of knots with zero to five crossings are shown in Fig. 1 and include an unknot (0 crossings), a trefoil knot (three crossings), a figure-eight knot (four crossings) and a star knot (five crossings). Starting from five-crossing knots, there are more than two non-equivalent knots with the same number of crossings. They are labeled by the number of crossings and randomly assigned subscripts as 5_1, 5_2, 6_1, 6_2, 6_3, 7_1, etc.[1]

In addition to their topological characteristics, knots as physical objects must possess metric and other properties such as size, volume, geometric configuration, energy and entropy. A simple model describes a knot as a longitudinally elastic and transversely incompressible cylindrical closed tube of length L and diameter D. If the L/D ratio is large, the tube shrinks and thus reduces the size of a knot (Fig. 2). A tubular knot with the lowest L/D ratio is called an ideal knot.[2] The L/D ratios for these knots have been reported previously.[3] Their average values for knots with a given number of crossings are listed in Table 1. Naturally, these values increase with the complexity of knots. It is interesting, however, that this dependence is practically linear in the number of crossings, n:

$$L/D_{\text{ave}} = 3.86n + 5.11 \quad (\text{correlation coefficient } R^2 = 0.999) \tag{1}$$

The implication of this result is that every additional crossing requires an extra loop of constant length $L = 3.86D$.

MOLECULAR KNOTS

Long-chain molecules, such as DNA or polymers, can easily form knots.[4–6] Liang and Mislow[7] discovered knots in proteins (see also Ref. 8). All of these molecules, however, possess a very high molecular mass. A successful synthesis by Dietrich-Buchecker and Sauvage[9,10] of a molecular knot with a substantially lower molecular mass (see Fig. 3) opened up the field for subsequent work in that area.[11–15]

Although substantially smaller, these molecules are still relatively large, sufficiently large to avoid energy

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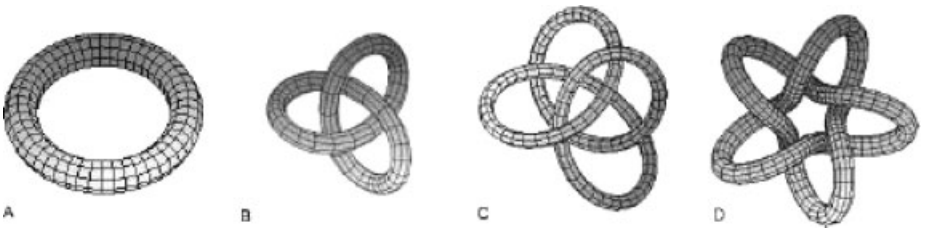


Figure 1. Examples of knots: (A) unknot (no crossings); (B) trefoil knot 3_1 (three crossings); (C) figure-eight knot 4_1 (four crossings); (D) star knot 5_1 (five crossings)

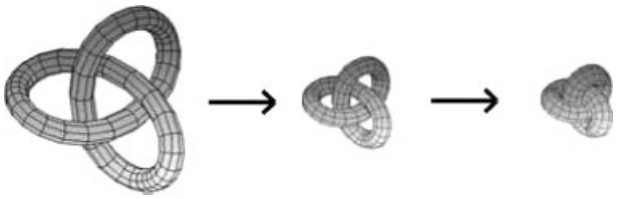


Figure 2. Tightening of a trefoil knot. The rightmost figure represents an ideal trefoil knot

Table 1. Average values of *L/D* ratios for knots with 3–9 crossings (obtained from the results reported in Ref. 3)

No. of crossings	L/D_{ave}
3	16.33
4	20.99
5	24.12
6	28.55
7	32.24
8	35.82
9	39.74

penalty for the presence of a knot. This raises a legitimate question: How big should a molecule be to be able to sustain a knot? Wasserman[19] posed this question more than 40 years ago and found, using scale models, that the smallest hydrocarbon trefoil knot C_kH_{2k} should contain at least 50 carbon atoms, and that the smallest figure-eight knot should contain at least 74 carbon atoms. A tubular model, similar to that described in the preceding section, can be used to answer Wasserman's question for a variety of knots.

TUBULAR MODEL OF MOLECULAR KNOTS

We approximate a C_NH_{2N} hydrocarbon chain as a tube of diameter D and length L. Since the chain has a zigzag shape, the length of the knot L is not equal to the sum of the lengths of the C—C bonds. If the average C—C bond length is l and the average C—C—C bond angle is θ, the length of an N-unit knot can be estimated as

$$L = Nl\sin(\theta/2) \tag{2}$$

The tube diameter D could be approximated by the van der Waals diameter of a carbon atom, D_W, plus an additional increment due to the shape of the chain:

$$D = D_W + l\cos(\theta/2) \tag{3}$$

Combination of Eqns (1), (2) and (3) gives the following relationship between the minimum size of the knotted closed chain N and the number of crossings n:

$$\begin{aligned} N &= \frac{D_W + l\cos(\theta/2)}{l\sin(\theta/2)}(L/D) \\ &= \frac{D_W + l\cos(\theta/2)}{l\sin(\theta/2)}(3.86n + 5.11) \end{aligned} \tag{4}$$

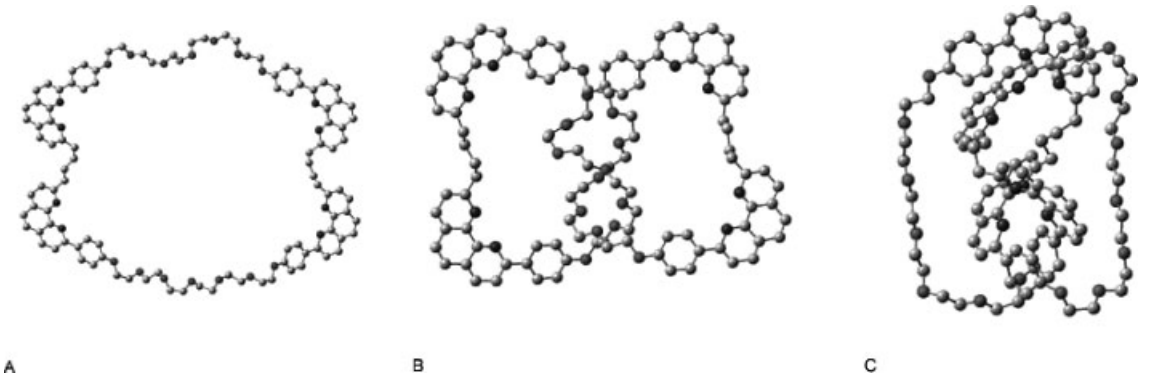


Figure 3. Two UFF-optimized conformations (B and C) of the molecular trefoil knot synthesized by Dietrich-Buchecker and Sauvage[9,10] and a topologically isomeric unknot (A). Here and in later figures, UFF[16] and AM1[17] calculations were performed using Gaussian 98[18]

If one assumes that $D_W = 3.6$ Å[20] and that $l = 1.53$ Å and $\theta = 111°$ (estimated as an average for the bonds and angles involving only secondary carbon atoms of decane), Eqn (4) predicts that $N = 59$ for a trefoil knot ($n = 3$) and $N = 73$ for a figure-eight knot ($n = 4$), in reasonably good agreement with Wasserman's estimates.[19] For a five-crossing knot, the expected value of N is 86.

HYDROCARBON KNOTS: RANDOM SEARCH

An important difference between the tubular model of in the first section and that suitable for molecular knots is that the tube diameter D can no longer be considered incompressible. Stable knots of sizes smaller than those predicted by Eqn (4) can exist, although their energy is expected to be higher than that of the unknotted rings of the same size. Surprisingly, even a knot as small as $C_{12}H_{24}$ (Fig. 4) has been found as a stable minimum in a random search of the conformational space of cyclododecane.[21] This knot is obviously highly stressed and exists as a stable structure only within the realm of molecular mechanics methods where molecular topology is relatively rigid owing to the fixed bonding pattern (connectivity) imposed on molecules. No other knots were observed for cyclododecane. However, random search of conformational space of $C_{30}H_{60}$ and $C_{50}H_{100}$ rings (N. Weinberg and K. Mislow, unpublished results) revealed the presence of multiple knots of various types. Examples of these knots are shown in Figs 5 and 6.

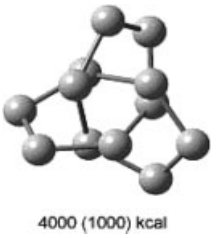


Figure 4. $C_{12}H_{24}$ trefoil knot[21] (hydrogen atoms are not shown for clarity). The numbers represent approximate UFF and MM3 (in parentheses) energies,[16–18,22] relative to the unknot

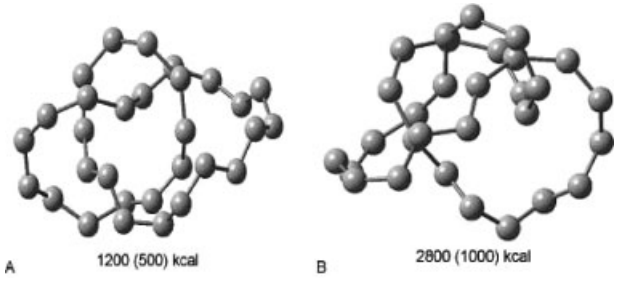


Figure 5. $C_{30}H_{60}$ knots (N. Weinberg and K. Mislow, unpublished results) (hydrogen atoms are not shown for clarity): (A) trefoil knot; (B) figure-eight knot. The numbers represent approximate UFF and MM3 (in parentheses) energies,[16–18,22] relative to the unknot

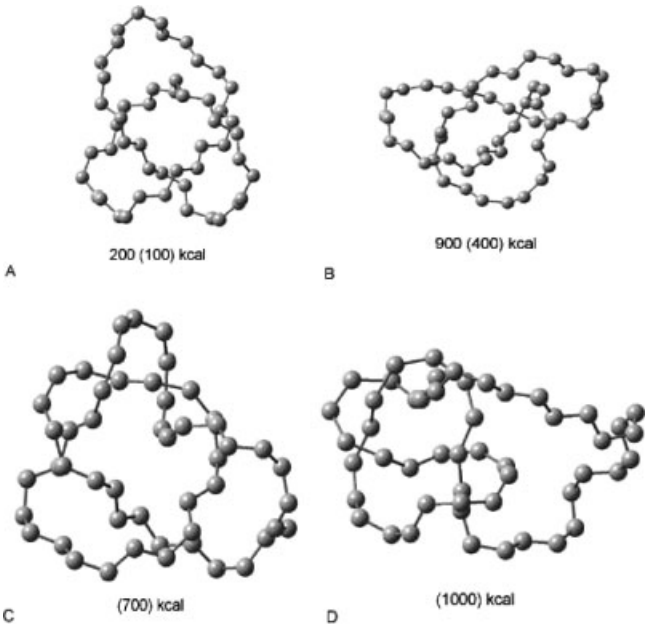


Figure 6. $C_{50}H_{100}$ knots (N. Weinberg and K. Mislow, unpublished results) (hydrogen atoms are not shown for clarity): (A) trefoil knot, (B) figure-eight knot, (C) 5_1 knot, (D) 5_2 knot. The numbers represent approximate UFF and MM3 (in parentheses) energies,[16,24] relative to the unknot. Only MM3 energies are available for the five-crossing knots because the UFF optimization of these structures produced trefoil knots

Predictably, both UFF and MM3 energies decrease rapidly with increasing size of a knot of a given complexity, and increase substantially with increasing complexity of a knot of a given size. In agreement with the prediction of the tubular model, an $N = 50$ size trefoil knot is still somewhat strained compared with the unknot although, on average, the excess energy constitutes only 2–4% of the C—C bond energy per bond, thus signaling that this size is fairly close to the size of the ideal knot.

HYDROCARBON KNOTS: SIZE-DEPENDENT TRENDS

As the next step in our study of hydrocarbon knots, we performed UFF and AM1 calculations of C_NH_{2N} trefoil knots and rings for $N = 12$–59.[16–18] Every size was represented by a single knot produced from a 59-unit knot by deletion of a CH_2 unit and subsequent geometry optimization. The differences ΔE between the energies of optimized knot and unknot systems are shown in Fig. 7. The relative UFF energies ranged from 4000 kcal mol^{-1} for $N = 12$ to -1.4 kcal mol^{-1} for $N = 59$. The relative AM1 energies ranged from 190 kcal mol^{-1} for $N = 43$ to 0.5 kcal mol^{-1} for $N = 59$. In both cases $N = 59$ was the only knot for which the energy difference with the unknotted ring was practically zero, which is consistent with the prediction of the tubular model. None of the

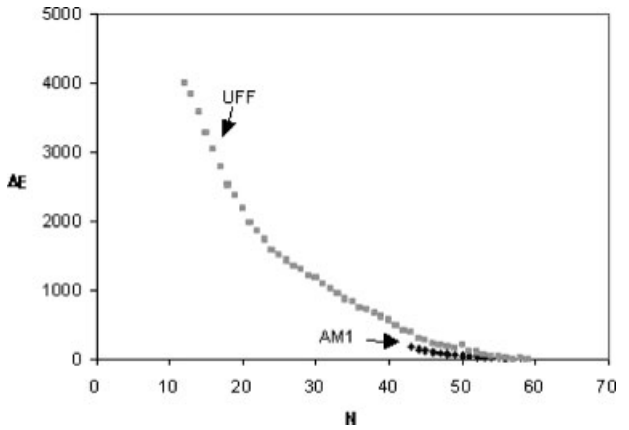


Figure 7. Size dependence of the relative UFF and AM1 energies (kcal mol^{-1}) of C_NH_{2N} trefoil knots (1 kcal = 4.184 kJ)

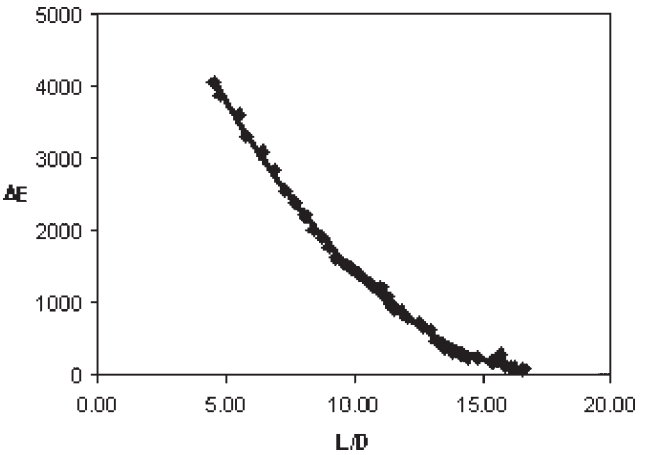


Figure 9. Relative energy ΔE (kcal mol^{-1}) as a function of *L/D* ratio for a series of UFF-minimized C_NH_{2N} trefoil knots (symbols). The solid line is the approximating quadratic polynomial

AM1 structures with $N < 43$ converged to a stable knot. However, this does not imply that AM1 knots smaller than $N = 43$ do not exist, because excess energy of 200 kcal evenly spread over 40 C—C bonds constitutes only 5 kcal mol^{-1} excess per bond and therefore can be tolerated. In our case, the instability of knots is probably caused by unevenness of the energy distribution in the starting structure. A more accurate determination of the lower stability boundary would require a much delicate handling of the probe structures subjected to energy minimization.

The size dependence of the average bond lengths and bond angles is shown in Fig. 8.

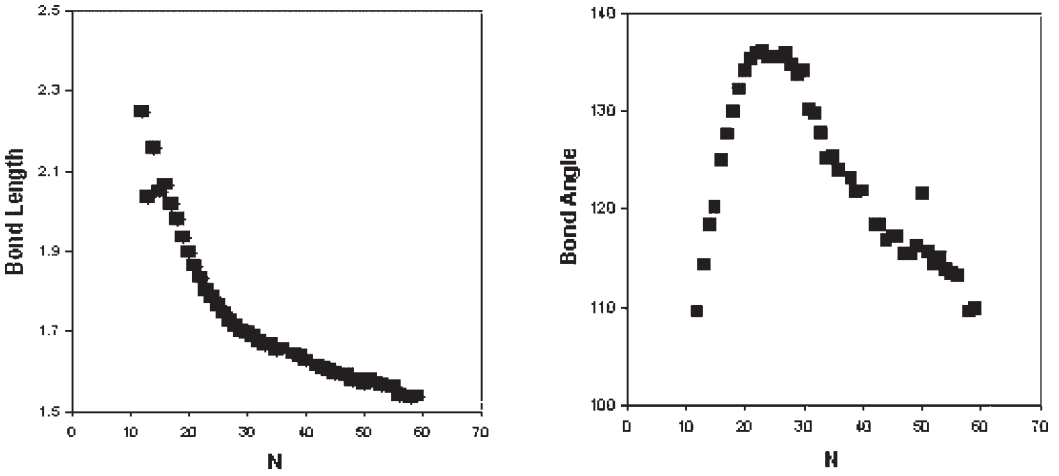
The average bond length demonstrates fairly simple behavior: it is the longest in the smallest knot $C_{12}H_{24}$, reaching 2.25 Å, and then rapidly decreases, reaching 1.54 Å for $N = 59$. The average bond angle demonstrates a more peculiar behavior as it starts at 109.47° for $N = 12$, then quickly reaches 136° for $N = 22$ and stays at approximately that value until $N = 27$, after which drops to 110° for $N = 58$–59.

Equations (2) and (3) can be used to calculate the *L/D* ratio for every size *N* from the average bond length and bond angle. This, combined with the size dependence of relative energy ΔE, allows one to obtain the dependence of ΔE on *L/D* shown in Fig. 9.

Interestingly, the dependence of ΔE on *L/D* is notably simpler than its dependence on *N*. In fact, the quadratic polynomial

$$\Delta E = 22.932(L/D)^2 - 815.51(L/D) + 7293 \qquad (5)$$

approximates it fairly well (correlation coefficient $R^2 = 0.998$). According to Eqn (5), ΔE reaches its



A **B**

Figure 8. Size dependence of the geometric parameters of the UFF-optimized C_NH_{2N} trefoil knots: (A) average C—C bond length (Å); (B) average C—C—C bond angle (degrees)

minimum value of $45\,\text{kcal mol}^{-1}$ at $L/D = 17.78$, which is higher than 16.33 expected for the ideal trefoil knot.[3]

CONCLUSION

The question of the stability of small molecular knots gains further importance with the advancement of synthetic methods. Although the inner cycle of the first synthetic knot (Fig. 3) includes 86 atoms, 48 of them form four rigid fragments, thus leaving only 38 for the flexible parts. Unsurprisingly, the knot in Fig. 3(B) is substantially more stable than that in Fig. 3(C). In addition, due to these rigid fragments, the effective diameter of the molecular 'chain' is substantially greater than that of a polymethylene chain. Therefore, the size of the knot in Fig. 3 should be regarded as much closer to the size of the ideal knot than it might seem at first sight.

It is remarkable that a simple tubular model appears to work so well. Although it is more suitable for the cases of knots without internal stress, the surprisingly simple quadratic dependence in Fig. 9 hints that it might be appropriate to extend this model to cover also highly stressed knots.

Finally, it is interesting that the range of stability of the UFF and MM3 knots extends as far as to cyclododecane. Similar results were recently obtained by Arteca,[23] who analyzed the stability of hydrocarbon pseudoknots $Ph(CH_2)_kPh$ at the MM2 level[24] and concluded that the lower boundary of stability is as low as $k = 10$. The MM2 energies of these pseudoknots were found to be of the order of $1000\,\text{kcal mol}^{-1}$, which is consistent with the $1000\,\text{kcal mol}^{-1}$ MM3 energy of the cyclododecane knot in Fig. 4.

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