A Novel Type of Rigid Macrocycle with Bis(3-uracilyl)methane and Hexadiyne Units. The Uracilophane

Vesna Čaplar, Lidija Tumir, and Mladen Žinić*

Laboratory of Supramolecular and Nucleoside Chemistry, Department of Chemistry, Ruđer Bošković Institute, P.O.B. 1016, 10001 Zagreb, Croatia

Synthesis of the first uracilophane **15**, constructed from two bis(3-uracilyl)methane units and two hexadiyne bridges connecting uracil N(1)-atoms, is described. The conformational properties of **15** investigated by molecular dynamics revealed low energy conformations with partly or fully stacked phenyl-uracil or phenyl-phenyl pairs.

INTRODUCTION

The construction of rigid macrocyclic compounds possessing well defined cavities has been of recent interest in supramolecular chemistry research.[1] In solution, such macrocycles are able to bind in their cavity various smaller molecules or ions of appropriate shape and size which make them of interest as enzyme[2] or receptor[3] models. In the present work, we report on the synthesis of a novel type of macrocyclic cyclophane, the uracilophane **I**, constructed from two units of bis(3-uracilyl)methane and two rigid hexadiyne bridges connecting uracil nucleic bases at N(1)-positions. Such uracilophane could adopt conformations with an elongated cavity about 0.7 nm long and 0.4 nm wide as apparent from examination of CPK model of **I**. Consequently, binding of linear or aromatic guests fitting its cavity may be anticipated. Structurally, **I** could be compared with Diederich's uncharged cyclophane receptors[2a] constructed from two diphenylmethane units which have shown very interesting apolar complexation of aromatic guests in organic solvents.[4]

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* Author to whom correspondence should be addressed.

I
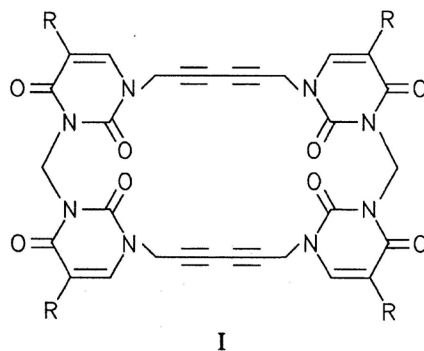
On the other hand, etheno-anthracene-based cyclophanes[5] and crypto-phanes[4c] were found able to form inclusion compounds with ammonium ions. Bis(3-uracilyl)methane based cyclophane **I** possesses 8 carbonyl oxygens of which some may point inside the cavity so that their interactions with hydrogen bond donating guests may be anticipated. In this case, enhanced binding and recognition of such guests may result. Also, the striking difference between diphenylmethane based cyclophanes and uracilophane **I** emerges from the charge distribution and existence of strong permanent dipoles in uracil.[7] This could considerably influence the binding of polar but also of apolar aromatic guests through polarization effects.[2a]

In this paper, we describe the first synthesis of uracilophane **15** and its spectroscopic properties as well as investigation of its conformational space by molecular modelling studies.

RESULTS AND DISCUSSION

Synthesis

In our recent preliminary paper[8] we reported on the preparation of bis(1-uracilyl)hexadiyne derivative **7** and methylene bridged 1-propargyluracil derivative **8**. Both compounds could be considered as precursors of uracilo-phane **I**: compound **7** could be transformed to **I** by macrocyclization through methylene bridging at uracil N(3) positions using CH_2Cl_2/DBU[9,10] and **8** by 1 : 1 macrocyclization using the classical Eglinton's method[11] of oxidative coupling of acetylenes in the presence of Cu(II)acetate (Chart 1). The latter method has been often successfully used in preparations of various macro-cyclic cyclophanes with hexadiyne bridges.[12]

The synthesis of **7** started with propargylation of uracil **1** (previously protected at C(2)-O and C(4)-O using HMDS – hexamethyldisilazane or BSA – bis(trimethylsilyl)acetamide) to give 1-propargyluracil **2** in 62% yield
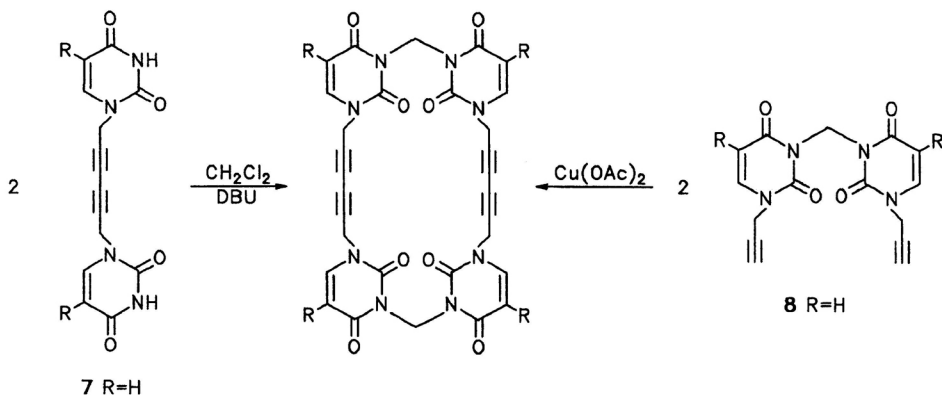
Chart 1.

(Scheme 1). However, the attempted oxidative coupling of acetylenic fragments in **2** using $Cu(OAc)_2 \cdot H_2O$ in pyridine failed giving a complicated mixture of products. Next, we tried this reaction with methyl N(3)-protected derivative **3**, which underwent successful coupling to diacetylenic compound **4** (53% yield). In the same way, the p-methoxybenzyl protected **5** was coupled to **6** (88%). p-Methoxybenzyl protecting group of **6** was then easily removed by $AlCl_3$/anisole,[14] and 1,6-di(uracil-1-yl)hexadi-2,4-yne **7** was obtained in a practically quantitative yield. The recently introduced modification of Eglinton's reaction, using acetonitrile as solvent instead of pyridine,[13] offered better results and shorter reaction times (2–3 h instead of 24 h in pyridine) so that **7** (73.5%) could be obtained directly from **2**. Also, **5** gave in acetonitrile a 95% yield of **6** while in pyridine only a 61% yield of **6** could be obtained. The fact that oxidative acetylene coupling was efficient in pyridine only with N(3)-protected uracyl derivatives **3** and **5,** together with that of successful coupling of unprotected **2** in acetonitrile, implies that N(3)-deprotonation of **2** in pyridine and its reaction with Cu^{2+} could be responsible for the observed formation of various by-products. However, in much less basic acetonitrile, the coupling of **2** proceeds as expected.

Based on our previous work on methylene bridged nucleoside analogs,[9,10] we subjected diacetylenic compound **7** to macrocyclization using 1,8-diazabicyclo [5.4.0]undecene (DBU) in dichloromethane (Chart 1). However, due to the poor solubility of **7** in CH_2Cl_2, the reaction failed and predominantly unreacted starting material could be isolated. Even the addition of dimethyl formamide to improve solubility was unsuccessful. On the other hand, this reaction proceeded well with 1-propargyluracil **2** and the methylene-bridged product **8** (56%) was obtained together with some 3-chloromethyluracil intermediate **9** (5%). It was found that a higher yield of **8** could be obtained
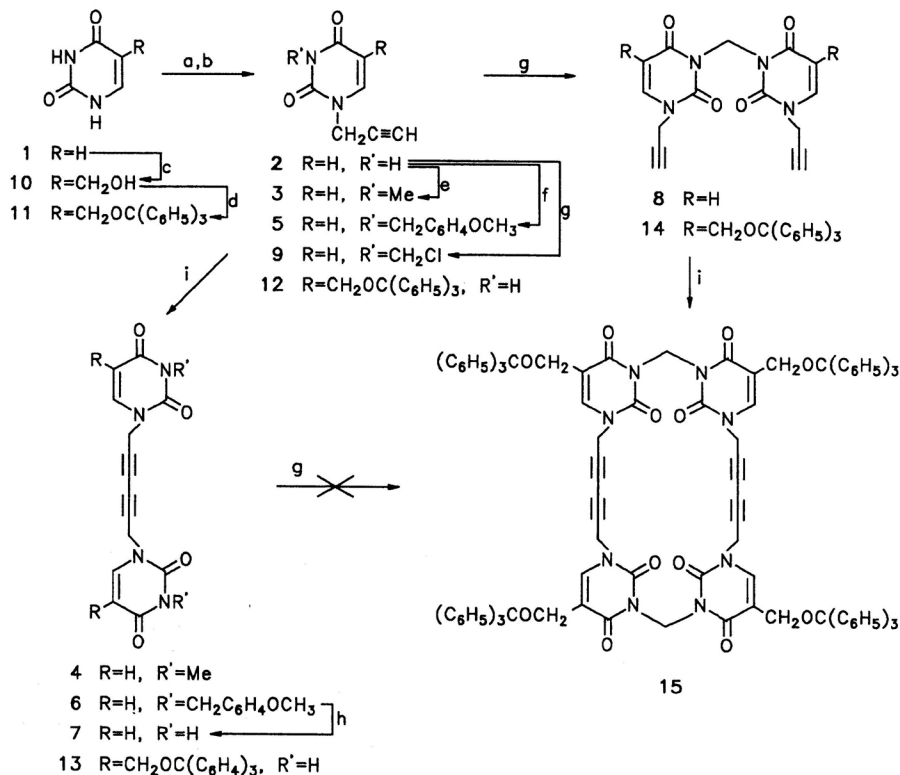
a) BSA, 0.5 h, 80 °C; b) BrCH$_2$C≡CH/MeCN, 10–14 days, RT; c) (CH$_2$O)$_n$, KOH/H$_2$O;
d) TrCl/py.; f) CH$_3$N$_2$; g) CH$_2$Cl$_2$/DBU, reflux; h) AlCl$_3$/anisole; i) Cu(OAc)$_2$.H$_2$O, 60 °C

Scheme 1.

if DBU was added in small portions and the volume of dichloromethane was kept as small as possible. Both modifications are expected to minimize the possibility of concurrent reaction of intermediate compound **9** with DBU.

The macrocyclization by oxidative coupling of propargyl chains in methylene-bridged compound **8**, using copper (II) acetate in high dilution conditions (Chart 1), gave an almost insoluble high-melting product, which prevented its purification and proper characterization. However, its IR (disappearance of the strong sharp band at 3230–3270 cm^{-1} and the weak one at 2110 cm^{-1} originating from C≡CH fragment) and NMR spectra (taken in DMSO-d_6 at 80 °C; disappearance of -C≡CH signal at $\delta = 3.45$ ppm) indicated that the propargyl chains were coupled into hexadiyne ones. Searching for convenient substitutions at nucleobase that would enhance the solubility

of macrocyclic end-product, we have chosen the hydroxymethylation at C(5)-atom of uracil. This reaction proceeds in high yield with free uracil **1**, and the resulting 5-hydroxymethyluracil **10** (80% yield)[15] is a stable compound with primary hydroxyl group that could be easily further transformed.[15]

First, we made the benzyl ether of **10** and successfully performed subsequent propargylation, methylene-bridging and oxidative coupling steps as described for **8**, but again the obtained macrocyclic product was practically insoluble and impossible to purify.

Finally, we introduced triphenylmethyl group at C(5)-hydroxymethyl of **10**. Tritylation of **10** with triphenylmethylchloride in pyridine afforded 5-triphenylmethoxymethyluracil **11** (93%). Then, **11** was alkylated (previously protected at C(2)-O and C(4)-O with BSA), with propargylbromide in acetonitrile to give **12** (74%). Oxidative dimerization of **12** with copper (II) acetate gave 1,6-di(5-triphenylmethoxymethyluracilyl)-hexadi-2,4-yne **13** (78%). The attempt at methylene-bridging at N(3)-positions of **13** with DBU in dichloromethane failed, although the propargyl derivative **12** was successfully bridged in the same conditions giving 3,3''-methylenebis(1-propargyl-5-triphenylmethoxymethyluracil) **14** (47%). The oxidative dimerization of **14** in high-dilution conditions gave the macrocyclic compound **15** sufficiently soluble in chloroform to be purified by TLC and fully characterized. The ^{1}H- and ^{13}C-NMR data for **15** and all newly prepared compounds are collected in Tables I and II.

Structure of Uracilophane 15

Examination of the CPK model of **15** shows considerable rigidity of bis(3-uracilyl) units as a consequence of hindered rotation around N(3)-methylene bonds. The units adopt distorted »V« shaped conformations due to the steric hindrance between uracil C(2) and C(4) carbonyl oxygens. On the other hand, the rotations around N(1)-methylene-C(2') bonds seem less strained, so various conformations resulting from such rotations may be anticipated. Comparison of ^{1}H-NMR spectra of acyclic precursors **13** and **14** with that of uracilophane **15** (Table I) shows only slight differences. The chemical shifts of respective protons in acyclic and macrocyclic compounds are similar, except for uracil C(6)-proton which appears upfield by about 0.5 ppm in the spectrum of **15**. This points to the existence of conformations of **15** with uracil C(6)-proton close to one of the triphenylmethane phenyls or close to the diacetylenic fragment so that shielding by π-electrons of these groups may occur. The high symmetry of ^{1}H-NMR spectrum of **15** indicates that, in solution at 30 °C, all possible conformers interconvert quickly on the NMR time scale. To get a better insight into the conformational space of uracilophane **15**, the molecular modelling study using TRIPOS force field included in the Sybyl programme was undertaken. Search for the conforma-

TABLE I

^{1}H-NMR Data (δ/ppm, J/Hz, internal standard TMS, solvent DMSO-d_6)

| Co.	NH, bs	H-C(6)	arom.	H-C(5)	CH$_2$N(3) s	H-C(1')	CH$_2$N(5) s	H-C(3')
2	11.39	7.70d, (J = 7.9)	–	5.63d, (J = 7.8)	–	4.51d, (J = 2.4)	–	3.34t, (J = 2.5)
3[a]	–	7.76d, (J = 7.9)	–	5.78d, (J = 7.9)	–	4.58d, (J = 2.5)	–	3.45t, (J = 2.5)
4[a]	–	7.75d, (J = 7.9)	–	5.78d, (J = 7.9)	–	4.74s	–	–
5[b]	–	7.78d, (J = 7.9)	7.25d, 6.78d	5.81d, (J = 8.0)	4.91	4.58d, (J = 2.2)	–	3.45t, (J = 2.4)
6[b]	–	7.74d, (J = 7.9)	7.14d, 6.84d	5.79d, (J = 7.9)	4.89	4.72s	–	–
7	11.44	7.70d, (J = 7.9)	–	5.64d, (J = 7.9)	–	4.68s	–	–
8	–	7.71d, (J = 8.0)	–	5.73d, (J = 8.0)	5.90	4.54d, (J = 1.9)	–	3.45t, (J = 2.5)
9	–	7.86d, (J = 8.0)	–	5.87d, (J = 8.0)	5.67	4.62d, (J = 2.5)	–	3.50t, (J = 2.4)
10[c]	10.8	7.25s	–	–	–	–	4.11	–
11	11.19, 10.86	7.44s	7.44–7.21 m	–	–	–	3.74	–
12	11.52	7.79s	7.46–7.26 m	–	–	4.62d, (J = 2.2)	3.75	3.53t, (J = 2.3)
13	11.55	7.74s	7.44–7.24 m	–	–	4.79s	3.74	–
14[d]	–	7.75s	7.47–7.20 m	–	6.08	4.58d, (J = 2.5)	4.04	2.53t, (J = 2.5)
15[d]	–	7.33s	7.50–7.19 m	–	6.03	4.60s	4.07	–

[a] CH$_3$-N(3) at 3.17 ppm (s); [b] OCH$_3$ at 3.72–3.70 ppm (s); [c] OH at 3.41 ppm (bs); [d] in CDCl$_3$.

tional space was performed by molecular dynamics calculations using simulated annealing as a type of dynamics experiment. The calculations revealed several types of low energy conformations differing in mutual orientation of »V« shaped bis(3-uracilyl)methane fragments (Figure 1). The most stable conformation **A** (Figure 2) is characterized by three stacking interactions be-

TABLE II

^{13}C-NMR Data (δ/ppm, internal standard TMS, solvent DMSO-d_6)

Co.	C(4)	C(2)	C(6)	C(5)	C(2')	C(3')	CH$_2$-C(5)	CH$_2$-N(3)	C(1')	other
2	164.09	150.09	144.98	102.20	78.95	76.35	–	–	37.13	–
3	162.49	150.44	142.90	100.85	78.50	76.13	–	–	37.75	27.43 (Me)
4	162.47	150.79	142.95	101.02	74.72	67.72	–	–	38.71	27.43(Me)
5	162.28	150.64	143.27	101.04	78.37	76.22	–	43.03	37.93	158.60, 129.54, 129.09, 113.77 (arom.), 55.13 (OMe)
6	162.24	150.68	143.35	101.19	74.66	67.83	–	43.12	37.98	158.64, 129.57, 129.06, 113.83 (arom.), 55.30 (OMe)
7	162.87	149.95	143.68	101.64	74.27	67.61	–	–	37.02	–
8	161.85	150.13	143.49	101.12	78.42	76.33	–	46.53	37.61	–
9	160.84	149.62	144.53	100.79	78.97	76.24	–	49.55	38.15	–
10	164.16	151.69	138.54	112.96	–	–	55.96	–	–	–
11	163.84	151.48	139.01	109.52	–	–	58.86	–	–	143.92, 128.71. 126.89 (Ph), 86.66 (CPh$_3$)
12	163.05	150.39	141.83	110.83	78.70	76.41	58.82	–	36.91	143.83, 128.49, 128.28, 127.43 (Ph), 86.87 (CPh$_3$)
13	163.04	150.36	141.29	111.04	74.95	67.90	58.85	–	37.69	143.81, 128.50, 128.22, 127.40 (Ph), 86.84 (CPh$_3$)
14[a]	161.15	150.22	136.75	112.10	76.08	75.87	58.91	47.07	37.81	143.56, 128.49, 127.94, 127.23 (Ph), 87.25 (CPh$_3$)
15[a]	160.78	149.60	136.91	112.59	72.46	69.75	59.03	46.01	38.20	143.40, 128.39, 127.82, 127.09 (Ph), 87.30 (CPh$_3$)

[a] in CDCl$_3$.
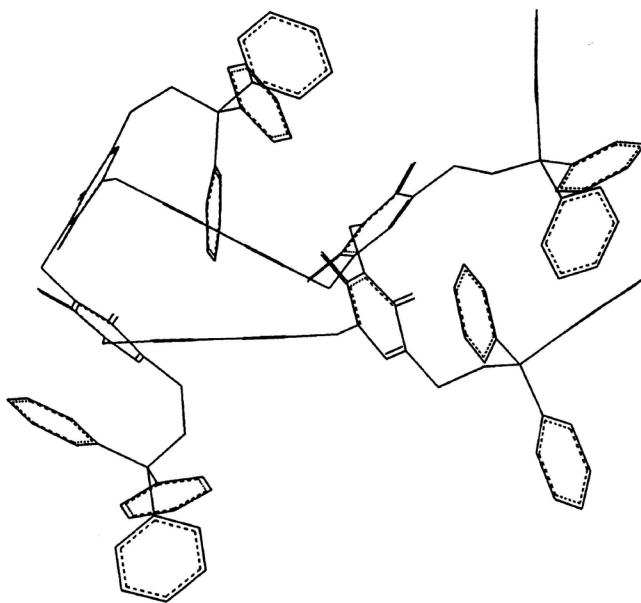
A, energy -52.15 kcal/mol
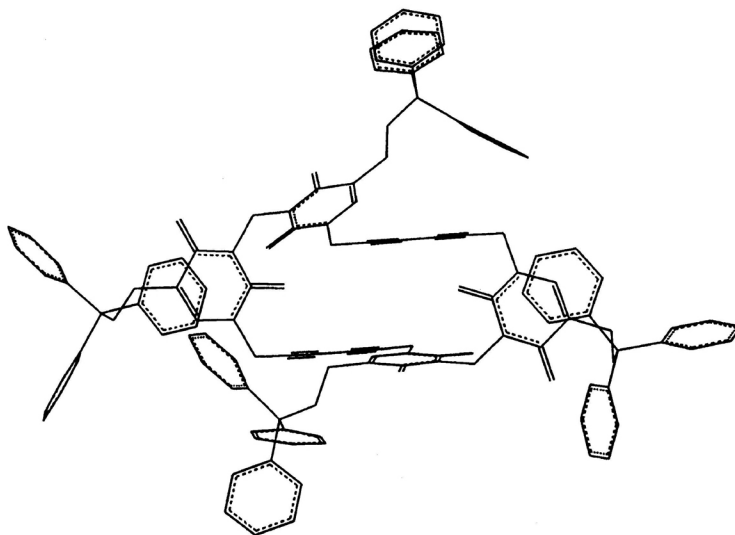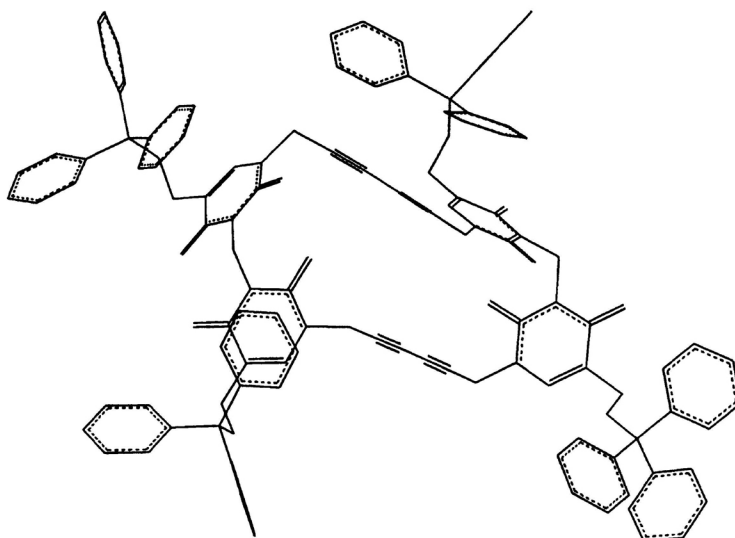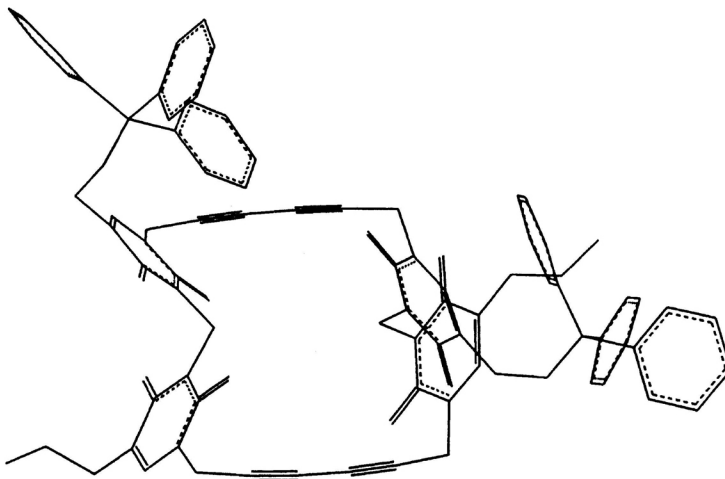

C, energy -45.55 kcal/mol

B, energy –48.4 kcal/mol

D, energy -25.76 kcal/mol

Figure 1. Four representative conformations of **15** (hydrogens and heteroatoms omitted for clarity) obtained by the simulated annealing dynamics experiment using TRIPOS force fiel; conformers **A–D** of –52.15; –45.55, –48.4 and –27.76 kcal/mol of TRIPOS energy, respectively.
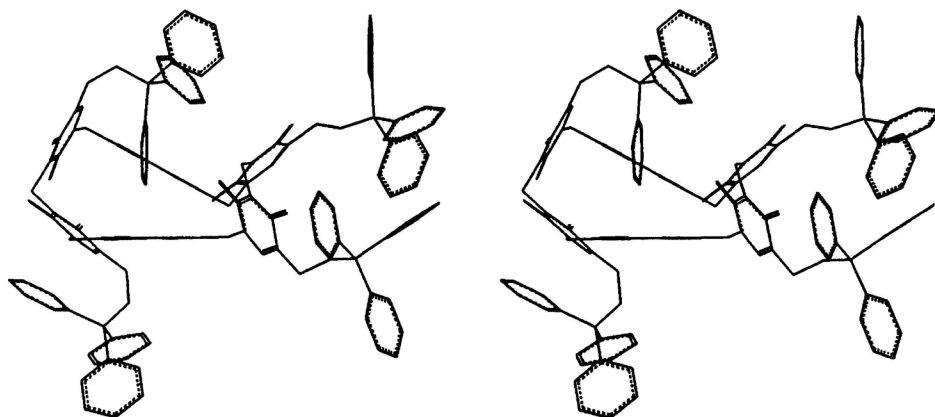
Figure 2. Stereo view of structure **A**.

tween triphenylmethane phenyls and uracils, one of them positioning one of the phenyls inside the cavity. Such a conformation indicates possible binding of aromatic guests in the cavity of uracilophane **15**. Other low energy conformations contain one, two or none of fully or partly stacked phenyluracil or phenyl-phenyl pairs. The less stable conformation **D**, being by 26 kcal/mol higher in energy than **A**, contains the bis(uracilyl)methane units in such orientation that N(3)-N(3») methylene hydrogens point inwards into the cavity. Besides two stacking pairs in **D**, the orientation of bis(uracilyl) units seems responsible for the lower stability of **D**.

The obtained results of molecular modelling studies show that different conformations with phenyl-uracil stacking interactions are possible, which nicely explains the observed upfield shift of uracil C(6)-hydrogen in the ^{1}H-NMR spectrum of **15**. The cavity dimensions vary with conformational changes and depend on the mutual orientation of bis(uracilyl)units in the macrocyclic ring but still remain sufficient for inclusion of small aromatic or linear molecules.

EXPERIMENTAL

General

Solvents were dried and redistilled shortly before use. Extracts were dried (MgSO$_4$) and evaporated *i.v.* Anal. samples were dried *i.v.* Syringe pump model 355 (Sage Instruments). Flash CC: silica gel (Merck 60, 230–400 mesh ASTM); eluent CH$_2$Cl$_2$/MeOH (30 : 1). TLC: plastic sheets silica gel 60 F$_{254}$ (Merck). Spots were made visible by UV light or iodine vapours. Prep. TLC: silica gel 60 HF$_{254}$ (Merck) activated at 110 °C for 60 min; eluent CH$_2$Cl$_2$/MeOH (9 : 1) (*A*) or CH$_2$Cl$_2$/MeOH (29

: 1) (B). M.p.: Kofler hot-bench apparatus. UV spectra ($\lambda_{max.}$ (log ε) in nm): Philips PU 8700 UV/visible spectrophotometer. IR spectra (v in cm^{-1}): Perkin-Elmer 297 spectrometer; in KBr pellets. ^{1}H-NMR spectra (δ in ppm rel. to Me$_4$Si and J in Hz) and ^{13}C-NMR spectra: Varian Gemini 300 instrument. Mass spectrum: Extrell FTMS 2001-DD Fourier-Transform Mass Spectrometer (Madison, WI, USA) equipped with 3 T superconducting magnet and a Nicolet 1280 Data Station.

1-Propargyluracil 2

Uracil 1 (2.242 g, 20 mmol) was suspended in dry MeCN (40 ml), BSA (11.8 ml, 48 mmol) was added and under argon stirred at 80 °C for 0.5 h. The clear solution was cooled down in an ice-bath and 80% solution of propargyl bromide in toluene (4.46 ml, 40 mmol) was added. The mixture was kept in the dark at room temp. for 10 days, then poured into crushed ice and water (100 ml) and neutralized with solid NaHCO$_3$ under stirring. The product was extracted into EtOAc (3 × 50 ml). The aqueous layer was saturated with NaCl and again extracted with EtOAc. The combined extracts were dried (MgSO$_4$) and evaporated: 2.648 g (88%). Recrystallization from 96% EtOH gave 1.385 g, and FC purification of mother liquors yielded additional 0.467 g; total yield: 1.852 g (62%); m.p. 168–70 °C; UV(EtOH) λ_{max}/nm (log ε): 261.9 (3.87); IR v_{max}/cm^{-1}: 3240s, 3005m, 2820m, 2110w, 1690s, 1620m, 1460m, 1420m, 1410m, 1385m, 1330m, 1240m, 1200m, 1180s, 1095w, 940w, 880m, 825m, 765m, 755m, 700m.

Anal. Calcd. for C$_7$H$_6$N$_2$O$_2$ (M_r = 150.13): C 56.00, H 4.03, N 18.66%; found: C 56.05, H 4.28, N 18.48%.

3-Methyl-1-propargyluracil 3

Compound 2 (375 mg, 2.50 mmol) was dissolved in MeOH (10 ml) and added dropwise into the cooled (0 °C) ethereal solution of diazomethane (freshly prepared from *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (2.141 g, 10 mmol) in ether (30 ml) and KOH (561 mg, 10 mmol) in 96% EtOH (15 ml).[16] After 0.5 h at room temp., the reaction mixture was evaporated and the crude residue crystallized from MeOH: 288 mg (70%) of 3, m.p. 187–9 °C; UV(EtOH) λ_{max}/nm (log ε): 261.9 (2.96); IR v_{max}/cm^{-1}: 3230s, 2110w, 1710s, 1670s, 1620s, 1455s, 1420m, 1405m, 1380m, 1360m, 1280m, 1225m, 1160w, 1100w, 960w, 940w, 920w, 825m, 805m, 760s, 735m, 710m, 690m.

Anal. Calcd. for C$_8$H$_8$N$_2$O$_2$ (M_r = 164.16): C 58.53, H 4.91, N 17.06%; found: C 58.44, H 5.08, N 18.89%.

1,6-Di(3-methyluracil-1-yl)hexadi-2,4-yne 4

A solution of 3 (182 mg, 1.11 mmol) in pyridine (8 ml) was added into a solution of Cu(OAc)$_2$·H$_2$O (996 mg, 5.00 mmol) in pyridine (29 ml) and stirred under argon at room temp. for 3 h. Pyridine was evaporated, water (20 ml) and EtOAc (20 ml) were added. The brown precipitate was filtered and the layers separated. The aqueous layer was extracted twice with EtOAc (20 ml). The combined extracts were washed with sat . NH$_4$Cl solution, dried and evaporated. The crude product was purified by prep. TLC (A): 96 mg (53%) of 4; m.p. 183–5 °C (MeOH); UV(EtOH) λ_{max}/nm (log ε): 262.2 (4.28); IR v_{max}/cm^{-1}: 2920m, 2840m, 1710s, 1655s, 1460s, 1380m, 1350m, 1220s, 1100m, 950w, 915w, 800m, 760m.

Anal. Calcd. for C$_{16}$H$_{14}$N$_4$O$_4$ (M_r = 326.31): C 58.88, H 4.33, N 17.18%; found: C 58.87, H 4.54, N 17.07%.

3-(4-Methoxybenzyl)-1-propargyluracil **5**

To a solution of **2** (449 mg, 3.00 mmol) in MeCN (6 ml) and DBU (0.9 ml, 6.00 mmol), PMBCl (0.75 ml, 5.40 mmol) was added, the solution was stirred at room temp. for 3 h, then acidified with 0.5 M NaHSO$_4$ (10 ml) and extracted with EtOAc (3 × 10 ml). The combined extracts were washed with a brine, dried (Na$_2$SO$_4$) and evaporated. The oily residue was crystallized from MeOH: 517 mg, and from mother liquors by preparative TLC (*B*) additional 247 mg of pure product **5** was obtained. Yield: 764 mg (94%), m.p. 115–7 °C; UV(EtOH) λ_{max}/nm (log ε): 222.1 (infl. 4.29), 263.6 (4.08); IR ν_{max}/cm^{-1}: 3230s, 2990m, 2835w, 2110w, 1705s, 1660s, 1630s, 1605s, 1585m, 1510s, 1450s, 1390s, 1360m, 1310s, 1290s, 1250s, 1225s, 1200m, 1175s, 1100m, 1030m, 945w, 920w, 885w, 845w, 825m, 800s, 770m, 745m, 710w, 690m.

Anal. Calcd. for C$_{15}$H$_{14}$N$_2$O$_3$ (M_r = 270.29): C 66.64, H 5.22, N 10.37%; found: C 66.52, H 5.51, N 10.33%.

1,6-Di[3-(4-methoxybenzyl)luracil-1-yl]hexadi-2,4-yne **6**

To a solution of **5** (720 mg, 2.66 mmol) in dry MeCN (67 ml), Cu(OAc)$_2$.H$_2$O (2.659 g, 13.32 mmol) was added and stirred under argon at 60 °C for 2.5 h. The mixture was cooled, water was (133 ml) added, the white precipitate was filtered, washed with water and dried to 682 mg (95%) of **6**, recrystallized from MeCN (20 ml): 603 mg (88%); m.p. 184–6 °C; R_f = 0.50 (*B*); UV(EtOH) λ_{max}/nm (log ε): 219.0 (infl. 3.49), 263.6 (3.34); IR ν_{max}/cm^{-1}: 1700*s*, 1665*s*, 1510*m*, 1450*s*, 1360*m*, 1345m, 1300m, 1245*s*, 1225m, 1170m, 1105*w*, 1020m, 805m.

Anal. Calcd. for C$_{30}$H$_{26}$N$_4$O$_6$ (M_r = 538.56): C 66.91, H 4.87, N 10.40%; found: C 66.98, H 4.93, N 10.23%.

1,6-Di(uracil-1-yl)hexadi-2,4-yne **7**

a) A solution of AlCl$_3$ (3.448 g, 15.86 mmol) in anisole (12.5 ml) was added to compound **6** (1.741 g, 3.23 mmol) under argon and stirred at 65 °C for 2 h. The dark red mixture was then cooled in ice-water and diluted with 1 M HCl (20 ml) under vigorous stirring. The white precipitate was filtered and thoroughly washed with water and ether (to remove anisole): 943 mg (98%) of **7**; m.p. decomp. above 300 °C; IR ν_{max}/cm^{-1}: 3020m, 2830m, 1710s, 1670s, 1470s, 1430s, 1385m, 1345m, 1240s, 1200m, 1180m, 1100w, 990w, 930w, 870w, 815m, 755m, 730w.

Anal. Calcd. for C$_{14}$H$_{10}$N$_4$O$_4$ (M_r = 298.26): C 56.38, H 3.38, N 18.78%; found: C 56.40, H 3.46, N 18.64%.

b) To a solution of **2** (300 mg, 2.00 mmol) in MeCN (100 ml), Cu(OAc)$_2$·H$_2$O (998 mg, 5.00 mmol) was added and stirred under argon at 60 °C for 3 h. The mixture was diluted with water (500 ml), the white precipitate was filtered, washed with water and air-dried: 219 mg (73.5%) of **7**. The product becomes red on standing, but all spectroscopic data are identical to those obtained by method a).

3,3″-Methylene-bis(1-propargyluracil) **8** *and 3-chloromethyl-1-propargyluracil* **9**

To a suspension of **2** (1.051 g, 7.00 mmol) in CH$_2$Cl$_2$ (70 ml), at reflux, a solution of DBU (2.1 ml, 14.00 mmol) in CH$_2$Cl$_2$ (14 ml) was added dropwise during 48 h by means of a syringe pump. After additional 24 h at reflux, the solution was concentrated and separated by FC, giving 615 mg (56%) of **8** and 68 mg (5%) of **9**.

Data of **8**. – M.p. 163–5 °C (MeOH); UV(EtOH) λ_{max}/nm (log ε): 261.2 (3.68); IR ν_{max}/cm^{-1}: 3265s, 3240s, 3080m, 2110w, 1725s, 1700s, 1670s, 1460s, 1450s, 1395m,

1315s, 1240m, 1210m, 1140m, 1095w, 1020w, 970w, 900w, 830m, 815m, 795m, 770w, 760w, 735m, 700m.

Anal. Calcd. for $C_{15}H_{12}N_4O_4$ (M_r = 312.28): C 57.69, H 3.87, N 17.94%; found: C 57.60, H 3.94, N 17.79%.

Data of 9. – M.p. 148–50 °C (MeCN); UV(EtOH) λ_{max}/nm (log ε): 267.6 (3.85); IR ν_{max}/cm^{-1}: 3270s, 2110w, 1735s, 1680s, 1445s, 1430m, 1415m, 1390m, 1360s, 1300m, 1225m, 1175m, 1120w, 1010w, 930w, 820m, 770m, 700m, 680m.

Anal. Calcd. for $C_8H_7ClN_2O_2$ (M_r = 198.62): C 48.38, H 3.55, N 14.11%; found: C 48.57, H 3.64, N 14.23%.

5-(Triphenylmethoxymethyl)uracil 11

To a suspension of 10[15] (734 mg, 5.17 mmol) in pyridine (10.5 ml), tritylchloride (1.469 g, 5.27 mmol) was added and stirred at 95–100 °C for 3 h. Pyridine was evaporated, some water (20 ml) was added, the crude product was filtered, thoroughly washed with water and air-dried: 1.848 g (93%), m.p. 292–4 °C; UV(EtOH) λ_{max}/nm (log ε): 261.9 (3.69). IR ν_{max}/cm^{-1}: 3050m, 1710s, 1080s, 1490m, 1450m, 1230w, 1215m, 1075w, 700m.

Anal. Calcd. for $C_{24}H_{20}N_2O_3$ (M_r = 384.43): C 74.98, H 5.24, N 7.29%; found: C 74.96, H 5.55, N 7.29%.

1-Propargyl-5-(triphenylmethoxymethyl)uracil 12

To a suspension of 11 (821 mg, 2.14 mmol) in dry MeCN (5 ml), BSA (1.25 ml, 5.13 mmol) was added and in an argon atmosphere stirred at 80 °C for 0.5 h. The resulting solution was cooled, propargyl bromide (0.476 ml, 4.27 mmol) was added and the reaction mixture was left in the dark for 10 days. It was then poured on crushed ice and water, neutralized with NaHCO$_3$, the precipitate was filtered, washed with water and dried. Product 12 was separated from unreacted 11 by recrystallization from acetone and by preparative TLC (*B*) of mother liquors, giving 665 mg (74%) of 12, m.p. 218–220 °C. UV(EtOH) λ_{max}/nm (log ε): 265.6 (3.71); IR ν_{max}/cm^{-1}: 3240s, 3060m, 2120w, 1710s, 1680s, 1490m, 1470m, 1450m, 1430m, 1350m, 1335m, 1240m, 1215m, 1075m, 750m, 710m, 700m.

Anal. Calcd. for $C_{27}H_{22}N_2O_3$ (M_r = 422.48). C 76.76, H 5.25, N 6.63%; found: C 76.58, H 5.51, N 6.45%.

1,6-Di[5-(triphenylmethoxymethyl)uracil-1-yl]hexadi-2,4-yne 13

To a solution of 12 (84.5 mg, 0.20 mmol) in dry MeCN (10 ml) at 60 °C, Cu(OAc)$_2$·H$_2$O (200 mg, 1.00 mmol) was added and under argon stirred at 60 °C for 2.5 h. The mixture was cooled, water (50 ml) was added, and the precipitate was collected: 65.5 mg (78%) of 13; m.p. 148–50 °C (MeCN-H$_2$O); R_f = 0.50 (*B*); UV(EtOH) λ_{max}/nm (log ε): 265.6 (3.90); IR ν_{max}/cm^{-1}: 3440m, 3060m, 1715s, 1675s, 1490m, 1465m, 1450m, 1340m, 1235m, 1055m, 760m, 700m.

Anal. calc. for $C_{54}H_{42}N_4O_6$ (M_r = 842.95): C 76.94, H 5.02, N 6.65%; found: C 76.75, H 5.25, N 6.67%.

3,3''-Methylene-bis[1-propargyl-5-(triphenylmethoxymethyl)uracil] 14

To a suspension of 12 (863 mg, 2.04 mmol) in CH$_2$Cl$_2$ (20 ml) at reflux, a solution of DBU (0.63 ml, 4.08 mmol) in CH$_2$Cl$_2$ (9.5 ml) was added dropwise during 72 h by means of a syringe pump. After additional 24 h at reflux, the solution was evapo-

rated to a small volume and separated by FC, giving 69 mg (8%) of unreacted **12** and 412 mg (47%) of **14**; m.p. 106–8 °C (MeOH); UV(CH$_2$Cl$_2$) λ_{max}/nm (log ε): 266.5 (4.29); IR ν_{max}/cm^{-1}: 3280s, 1710s, 1680s, 1665s, 1495m, 1470s, 1450m, 1340m, 1230m, 1155w, 1095m, 1030w, 990w, 900w, 765m, 750m, 705m.

Anal. Calcd. for C$_{55}$H$_{44}$N$_4$O$_6$ (M_r = 856.98): C 77.09, H 5.18, N 6.54%; found: C 76.98, H 5.34, N 6.46%.

Uracilophane **15**

A solution of **14** (857 mg, 1.00 mmol) in MeCN (100 ml) was added dropwise by means of a syringe pump during 48 h into the solution of Cu(OAc)$_2$.H$_2$O (2.00 g, 10.00 mmol) in MeCN (400 ml), stirred at 60 °C under argon. After additional 24 h at r.t., the reaction mixture was evaporated to dryness, slurried in CH$_2$Cl$_2$ and undissolved inorganic material removed. The filtrate was separated by preparative TLC (CH$_2$Cl$_2$): 188 mg (22%) of **15**; m.p. 196–8 °C; UV(CH$_2$Cl$_2$) λ_{max}/nm (log ε): 266.7 (4.03); IR ν_{max}/cm^{-1}: 1720s, 1680s, 1490m, 1450s, 1225w, 1150w, 900w, 760m, 700m; MS: m/z 515, 429, 413, 370, 301, 243.

Anal. Calcd. for C$_{110}$H$_{86}$N$_8$O$_{12}$ (M_r = 1711.94): C 77.18, H 5.06, N 6.55%; found: C 77.14, H 5.15, N 6.60%.

Molecular Modelling Studies

The initial structure building as well as molecular modelling studies were conducted using Sybyl software (Version 6.2, Tripos force field) running on Silicon Graphics Indy workstation. Simulated annealing was used as a type of molecular dynamics experiment. The number of cycles to run was 30, initial temperature for annealing was 1000 K. The system was held at this temperature for 1000 fs, then the temperature was reduced during 1000 fs until 50 K was reached. Annealing function (temperature *vs* time) was exponential.

Four resulting conformations were selected among thirty low energy conformations. Selected conformers were used as starting points for energy minimization setting the convergence criteria RMS displacement 0.01 kcal/mol nm, and using 3000 steps of Powel minimization until the energy gradient of 0.5 kcal/mol nm was reached. Atomic partial charges were computed by the Gasteiger-Hückel method.

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SAŽETAK

Novi tip ukrućenog makrocikla sa bis(3-uracilil)metanskim i heksadiinskim jedinicama. Uracilofan

Vesna Čaplar, Lidija Tumir i Mladen Žinić

Opisana je sinteza prvog uracilofana **15**, koji je konstruiran iz dviju jedinica bis(3-uracilil)metana i dva heksadiinska mosta u N(1)-položajima uracila. Konformacijska svojstva uracilofana **15** istraživana su molekulskom dinamikom. Utvrđeno je postojanje konformacija niske energije s djelomično ili potpuno preklopljenim (engl. stacked) parovima fenil-uracil ili fenil-fenil.