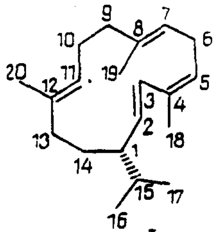
NMR SPECTRA AND CONFORMATION OF CEMBRENE IN SOLUTION

A. V. Vorob'ev, G. E. Sal'nikov,
M. M. Shakirov, and V. A. Raldugin

UDC 543.422.25:547.913.6

Using dimeric NMR spectroscopy, a complete interpretation of the ^1H and ^{13}C NMR spectra of the diterpene hydrocarbon cembrene has been made. The experimental values of the SSCs for the ^1H atoms in the PMR spectra of cembrene agree well with those calculated for the lowest-energy ("crystal") conformation. In the light of the observation of intramolecular NOEs and of the low-temperature ^{13}C NMR spectra, it has been concluded that the cembrene molecule retains the "crystal" conformation in solution.

The hydrocarbon cembrene (I) is the first known representative [1, 2] of a voluminous class of macrocyclic diterpenoids that are widespread in various living organisms [3]. The conformation of the molecule of (I) in the crystal and the configuration of its trisubstituted double bonds have been established by the XSA method [4]. The stereochemistry of the products of the epoxidation [5], photooxidation [6], and acid cyclization [7] of cembrene have shown that in all these cases the reacting conformation in solution is close to or identical with that in which the cembrene molecule exists in the crystal (the "crystal conformation"). At the same time, the conformational state of the cembrene molecule in solution has not been investigated.



I

The first three studies in which a conformational analysis of cembranoid molecules has been made have been published [8-10]. In these, use was made of a combination of NMR spectroscopy and calculations by the method of molecular mechanics which has recommended itself as an effective tool of conformational analysis [11-13].

A necessary element of the conformational analysis of macrocyclic compounds by the method of molecular mechanics is, in the general case, the use of computer programs permitting the finding of a conformation with the lowest free energy [14]. In an investigation of the possibilities of a program of this type (RINGMAKER) it has been established that for the cembrene molecule the conformation with the lowest energy corresponds to the "crystal" conformation [15].*

Thus, the information available in the literature permitted the assumption that the reacting conformation of the cembrene molecule is close to the "crystal" conformation and is the main, or only, one existing in solutions.

In order to check these hypotheses experimentally, we have made a complete interpretation of the ^1H and ^{13}C NMR spectra of cembrene using dimeric NMR spectroscopy (^{13}C—^{13}C and ^1H—^{13}C correlations, Table 1), and ^1H NMDR. We then recorded ^{13}C NMR spectra with lowering of the temperature from room temperature to —100°C, whereupon only one set of signals was retained and these underwent no broadening. The small shifts of the signals observed on the

---

*In the paper cited an error crept into the illustration of the structural formula of cembrene — the isopropyl group was not shown.

Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 455-459, July-August, 1991. Original article submitted July 16, 1990.

0009-3130/91/2704-0396$12.50

TABLE 1. Chemical Shifts of the Signals in the ^{13}C and ^{1}H NMR Spectra of Cembrene (ppm)

Number	C*	H*	H**
1	48,11	1,69	1,69
2	130,53	5,21	5,25
3	130,44	6,14	6,18
4	134,87	—	—
5	125,32	5,57	5,58
6	26,12	H_a 3,10; H_b 2,45	H_a 3,06; H_b' 2,42
7	125,49	5,16	5,10
8	133,79	—	—
9	38,89	H_a 2,25; H_b ≈2,1	H_a 2,24; H_b ≈2,0
10	23,39	H_a 2,34; H_b ≈2,0	H_a 2,35; H_b' ≈2,0
11	125,67	4,94	4,87
12	132,69	—	—
13	36,43	≈2,0 (H_a+H_b)	≈2,0 (H +H_b')
14	27,70	H 1,76; H_b 1,27	H_a 1,76; H_b 1,27
15	32,72	1,53	1,53
16	20,77	0,93	0,89
17	19,72	0,89	0,85
18	19,72	1,84	1,84
19	14,07	1,64	1,62
20	14,07	1,54	1,54

*c = 45% in $CDCl_3$.
**c = 0.01 M in $(CD_3)_2CO$.

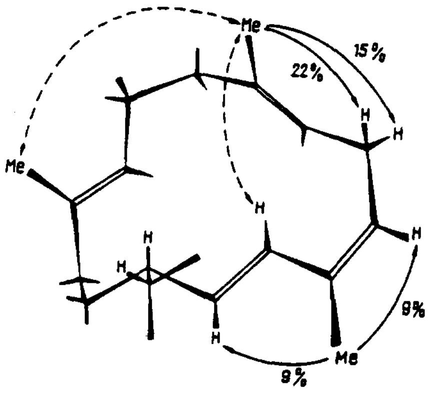


Fig. 1. Conformations of the cembrene molecule calculated by the method of molecular mechanics (the projection of the figure was selected with the use of the program of [19]). The arrows show observed nuclear Overhauser effects (↔NOESY, ←simultaneous NOE).

lowering of the temperature (Table 2) can be explained by the change in the density of the solution [16]. The result obtained does not contradict the hypothesis of the conformational homogeneity of the cembrene molecule in solution.

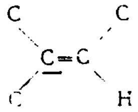
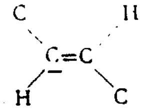
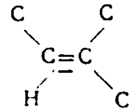
On the qualitative level, we established the correspondence of the conformation of the cembrene molecule in solution to the "crystal" conformation on the basis of an observation of intramolecular nuclear Overhauser effects between the following protons: 3H-18↔H-2, H-5; 3H-19 ↔ H-3, H-6a, H-6b, 3H-20 (Fig. 1). We made a quantitative evaluation of the closeness of the conformations in solution and in the crystal by the use of known relationships (of the type of the Karplus equation) [17, 18] between the dihedral angles and spin-spin coupling constants (SSCCs) in PMR spectra.

We obtained the values of the proton SSCCs given in Table 3 by using double nuclear resonance spectra. The same Table gives the SSCC values calculated from the Karplus equation (with the aid of the program of [19]) for the conformation of the cembrene molecule in the crystal [4]* and also for the same conformation but optimized by the method of molecular mechanics with the aid of the MMP2 program [20] (optimized "crystal" conformation).

---

*In the paper cited, the crystallographic coordinates of the atoms and an illustration of the conformation are given for the antipode of the (+)-cembrene molecule.

TABLE 2. Changes in the Chemical Shifts (ppm) in the ^{13}C NMR Spectra of Cembrene (ppm)

C_i	$\Delta^{*}=\delta^{13}C_i$ (288°K)—$\delta^{13}C_i$ (193 K)	$\Delta^{**}=\delta^{13}C_i$ (296°K)—$\delta^{13}C_i$ (173°K)	Type of substitution
C-1 C-8 C-12	—0,19 —0,17 —0,21	—0,32 —0,18 —0,42	
C-2 C-3	—0,16 +0,10	—0,08 +0,02	
C-5 C-7 C-11	—0,02 +0,13 +0,02	—0,12 +0,41 +0,18	
C-1 C-6 C-9 C-10 C-13 C-14 C-15	+0,01 +0,04 +0,02 +0,05 0,00 +0,01 —0,04	+0,02 +0,04 —0,08 +0,06 +0,08 +0,15 —0,04	$-\underline{C}H-$ $-\underline{C}H_2-$
C-16 C-17 C-18 C-19 C-20	—0,31 —0,21 —0,59 —0,42 —0,27	—0,72 —0,47 —0,82 —0,67 - 0,37	$-\underline{C}H_3$

---

*c = 0.1 M in $(CD_3)_2CO$.

**c = 0.1 M in a mixture of $CDCl_3$ and $(CD_3)_2CO$ (3:1).

To characterize the degree of pairwise correspondence between the three sets of SSCCs (experimental, calculated for the "crystal" and the optimized "crystal" conformations), we chose the mean square deviations (σ), the values of which are given at the end of Table 3. These values show that the differences between all the pairs from the three sets of SSCCs are of approximately the same order but that the set for the optimized "crystal" conformation is closer to the experimental values.

A consideration of two conformations (the "crystal" and the optimized "crystal" helps to establish the significance of the differences between the sets of SSCCs obtained. These conformations are very close to one another geometrically — the dihedral angles between the atoms forming the ring differ on average 2.47°; while the maximum difference does not exceed 7.14°. In view of the fact that the values of σ are of the same order (see Table 3), it must be concluded that the differences between the experimental and calculated sets of SSCCs can be regarded as insignificant.

Thus, the results obtained agree with the hypothesis that the cembrene molecule exists in solution in a conformation close to the "crystal" conformation, which explains the total stereoselectivity of the chemical transformations of this natural macrocyclic diterpenoid. In this conformation, the attack of voluminous electrophilic particle on any trisubsituted double bond is possible from only one side since the other side is screened by the remainder of the molecule.

EXPERIMENTAL

Cembrene was isolated from the oleoresin of Pinus sibirica R. Mayr. The physicochemical constants of the specimen corresponded to those given in the literature [22].

NMR spectra were recorded on a Bruker AM-400 instrument (400.13 MHz for ^1H and 100.614 MHz for ^{13}C). The low-temperature ^{13}C NMR spectra were recorded on a Bruker WP-200SY instrument (50.32 MHz for ^{13}C). The ^1H chemical shifts (δ) were measured relative to the signals

TABLE 3. Values of the Vicinal SSCCs in the PMR Spectrum of Cembrene, Hz

H_i—H_j	J^X_{exp}	J^Y_{calc}	J^Z_{calc}
1—2	9,5	11,48	11,16
1—14a	2,5	1,21	2,91
1—14b	12,0	8,37	11,63
5—6 a	6,1*	6,55	5,42
5—6 b	9,0*	6,17	6.52
6a—7	10,9*	10,79	11,38
6 b—7	3,1*	2,62	3,03
9 a—10	4,0	2,94	4,17
9a—10	4,0	0,02	3,68
10a—11	7,5	9,34	7,73
10b—11	1,5	2,75	3,12

$$\sigma_{A,B} = \sqrt{\frac{\Sigma(J^A - J^B)^2}{-1}}$$

$\sigma_{X,Y} = 2,22$ $\sigma_{X,Z} = 1,13$

$\sigma_{Y,Z} = 1,82$

X) Experimental values, c = 0.01 M in $(CD_3)_2CO$; J = ±0.3 Hz; Y) "crystal" conformation; Z) optimized "crystal" conformation. The values marked by asterisks were obtained by the use of an iteration program [21].

of the residual protons of the solvents – 7.24 ppm ($CDCl_3$) and 2.07 ppm ($(CD_3)_2CO$). In the ^{13}C NMR spectra, the signals of the solvents were taken as 76.90 and 29.79 ppm, respectively.

Standard pulse sequences with complete decoupling from protons were used for recording the two dimensional NMR spectra; ^1H–^{13}C correlation (free induction decay (FID) 1024 × 512, spectrum 8192 × 2048); ^{13}C–^{13}C correlation (FID 1024 × 8192, spectrum 8192 × 2048, unsymmetrized); and NOESY (FID 256 × 4096, spectrum 4096 × 2048, mixing time 1 s). The integral intensities of the intramolecular Overhauser effects were measured for the one-dimensional spectra.

In the analysis of the PMR spectra of cembrene, in addition to those given in Table 3 the following SSCCs were determined: geminal between protons 2H-6 (16.0 Hz), 2H-9 (13.5 Hz), 2H-10 (12.0 Hz) and 2H-14 (12.0 Hz); vicinal between the protons H-2 and H-3 (15.5 Hz), H-1 and H-15 (5.7 Hz), 3H-16 and H-15 (7.0 Hz), 3H-17 and H-15 (7.0 Hz); and long-range SSCCs between 3H-18 and H-5 (1.5 Hz*), 3H-18 and H-6a (1.5 Hz*), 3H-18 and H-6b (0.0 Hz*), 3H-19 and H-6b (1.5 Hz*), 3H-19 and H-6a (0.0 Hz*), 3H-19 and H-7 (1.5 Hz*), 3H-20 and H-10a (0.7 Hz), 3H-20 and H-10b (1.5 H), 3H-20 and H-11 (1.5 Hz), H-1 and H-3 (0.7 Hz), H-3 and H-5 (0.7 Hz), H-5 and H-7 (0.7 Hz*), H-7 and H-9a (1.5 Hz) (the values marked with asterisks were obtained by the use of the iteration program of [21]).

LITERATURE CITED

1. A. J. Haagen-Smit, T. H. Wang, and N. T. Mirov, J. Am. Pharm. Assoc., 40, 557 (1951).
2. W. G. Dauben, W. F. Thissen, and P. R. Resnik, J. Org. Chem., 30, 1693 (1965).
3. A. J. Weinheimer, C. W. L. Chang, and J. A. Matson, Progr. Chem. Org. Nat. Prod., 36, 285 (1979).
4. M. G. B. Drew, D. H. Templeton, and A. Zalkin, Acta Cryst., B25, 261 (1969).

5. V. A. Raldugin, L. Ya. Korotkikh, A. I. Rezvukhin, and V. A. Pentegova, Khim. Prir. Soedin., 525 (1977).
6. V. A. Raldugin, V. L. Salenko, N. I. Yaroshenko, V. G. Storozhenko, A. I. Rezvukhin, and V. A. Pentegova, Khim. Prir. Soedin., 60 (1981).
7. V. A. Raldugin, S. A. Shevtsov, V. I. Mamatyuk, and V. A. Pentegova, Izv. Sibirskogo Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, 1. No. 2, 98 (1986).
8. W. Inman and P. Crews, J. Org. Chem., 54, 2526 (1989).
9. Y. Fukazawa, S. Usui, and Y. Uchio, Tetrahedron Lett., 27, 1825 (1986).
10. J. A. Marshall, E. D. Robinson, and R. D. Adams, Tetrahedron Lett., 48, 4913 (1988).
11. C. Jaime, E. Osawa, Y. Takeuchi, and P. Camps, J. Org. Chem., 48, 4514 (1983).
12. W. Inman and P. Crews, J. Am. Chem. Soc., 111, 2822 (1989).
13. A. V. Tkachev, O. V. Toropov, G. E. Sal'nikov, Yu. V. Gatilov, and I. Yu. Bagryanskaya, Zh. Org. Khim., 25, No. 2, 249 (1989).
14. E. Osawa, H. Goto, T. Oishi, Y. Ohtsuka, and T. Chuman, Pure Appl. Chem. 61, 597 (1989).
15. W. C. Still, in: Current Trends in Organic Synthesis (ed. H. Nozaki), Pergamon Press, Oxford (1983), p. 233.
16. J. B. Lambert, A. R. Vagenas, and S. Somani, J. Am. Chem. Soc., 103, 6398 (1981).
17. M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963).
18. E. V. Garbish, J. Am. Chem. Soc. 86, 5561 (1964).
19. B. F. Muratshin, A. V. Tkachev, and O. V. Toropov, "Dialogue program for calculating spin-coupling constants," in: VIIIth All-Union Conference on the Use of Computers in the Spectroscopy of Molecules and in Chemical Studies: Abstracts of Lectures [in Russian], Novosibirsk (1989), p. 101.
20. U. Burkert and N. L. Allinger, Molecular Mechanisms, ACS Monograph No. 177, American Chemical Society, Washington, DC (1982).
21. Bruker Aspect 3000 Software Manual 1985. NMR Simulation and Iteration.
22. V. A. Pentegova, O. Motl, and V. Herout, Collect. Czech. Chem. Commun., 26, 1362 (1961).

SEQUENCE OF ALKYLATION OF CYCLOHEXANE-1,3-DIONE. ALTERNATIVE SYNTHESIS OF (±)-ANGUSTIONE

A. A. Zenyuk, L. G. Lis,
L. I. Ukhova

UDC 547.443.3+547.594.3+547.914.4

A method is proposed for introducing one, two, or three alkyl substituents into positions 4 and 6 of the cyclohexane-1,3-dione molecule by successive alkylation under the action of strong bases. (±)-Angustione (a natural β-diketone) has been synthesized.

In the course of a study of the alkylation of enaminodiketones of the cyclohexane series under the action of strong bases, we developed a convenient method for the successive introduction of several alkyl groups into the cyclic part of the molecule and proposed a scheme for the synthesis of (±)-angustione [1]. We considered it desirable to employ an analogous approach for the alkylation of cyclohexane-1,3-dione with the aim of obtaining substituted β-diketones, which are intermediates in the synthesis of heteroanalogs of steroids [2], glutarimide antibiotics [3], and other natural compounds and their analogs.

A method is known for obtaining substituted β-diketones of the cyclohexane series by the alkylation of enol ethers of cyclohexane-1,3-dione under the action of strong bases with subsequent hydrolysis of the ether groups [4]. A more convenient, in our view, method of introducing an alkyl substituent by the direct alkylation of a cyclohexane β-diketone has also been described [5].

In the present communication we propose a method which permits monomethyl derivatives of cyclohexane-1,3-dione to be obtained with a higher yield, and also a method for obtaining derivatives of β-diketones with several alkyl groups by the successive alkylation of cyclohexane-1,3-dione under the action of strong bases.

Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk.
Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 460-463, July-August, 1991. Orginial article submitted August 21, 1990.

0009-3130/91/2704-0400$12.50