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The First Synthesis of Uracil Based Calix[4]arene Derivatives

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Abstract: The newly synthesized uracil based calix[4]arenes (**4**) possess anti-configuration (^{1}H nmr and energy minimization), where the substituents (R_1) on aryl ring between N_1-positions of uracil face the π-cloud of the ring between N_3-positions.
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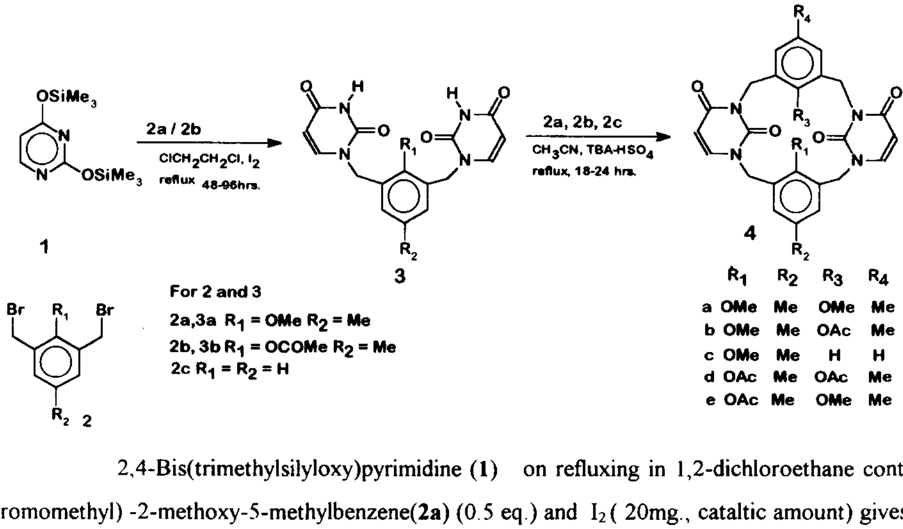
The significance of uracil and its derivatives towards complexation with H' and other biological cations is displayed remarkably in RNA strands[1] and other catalytic functions[2]. Despite the fact that most of these functions arise due to association behaviour of embedded urea unit of the uracil and the urea oxygen is less sterically hindered and a stronger binding group than ether and ester oxygens[3]; the uracil based receptors have scarcely been studied. The only reported uracil based cyclic receptor[4] has been synthesized in 0.2% yield. Here we present the facile two step synthesis of uracil based receptors which possess three dimensional structures (^{1}H nmr and energy minimization studies) quite resembling with the calix[4]arenes[5].



For 2 and 3
2a,3a R_1 = OMe R_2 = Me
2b, 3b R_1 = OCOMe R_2 = Me
2c R_1 = R_2 = H

	R_1	R_2	R_3	R_4
a	OMe	Me	OMe	Me
b	OMe	Me	OAc	Me
c	OMe	Me	H	H
d	OAc	Me	OAc	Me
e	OAc	Me	OMe	Me

2,4-Bis(trimethylsilyloxy)pyrimidine (**1**) on refluxing in 1,2-dichloroethane containing 1,3-bis(bromomethyl) -2-methoxy-5-methylbenzene(**2a**) (0.5 eq.) and I_2 (20mg., cataltic amount) gives 1,3-bis(1-uracilylmethyl)-2-methoxy-5-methylbenzene (**3a**) (90%), m.p. 263°C. **3a** reacts with dibromides **2a-2c** under phase transfer catalytic conditions (K_2CO_3 - CH_3CN-TBA HSO_4) to give macrocycle **4a** (20%), m.p. >340° C,

4b (27%), m.p. >340°C and **4c** (20%), m.p. 297°C, respectively. Further, **3b** (80%), m.p. 263°C, obtained by reaction of **1** with **2b,** cyclises with **2a** and **2b** under PTC conditions to give **4d**(20%), m.p. > 340°C and **4e** (28%), m.p. >340°C.

The compounds **3** in their ^{1}H nmr and off resonance ^{13}C nmr spectra exhibit NCH_2 as singlet and triplet, respectively. The macrocycles **4** in their ^{1}H nmr spectra exhibit two AB quartets (Table 1) due to N_1CH_2 and N_3CH_2 units. The ^{1}H nmr of **4a** exhibits two singlets for two methoxy groups and could be due to anti-configuration. One methoxy signal (δ 2.86) is shifted upfield by $\approx$1 ppm from its normal position in parent compound **3a** (δ 3.82). This upfield shift of methoxy group could be attributed to the interaction of methoxy group of the one aromatic ring with the π-cloud of the facing aromatic ring. The energy minimization[6] studies on syn- and anti- configurations of **4a** show that only in case of anti configuration one methoxy group can face the π-cloud of other ring (fig.1). So, **4a** possesses anti configuration.

Table 1: Selective ^{1}H nmr data for calix[4]arenes 4.

calix[4] arene	Me	OMe	OAc	NCH_2, AB quartet*	NCH_2, AB quartet*
4a	2.32, 2.33	2.86, 3.65	--	3.71, 5.74	4.20, 5.87
4b	2.32, 2.37	2.91	2.15	3.78, 5.75	4.22, 5.68
4c	2.31	2.95	---	3.91, 5.50	4.75, 5.82
4d	2.33, 2.41	---	1.50, 2.01	3.80, 5.46	4.20, 5.79
4e	2.29, 2.40	3.52	1.44	3.75, 5.42	4.19, 5.95

*The positions of AB quartets have been determined by decoupling experiments.

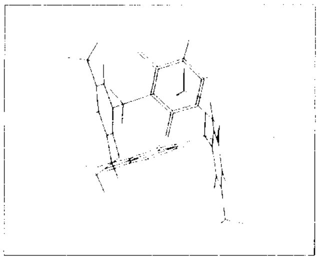


Fig. 1 Energy minimized anti-configuration of 4a

Similarly, in macrocycles **4b** and **4c**, the methoxy group is shifted to δ 2.85-2.95 and have anti configurations. In case of diacetyloxy derivative **4d**, one acetyl unit is shifted upfield by 0.75 ppm and would have anti- configuration with one acetyl group facing the aromatic ring. Further, in **4e** the acetyloxy unit is shifted upfield by 0.75 ppm and OMe (δ 3.54) is not affected. Therefore, in macrocycles **4a-4c**, N_1-methoxy group is shifted upfield and in **4d** and **4e** the N_1-acetyloxy unit is shifted upfield, which shows that the group attached on the ring between N-1 positions of uracil faces the π-cloud of other ring.

In conclusion, this two step approach provides a simple methodology for the synthesis of uracil based calix[4]arenes, which possess anti- configuration and aryl ring substituent (R_1) between N_1-positions of uracils faces the π-cloud of the ring between N_3- positions.

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