The Molecular Conformation of Cyclotri-β-alanyl

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The title compound has been studied by molecular mechanics calculations. There is no single, well defined global minimum energy conformation and the low energy conformations are unrelated to the conformation of the analogous alkene, *trans,trans,trans*-cyclodeca-1,5,9-triene. Electrostatic interactions between the amide groups are shown to be an important conformational determinant in the cyclic tripeptide. Not unexpectedly attempts to characterize a single conformation of cyclo-[β-ala]$_3$ by *X*-ray crystal structure analysis and ^{1}H n.m.r. were unsuccessful.

CYCLOTRI-β-ALANYL (CTBA) is probably the smallest cyclic peptide which can accommodate all *trans*-amide groups without introducing unacceptable Baeyer or Pitzer strain into the ring system. Cyclodi-β-alanyl, which we have previously studied by means of *X*-ray crystal structure analysis,[1] is forced to have *cis*-amide groups in order to effect ring closure and shows a ring conformation similar to that of *cis,cis*-cyclo-octa-1,5-diene.[2,3] This conformational homology between cyclic peptides and the corresponding cyclic alkene has been noted and commented on in a number of cases.[4,5] These observations can be utilized to good effect in the present instance by bearing in mind the results of both the *X*-ray crystal structure analysis [6] and the n.m.r.–molecular mechanics study of *trans,trans,trans*-cyclodeca-1,5,9-triene [7] (CDDT).

The present work describes the synthesis of CTBA and the analysis of its molecular conformation by means of molecular mechanics calculations, *X*-ray crystal structure analysis, and n.m.r.

EXPERIMENTAL

(a) *Crystal Data.*—Cyclotri-β-alanyl, $C_9H_{15}O_3N_3$, M = 213.1, space group R_{32} or R_{3m}, $a = b = c = 8.091(6)$ Å, $\alpha = \beta = \gamma = 116.17(5)°$, $U = 261.9$ Å^3, $Z = 1$, $F(000) = 114$, $D_c = 1.35$ g cm^{-3}, μ(Mo-K_α) = 0.64 cm^{-1}.

(b) *N.m.r.*—The 100 MHz ^{1}H n.m.r. spectrum of cyclotri-β-aminoisovaleryl in $CDCl_3$ is very simple and consists of methyl, methylene, and NH singlets at δ 1.4, 2.5, and 5.6, respectively. This spectrum showed no change between 40 and −60 °C. The methylene protons of CTBA show a symmetrical AA'BB' spectrum in D_2O with $J_{AB} = J_{A'B'} = 4.5$ Hz and $J_{AB'} = J_{A'B} = 7.5$ Hz.

(c) *Synthesis.*—*Benzyloxycarbonyl-β-alanyl-β-alanyl-β-alanine methyl ester.*[8] β-Alanine 2,4,5-trichlorophenyl ester hydrobromide was prepared as follows. Benzyloxycarbonyl-β-alanine 2,4,5-trichlorophenyl ester [9] (32.6 g, 81 mmol) was suspended in glacial acetic acid (20 ml) and hydrogen bromide in glacial acetic acid (50% w/v, 65 ml) added gradually at 0 °C with vigorous stirring. The mixture set to a gel. Dry ether (50 ml) was added and the mixture shaken for 2 h. The excess of hydrogen bromide was removed by water-pump suction and the reaction mixture poured off into dry ether (200 ml) at −15 °C. The salt was filtered off, washed with ether and reprecipitated from methanol solution by the addition of ether, yield 26.6 g (94%), m.p. 182—184 °C (Found: C, 31.0; H, 2.6; N, 4.0. $C_9H_9BrCl_3NO_2$ requires C, 30.9; H, 2.6; N, 4.0%). A solution of benzyloxycarbonyl-β-alanine [10] (558 mg, 2.5 mmol) in acetone (5 ml) was added gradually to a stirred and cooled (−20 °C) solution of isobutyl chloroformate (343 mg, 2.5 mmol) and triethylamine (252 mg, 2.5 mmol) in acetone (5 ml). β-Alanine 2,4,5-trichlorophenyl ester, derived from the hydrobromide (874 mg, 2.5 mmol), in acetone (10 ml) was added immediately. The mixture was stirred at −20 °C for 2 h and left to stand for 5 h at 0 °C and for 3 h at room temperature. The second amino-component, derived from β-alanine methyl ester hydrochloride [11] (350 mg, 2.5 mmol) in acetone (10 ml) was added and the mixture left to stand for two days. The usual separation procedure yielded the crude *tripeptide derivative* (384 mg, 40.5%), m.p. 159—161 °C raised to 172—173 °C (from ethyl acetate–ethanol), R_{FA} 0.50 (Found: C, 57.3; H, 6.7; N, 11.4. $C_{18}H_{25}N_3O_6$ requires C, 57.0; H, 6.6; N, 11.1%). A second crop (58 mg, 6.1%), m.p. 157—162 °C (from ethyl acetate), was isolated by chromatography on silica.

Benzyloxycarbonyl-β-alanyl-β-alanyl-β-alanine.[12] A solution of the foregoing ester (9.5 g, 25 mmol) in aqueous acetone (30%, 75 ml) was cooled to 0 °C and sodium hydroxide (25 ml, 1M) added gradually with stirring. The mixture was stirred for 3 h at room temperature, acidified (2M-hydrochloric acid) to Congo Red, and the precipitated product filtered off. Recrystallization from aqueous acetone (75%) gave the benzyloxycarbonyl-tripeptide (8.7 g, 95.5%), m.p. 186—188 °C raised to 188—190 °C on further recrystallization. (Adams [12] reported m.p. 195 °C.)

β-Alanyl-β-alanyl-β-alanine. The foregoing tripeptide derivative (4 g, 11 mmol) was dissolved in methanol (75 ml) containing glacial acetic acid (3 drops) and hydrogenolysed over 10% palladium on charcoal (500 mg) for 8 h, carbon dioxide having been undetectable in the effluent gas after 5 h. A small quantity of precipitated material was redissolved by the addition of water (*ca.* 20 ml), the mixture filtered, and the filtrate evaporated. The oily residue was crystallized by dissolution in a minimum quantity of aqueous methanol (50%) and dilution with acetone, yielding the tripeptide monohydrate (2.4 g, 87.5%), m.p. 218—222 °C (decomp.), R_{FA} 0.50 (Found: C, 43.5; H, 7.9; N, 17.0. $C_9H_{17}N_3O_4,H_2O$ requires C, 43.4; H, 7.7; N, 16.9%). (Adams [12] and Reid [13] reported the isolation of the hemihydrate which decomposed on heating.)

CTBA via *reaction with o-phenylene phosphorochloridite.*[14] A solution of the tripeptide hydrate (250 mg, 1 mmol) in diethyl phosphite (10 ml) was cooled to 0 °C and *o*-phenylene phosphorochloridite [15] (192 mg, 1.1 mmol) added gradually

with stirring. After 5 min the solution was diluted to 200 ml with diethyl phosphite and triethylamine (202 mg, 2 mmol) added. The mixture was stirred for 1 h at room temperature, then heated under reflux for 15 min. The crude product (110 mg, 51.6%), m.p. >300 °C (decomp.), R_{FA} 0.66 and 0.50, precipitated when the mixture was cooled, and was filtered off. A sample (10 mg) was sublimed (250° and 10^{-2} mmHg) yielding the crystalline cyclic tripeptide [16,17] (5.5 mg), m.p. >310 °C decomp., R_{FA} 0.50 (Found: C, 50.4; H, 6.8; N, 19.5%; $M^{+\bullet}$, 189. $[C_3H_5NO]_n$ requires C, 50.7; H, 7.1; N, 19.7%; $M^{+\bullet}$, 189).

M.p.s were recorded on a Gallenkamp apparatus. Solvents were purified by literature methods,[18] excepting that commercial diethyl phosphite was distilled at reduced pressure and the fraction used had b.p. 48—50 °C at 2.0 mmHg, n_D^{20} 1.4100.[19] Mass spectra were obtained with 70 eV on an AEI MS-902, the sample being introduced at 225 °C. In general neutral products were isolated by washing in ethyl acetate with 1M-hydrochloric acid (3 portions), 5% sodium hydrogencarbonate solution (3 portions), and then water to neutrality. Organic extracts were dried with ($MgSO_4$), and evaporations were carried out under reduced pressure on a rotary evaporator. T.l.c. on Kieselgel employed the following system (v/v): (A) ethanol–water–0.88 ammonia (8 : 1 : 1).

RESULTS AND DISCUSSION

A series of conformations of CTBA may be generated from that of Figure 1 by permutations and combinations of the S and A group rotation operations shown in Figure 2 where the $-CH_2-CH_2-$ and/or amide groups are

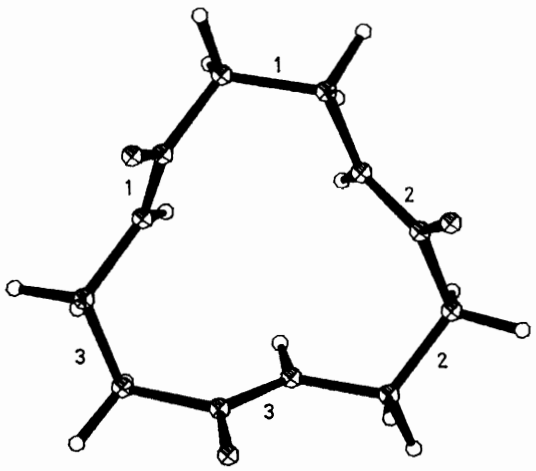

FIGURE 1 The unflipped (00) conformation of CTBA showing the numbering of the amide and $-CH_2-CH_2-$ groups which apply in the text and Figure 3

' flipped ' by one or two bond rotations, respectively. In this way it is possible to generate 64 conformations composed of 32 pairs of enantiomers. However, only 12 conformations out of these 32 are unique. This contrasts with the 10 conformations derived by Anet and Rawdah [7] from a similar analysis of CDDT, where the smaller number is a simple consequence of the higher symmetry of the base conformation (D_3 as opposed to C_3). The conformations are described by an octal-encoded binary number in a similar fashion to the scheme devised by Anet and Rawdah.[7] The binary number [000 000] describes the conformation of Figure 1 where the three most significant binary digits code for the ' flipped ' state of the amide groups 1—3, and the most significant digit describes the state of amide group 1 (1 ' flipped ', 0 as Figure 1) whilst the least significant

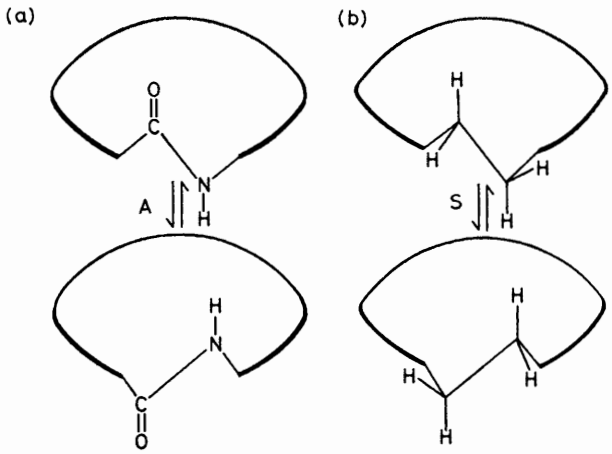

FIGURE 2 (a) Schematic representation of the amide flip (A) process and (b) the $-CH_2-CH_2-$ (S) flip process

describes that of amide group 3. The three least significant binary digits describe the ' flipped ' state of $-CH_2-CH_2-$ fragments 1—3 in an identical manner. This notation is rendered more concise by the encoding of the six digit binary descriptor into a two digit octal descriptor where the most significant digit describes the ' flipped ' state of the amide groups and the least significant that of the $-CH_2-CH_2-$ fragments. Where a number of equivalent conformations are possible subsequent references are to the one with the numerically smallest octal descriptor.

It should be noted that combinatorial application of A and S processes does not generate all possible local energy minima of CTBA, nor does a similar application of D and S processes locate all local energy minima for CDDT although Anet and Rawdah [7] did not discuss this point. Thus far it has been assumed that A and S or D and S operations involve an exact ' flip ' of the affected group; in fact it is possible to generate main and subsidiary energy minima by non-180° rotations of the amide groups and/or non-exact inversion of the $N-C_\beta-C_\alpha-C'$ torsion angles. Indeed it was sometimes possible, particularly in the case of amide group rotation, to locate three minima fairly close together in conformational space. Fortunately these calculations were performed on a dedicated minicomputer with high performance refreshed graphics facilities (Megatek MGS-7000) and it was a straightforward task to locate the lowest energy local minimum in cases of ambiguity.

The results of the molecular mechanics calculations,[20] performed with a previously described program [21] and force-field,[22] are shown in Table 1.

TABLE 1

The steric energies (V_s) and their various components, V_l bond stretching, V_θ angle bending, V_τ torsional, V_v van der Waals, V_o, out-of-plane bonding, and V_q coulombic potential energies ($V_s = V_l + V_\theta + V_\tau + V_v + V_q$/kcal mol^{-1})

Conformation	V_l	V_θ	V_τ	V_v	V_o	V_q	V_s	$V_s - V_q$
00	0.0892	0.3655	1.7204	−3.3593	0.0166	1.7320	0.56	−1.17
01	0.1036	0.4325	3.1262	−4.2353	0.0064	1.4342	0.87	−0.56
03	0.1325	0.8219	3.4562	−4.1128	0.0107	1.0721	1.38	0.31
07	0.1563	0.6029	4.1569	−4.1461	0.0047	0.9581	1.73	0.77
10	0.0935	0.6984	2.9151	−3.9265	0.0308	−0.8854	−1.07	−0.18
11	0.1068	0.5426	3.8274	−3.7877	0.0457	−1.2855	−0.55	0.74
12	0.1166	0.6426	3.4772	−4.1911	0.0200	−1.4605	−1.39	0.08
13	0.1104	0.6550	5.1448	−4.1170	0.0278	−1.7157	0.11	1.83
14	0.0823	0.5523	2.8168	−4.2674	0.0431	−0.4842	−1.26	−0.78
15	0.0952	0.7939	3.3202	−3.6713	0.0889	−0.8991	−0.27	0.63
16	0.1124	0.5896	2.3770	−4.3303	0.0174	−0.9249	−2.16	−1.24
30	0.1140	0.5673	3.2074	−4.1320	0.0419	−1.2963	−1.50	−0.20

The functional form of the force field included terms for bond stretching, angle bending, bond torsion, van der Waals interactions, coulombic interactions, and out-of-plane bending [equation (1) where l, θ, ω, and r are bond lengths, angles, torsion angles, and 1, 4 and higher

$$V_s = \sum_l \tfrac{1}{2}k_l(l_o - l)^2 + \sum_\theta \tfrac{1}{2}k_\theta(\Delta\theta^2 - k_\theta'\Delta\theta^3) + \sum_\omega \tfrac{1}{2}k_\omega(1 + s\cos n\omega) + \sum_r \varepsilon\{-2\alpha^{-6} + \exp 12(1 - \alpha)\} + \sum_q q_i q_j/D_r + \sum_\delta \tfrac{1}{2}k_\delta(\pi - \delta)^2 \quad (1)$$

$$\Delta\theta = \theta_o - \theta \quad (2)$$

$$\alpha = r/r_o \quad (3)$$

interatomic distances respectively and the corresponding subscripted symbols refer to the reference values]. k_l, k_θ and k_δ are the force constants for bond stretching, angle bending, and out-of-plane bending; ε is a constant with units of energy and k_ω is the barrier to free rotation with periodicity n and $s = 1$ or -1 for a staggered or eclipsed minimum respectively. q_i and q_j are partial atomic charges, D is the dielectric constant, and δ is an improper torsion angle defining out-of-plane bending. The van der Waals and coulombic potentials are scaled so as to obviate the need for a separate hydrogen bond potential. V_s is the steric energy. Energy minimization was accomplished by the iterative Newton–Raphson procedure [equation (4) where x^n and x^t are

$$x_i^n = x_i^t - F_{ij}^+\nabla V_s(x) \quad (4)$$

the new and trial vectors of cartesian atomic co-ordinates, F_{ij}^+ is the generalized inverse of the Hessian matrix $\partial^2 V_s/\partial x_i \partial x_j$, and $\nabla V_s(x)$ is the vector of first derivatives $\partial V_s/\partial x_j$].

All twelve conformations in Table 1 span a potential energy difference of only 3.9 kcal mol^{-1}. The global minimum energy conformation, 16, bears no conformational relationship to the global minimum of CDDT, in contrast to other instances where the alkene–peptide conformations are similar.[4,5] There are four major factors which mediate the similarities or otherwise between cyclic peptides and cyclic alkenes, namely: (a) the ring size of the systems; (b) the fact that amide groups have a dipole moment whereas –HC=CH– groups do not; (c) the height and/or phase of the –HC=CH–C–C–(τ) torsional barrier are different to those of the C′–N–C$_\beta$–C$_\alpha$(ϕ) and N–C′–C$_\alpha$–C$_\beta$(ψ) barriers; (d) the 2 kcal mol^{-1} *trans*-preference of the amide group in contrast to no preference with –HC=CH–. In the case of small ring structures, such as cyclodi-β-alanyl, the ring closure constraint is so severe as to over-ride most other conformational determinants and a similar condition prevailing in the alkene means that the similarity of amide and –CH=CH– groups is sufficient to force conformational similarity with –HC=CH– and amide groups invariably in the *cis*-configuration. In the case of medium, such as CTBA–CDDT, or large ring structures factor (a) plays no role as a conformational determinant and factors (b) and (c) become important, whilst factor (d) will usually ensure *trans*-amide groups. Given three amide groups disposed as in CTBA then the preferred arrangement from an electrostatic viewpoint will be when one (*trans*-)amide group occupies a different ' flip ' state to the other two as this minimizes the electrostatic potential energy. No such considerations apply in the case of –CH=CH– groups which have an essentially zero dipole moment. The heights and phases of the CH=CH–C–C, ϕ and ψ torsional barriers will make for differences between alkene and amide as the CH=CH–C–C barrier (1.5 kcal mol^{-1}) is much larger than the ϕ and ψ barriers (0.5 kcal mol^{-1}) and differs in phase from the ψ barrier [V_ψ 0 kcal mol^{-1} for ψ(N–C′–C$_\alpha$C$_\beta$) −60, 60, or 180° and V(CH=CH–C–C) 0 kcal mol^{-1} for τ(CH=CH–C–C) 0, −120, or 120°].[23] Conformation 16 of CTBA has favourable arrangements of the ϕ and ψ torsion angles as well as one amide group in a different ' flip ' state to the other two which is the optimum arrangement for the cyclic peptide but a very poor conformation of CDDT where the 16 (≡ 15) conformation has nearly the highest potential energy of those considered. Nevertheless, if V_q is subtracted from V_s for each conformation of CTBA as in Table 1 then it is apparent that conformations 16 and 00 are the joint global minima in the absence of electrostatic interactions, whereas the latter is one of the highest energy conformations when V_q is included.

An ORTEP diagram of conformation 16 of CTBA is shown in Figure 3 and the torsion angles defining the remaining eleven conformations are given in Table 2.

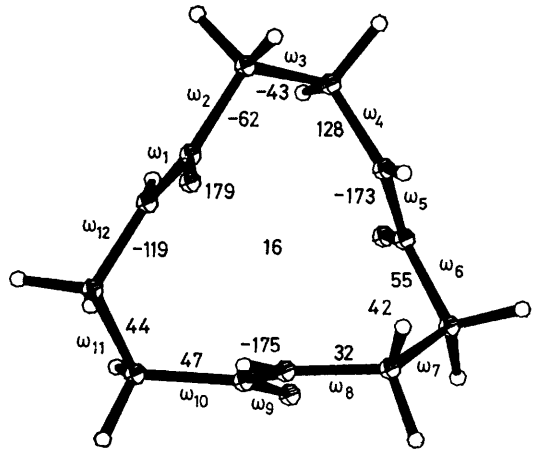

FIGURE 3 The 16 energy minimum of CTBA. The central number is the conformation code corresponding to Table 1 and the peripheral values are the main chain torsion angles. The labels ω_1—ω_{12} refer to Table 2

Other conformations of CTBA are given in Supplementary Publication No. 23224 (13 pp.).* On the basis of Table 1 CTBA would consist of *ca.* 51% of conformation 16, 16% of 30, 13% of 12, 11% of 14, and 8% of 10 and minor amounts of some other conformations in the gas phase at room temperature. In an attempt to check our calculations and define the global minimum energy conformation(s) in the liquid and solid states ^{1}H n.m.r. and *X*-ray crystallographic studies of CTBA and derivatives were undertaken.

The ^{1}H n.m.r. spectra of cyclotri-β-aminoisovaleryl and CTBA are consistent with ring conformations which have time-averaged three-fold symmetry and the methylene proton coupling constants derived from the cyclotri-β-alanyl spectrum indicates the presence of *gauche* C′(O)–C_α–C_β–N fragments. This information is not too helpful as it is obvious from Table 2 that all the plausible low-energy conformations of cyclotri-β-alanyl have *gauche*-C′(O)–C_α–C_β–N fragments exclusively. The mixture of conformations calculated above for the gas phase satisfactorily reproduces the experimental spin–spin coupling constants but then so does almost any arbitrary selection of conformations taken from Table 1. The ^{1}H n.m.r. data could also be interpreted in terms of a single three-fold symmetric conformation with gauche $-CH_2-CH_2-$ fragments, such as 00 or 07; but this is unlikely because of the high calculated energies of these conformations and the following *X*-ray crystallographic data.

Despite repeated attempts extending over some two years it proved impossible to obtain an interpretable electron density map, by direct methods, from the 450 unique diffraction maxima measured on an Enraf–Nonius CAD-4 diffractometer. This is not altogether surprising given that $Z = 1$ in the space groups R_{32} or R_{3m}, which have six equivalent positions, requires 32 or 3m molecular symmetry of CTBA. This is an impossible requirement for a single molecule of the tripeptide, and the crystal structure must be composed of molecules showing at least two different conformations. Molecular modelling studies show that it is possible to ' superimpose ' pairs of different CTBA conformations thereby producing an assemblage with 32 or 3m symmetry. The multi-conformation hypothesis is supported by the fact that Weissenberg photographs of CTBA show evidence of either high thermal motion or disorder in the crystal structure. The crystal structure is probably composed of a similar mix of conformations to those calculated for the gas phase and postulated for the liquid phase but the proportions, although not the contributors, will be different in solution (D_2O) where cyclic peptide–solvent hydrogen bonding will affect the relative stabilities of the various conformations.[24] The fact that there are only rare instances of major conformational differences between the same molecule in the gas, liquid and solid states supports the contention that CTBA exists as a mixture of conformations in the liquid as well as the solid state.

Conclusions.—It has been shown that CTBA, in common with a number of other cyclic peptides, has a range of local minima close in energy to the global minimum. This phenomenon manifests itself in a crystal structure composed of molecules in several conformations, as seen in cyclohexaglycyl,[25] and an ambiguous ^{1}H n.m.r. spectrum. This experimental data although mainly negative does at least provide a check on the molecular mechanics calculations in that one would have

TABLE 2

The torsion angles (°) of the twelve calculated conformations of CTBA. The labels refer to Figure 3 and SUP 23224

Conformation	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	ω_8	ω_9	ω_{10}	ω_{11}	ω_{12}
00	−179	−91	58	−138	−179	−91	58	−138	−179	−91	58	−138
01	180	−51	−44	−52	179	−86	51	−135	176	−107	59	−99
03	178	−39	−46	−17	173	−48	−37	−69	178	−92	53	−129
07	−177	40	41	51	−175	34	42	51	−177	37	42	47
10	177	66	51	−124	174	−111	46	−125	179	−105	59	47
11	−176	153	−47	−61	177	−95	42	−136	176	−111	55	39
12	−178	59	48	−110	175	−55	−40	−43	175	−108	51	40
13	180	117	−52	−35	174	−52	−37	−75	176	−103	51	60
14	−174	65	40	−145	172	−113	55	−102	−178	−60	−48	137
15	−168	133	−44	−88	177	−101	59	−129	−177	−59	−41	132
16	179	−62	−43	128	−173	55	42	32	−175	47	44	−119
30	−176	62	48	37	−177	59	46	−115	174	−137	47	49

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1981, Index issue.

been very suspicious had these predicted a single well defined global minimum energy conformation for CTBA.

Furthermore the molecular mechanics calculations have shown that cyclic peptide–cyclic alkene conformational homology is much more likely in small (up to eight-membered, say) ring structures where simple ring closure constraints are the predominant steric–geometric factor.

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