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Effect of 'Transannular Transmission' in Dibenzo-18-Crown-6

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Abstract. The effect of the nature of the substituent in the monosubstituted derivatives of dibenzo-18-crown-6 on the reactivity and direction of the electrophilic substitution reaction of the unsubstituted benzene ring has been determined. This transfer is carried out via the macrocycle and therefore is called 'transannular transmission'. The possible mechanism of this transmission is discussed.

Key words: 4′-*R*-Dibenzo-18-crown-6, reactivity, acetylation, butylation, substituent effect.

1. Introduction

Earlier [1] while investigating the acylation of dibenzo-18-crown-6 (DB18C6) by carboxylic acids in polyphosphoric acid (PPA) it was found that 4′,4″-diacyl-DB18C6 was formed in amounts 7–10 times higher than the 4′,5″-isomer.

Comparative analysis of DB18C6, dibenzo-24-crown-8 (DB24C8) and dibenzo-30-crown-10 (DB30C10) reactivities upon acetylation within the first 10-20 minutes has shown that the first acetyl group entered into DB18C6 more rapidly than into DB24C8 and DB30C10 [2,3]. However, it passivates the unsubstituted benzene ring more strongly in the case of DB18C6, which leads to a certain deceleration of the reaction in the second stage.

The data obtained allowed us to suggest that upon reaction the effect of the first substituent in DB18C6 is transmitted via the macrocycle to the unsubstituted benzene ring, which makes the 4″- and 5″-positions nonequivalent. This difference becomes more pronounced when the reaction occurs under mild conditions, as well as upon acylation by carboxylic acid salts. The conditions for the regioselective formation of 4′,4″-diacyl-DB18C6 have been determined [4].

The inequivalence of the 4″- and 5″-positions was confirmed by studies on ^{13}C NMR spectra of 4′-acetyl- and 4′-nitro-DB18C6, where the differentiation of $C^{1''}$ and $C^{2''}$, $C^{3''}$ and $C^{6''}$, $C^{4''}$ and $C^{5''}$ signals of the unsubstituted benzene ring was found [5].

Furthermore, earlier [6] we found that the chloromethylation of 4′-*tert*-butyl-DB18C6 proceeds more rapidly and in better yield than chloromethylation of 4′-acyl-DB18C6.

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This gave us much to think about the influence of the nature of the substituent on the reactivity of the unsubstituted benzene ring. So it is very interesting to investigate the influence of DB18C6 substituents on other electrophilic substitution reactions.

2. Experimental

The ^{1}H-NMR spectra were obtained on a Tesla BS-567 NMR-spectrometer in $CDCl_3$, the internal standard being GMDS.

UV spectra were obtained on a Lambda-16 spectrometer (Perkin-Elmer).

The molecular masses have been determined by mass spectrometry (Varian MAT-311) at 150 °C with ionized electron energy of 70 eV.

The C, H elemental analysis of the compounds obtained are in accordance with calculated values.

Neutral aluminium oxide has been used for chromatographic analysis and separation of products.

The starting compounds were obtained by published methods: 4′-acetyl-DB18C6 was obtained by the reported procedure [6]; 4′-*tert*- and 4′-*sec*-butyl-DB18C6 were obtained by the reported procedure [7]; 4′-butyryl–DB18C6 was synthesized by analogy with [6], yield was 22%, m.p. 146–148 °C, M_f 430, $C_{24}H_{30}O_7$, M_c 430.50. ^{1}H-NMR spectra (δ, ppm): 7.48 (1H, d), 7.40 (1H, s), 6.76 (1H, d) – ArH; 6.80 (4H, s) – ArH of unsubstituted benzene ring; 4.10–4.26 (8H, m) – α-OCH_2; 3.84–4.10 (8H, m) – β-OCH_2; 2.80 (2H, t) – $COCH_2$; 1.70 (2H, m) – CH_2; 0.92 (3H, t) – CH_3. 4′-n–Butyl-DB18C6 was obtained by reduction of 4′-butyryl-DB18C6 by analogy with the reported procedure [8], yield was 25%, m.p. 102–104 °C, M_f 416, $C_{24}H_{32}O_6$, M_c 416.51. ^{1}H-NMR spectra (δ, ppm): 6.80 (4H, s) – ArH of unsubstituted benzene ring; 6.60–6.74 (3H, m) – ArH of substituted benzene ring; 4.08-4.24 (8H, m) – α-OCH_2; 3.92–4.08 (8H, m) – β-OCH_2; 2.44 (2H, t) – α-CH_2; 1.10–1.70 (4H, m) – β- and γ-CH_2; 0.84 (3H, t) – CH_3.

Acetylation of DB18C6 and its 4′-R-substituted derivatives was carried out by analogy with the reported procedure [1] and butylation by analogy with [7]. The compounds obtained were purified by column chromatography. The reaction conditions, yields and m.p. of synthesized products are given in Table I. Below, the compound names, molecular mass found, empirical formula, calculated molecular mass and ^{1}H-NMR spectra (δ, ppm) are listed.

4′-*tert*-Butyl-4″(5″)-acetyl-DB18C6: M_f 458, $C_{26}H_{34}O_7$; M_c 458,55; 7.55 (1H, d) – ArH (5″), 7.50 (1H, s) – ArH (3″), 6.70–6.96 (4H, m) – ArH (6″, 3′, 5′, 6′); 4.10–4.40 (8H, m) – α-OCH_2, 3.94–4.10 (8H, m) – β-OCH_2; 2.54 (3H, s) – $COCH_3$; 1.27 (9H, s) – $C(CH_3)_3$.

4′-*sec*-Butyl-4″(5″)-acetyl-DB18C6: M_f 458; $C_{26}H_{34}O_7$; M_c 458,55; 7.56 (1H, d) – ArH (5″), 7.51 (1H, s) – ArH (3″), 6.64–6.90 (4H, m) – ArH (6″, 3′, 5′, 6′); 4.10–4.38 (8H, m) – α-OCH_2; 3.80–4.10 (8H, m) – β-OCH_2; 2.54 (3H, s) –

$COCH_3$; 2.94 (1H, sex) – CH; 1.50 (2H, quin) – CH_2; 1.16 (3H, d) – α-CH_3; 0.74 (3H, t) – ω-CH_3.

4′-n-Butyl-5′, 4″(5″)-diacetyl-DB18C6: M_f 500; $C_{28}H_{36}O_8$; M_c 500,59; 7.54 (1H, d) – ArH (5″), 7.50 (1H, s) – ArH (3″), 6.84 (1H, d) – ArH (6″); 7.19 (1H, s) – ArH (6′); 6.66 (1H, s) – ArH (3′); 4.10–4.40 (8H, m) – α-OCH_2; 3.92–4.10 (8H, m) – β-OCH_2; 2.54 (3H, s) – $COCH_3$(4″(5″)); 2.51 (3H, s) – $COCH_3$(5′); 2.82 (2H, t) – α-CH_2; 1.20—1.60 (4H, m) – β- and γ-CH_2; 0.9 (3H, t) – CH_3.

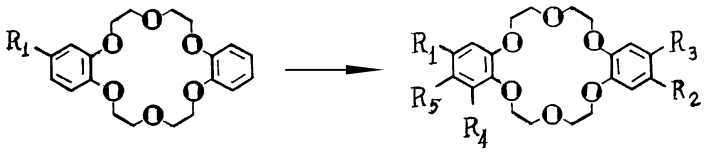
3. Results and Discussion

We have studied the effect of the nature of the substituent on the acetylation and butylation reactions of 4′-R-DB18C6 (where R is acetyl or *tert*-, *sec*- and n-butyl) in polyphosphoric acid (PPA).

The products separated in these reactions are shown in Figure 1.

The reactions which are compared were carried out in parallel. TLC was the method used to control the reaction; samples were removed every 15 minutes. The reaction time was calculated according to the disappearance of the starting materials.

The comparative analysis of 4′-acetyl-DB18C6 acetylation with isomeric 4′-butyl derivatives of DB18C6 has shown that 4′-acetyl-DB18C6 acetylation is complete within 1.5 h, whereas the acetylation of butyl derivatives occurs during 0.7–0.8 h (Table I, experiments 1–4). Thus, an acetyl group decreases the reactivity of an unsubstituted benzene ring approximately twofold. It was found upon acetylation of 4′-*tert*-butyl- and 4′-*sec*-butyl-DB18C6 that only one acetyl group enters into the 4″- or 5″- position of the unsubstituted benzene ring. Therefore, 4′-*tert*-butyl-4″(5″)-acetyl-DB18C6 (II) or 4′-*sec*-butyl-4″(5″)-acetyl-DB18C6 (III) are



I. $R_1 = R_2(R_3) = COCH_3$, $R_3(R_2) = R_4 = R_5 = H$;

II. $R_1 = tert\text{-}C_4H_9$, $R_2(R_3) = COCH_3$, $R_3(R_2) = R_4 = R_5 = H$;

III. $R_1 = sec\text{-}C_4H_9$, $R_2(R_3) = COCH_3$, $R_3(R_2) = R_4 = R_5 = H$;

IV. $R_1 = n\text{-}C_4H_9$, $R_2(R_3) = R_5 = COCH_3$, $R_3(R_2) = R_4 = H$;

V. $R_1 = R_2(R_3) = tert\text{-}C_4H_9$, $R_3(R_2) = R_4 = R_5 = H$;

VI. $R_1 = R_2 = R_3 = R_4 = sec\text{-}C_4H_9$, $R_5 = H$;

VII. $R_1 = R_2(R_3) = sec\text{-}C_4H_9$, $R_3(R_2) = R_4 = R_5 = H$.

Figure 1. Products of 4′-R-Dibenzo-18-Crown-6 acetylation and butylation.

Table I. Results of 4′-R-dibenzo-18-crown-6 acetylation and butylation reactions (ratio of substrate: agent: PPA = 1 : 2 : 5).

Exp. no.	R	Agent	React. temp. °C	React. durat. h.	Product yield %	Product m.p., °C	Index	Compound obtained
1.	4′-acetyl-	CH_3COOH	70	1.5	74	194–202	I	4′,4″(5″)-diacetyl-DB18C6*
2.	4′-*tert*-butyl-	CH_3COOH	70	0.7	53	100–110	II	4′-*tert*-butyl-4″(5″)-acetyl-DB18C6
					12	88–102	V	4′,4″(5″)-di-*tert*-butyl-DB18C6**
3.	4′-*sec*-butyl-	CH_3COOH	70	0.7	50	78–86	III	4′-*sec*-butyl-4″(5″)-acetyl-DB18C6
					15	oil	VI	3′,5′,4″,5″-tetra-*sec*-butyl-DB18C6**
4.	4′-*n*-butyl-	CH_3COOH	70	0.8	77	149–153	IV	4′-*n*-butyl-5′,4″(5″)-diacetyl-DB18C6
5.	4′-acetyl-	*tert*-C_4H_9OH	60	3.0	67	108–113	II	4′-acetyl-4″(5″)-*tert*-butyl-DB18C6
6.	4′-*tert*-butyl-	*tert*-C_4H_9OH	60	2.0	83	92–102	V	4′,4″(5″)-di-*tert*-butyl-DB18C6**
7.	4′-acetyl-	*sec*-C_4H_9OH	60	3.0	65	82–86	III	4′-acetyl-4″(5″)-*sec*-butyl-DB18C6
8.	4′-*sec*-butyl-	*sec*-C_4H_9OH	60	2.0	46	oil	VI	3′,5′,4″,5″-tetra-*sec*-butyl-DB18C6**
					32	79–87	VII	4′,4″(5″)-di-*sec*-butyl-DB18C6**

4″(5″) – means the substituent is at 4″- or 5″-position.
* Product described in [1].
** Product described in [7].

the main products of reaction, respectively (experiments 2, 3). It was discovered that disproportionation of starting *iso*-alkylderivatives proceeds under the reaction conditions and as a result di-*tert*-butyl- or tetra-*sec*-butyl-DB18C6, respectively, were isolated in small amounts. In contrast to this, disproportionation of starting alkylderivative was not observered in the case of acetylation of 4′-n-butyl-DB18C6. But two acetyl groups enter into 4′-n-butyl-DB18C6, one in the 4″- or 5″-position of the unsubstituted benzene ring and the other in the *ortho*-position to the n-butyl group. Therefore 4′-n-butyl-5′,4″(5″)-diacetyl-DB18C6 (IV, experiment 4) is the main product of this reaction.

tert- and *sec*-butylation of 4′-acetyl-DB18C6 leads to the same products (II, III), which were obtained upon acetylation of 4′-*tert*-butyl- and 4′- *sec*-butyl-DB18C6, respectively (experiment 5, 7). There are some differences in the melting points of the products obtained. This is perhaps connected with different ratios of *cis*- and *trans*-isomers in these products. Alkylation has been carried out in parallel to acylation. However, during the alkylation of 4′-acetyl- and 4′-*tert*- or 4′-*sec*-butyl-DB18C6 by isomeric butyl alcohols such a clear difference of unsubstituted benzene ring activity was not found (experiments 5–8). This appears to be connected with the fact that the formation of an attacking electrophilic particle is probably the rate-determining step in alkylation, rather than its interaction with the benzene ring. This stage does not depend on the substrate nature. However, it was found that the acetyl group is prevented from entering the second butyl group not just in 'its own' benzene ring, but also in the distant ones. Therefore, 4′-acetyl-4″(5″)-*sec*-butyl-DB18C6 (III) is the main product of 4′-acetyl-DB18C6's alkylation by *sec*-butyl alcohol, while *sec*-butylation of 4′-*sec*-butyl-DB18C6 under similar conditions (experiment 8) results in the formation of 3′,5′,4″,5″-tetra-*sec*-butyl -DB18C6 (VI).

The 'mixed' derivatives obtained have been characterized by NMR spectra. The protons of the aromatic ring with the acetyl group appear as a doublet at 7.54 ppm, a singlet at 7.5 ppm and a doublet at 6.84 ppm, corresponding to protons in the 5′-, 3′- and 6′-positions of the benzene ring. The doublet at 6.84 ppm appears together with a proton multiplet of the benzene ring containing an alkyl substituent. In 4′-n-butyl-5′,4″(5″)-diacetyl-DB18C6's (IV) NMR spectra the protons of the aromatic ring with two different substituents appear as two singlets at 7.19 ppm, and 6.66 ppm corresponding to protons in *ortho*-positions to the acetyl and alkyl groups. The acetyl groups in this compound appear as two singlets at 2.54 and 2.51 ppm as well. The triplet of the n-butyl substituent α - protons shifts upfield (2.8 ppm) in comparison with the initial substance n-butyl derivative (2.44 ppm). These data are in agreement with Ref. [9], where introduction of an acceptor substituent in the *para*-position of ethylbenzene led to a chemical shift of the alkyl proton signals upfield in NMR spectra. We also observed an analogous chemical shift of CH proton signal in compound III (2.94 ppm) in comparison with the signal of the CH proton of the initial 4′-*sec*-butyl-DB18C6 (2.44 ppm).

Thus, the substituent nature in monosubstituted DB18C6 affects both the reactivity of the unsubstituted benzene ring and the distribution of electron density in it.

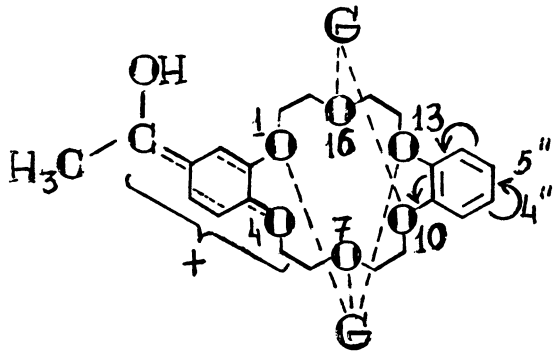


Figure 2. The assumed structure of theoxonium cation.

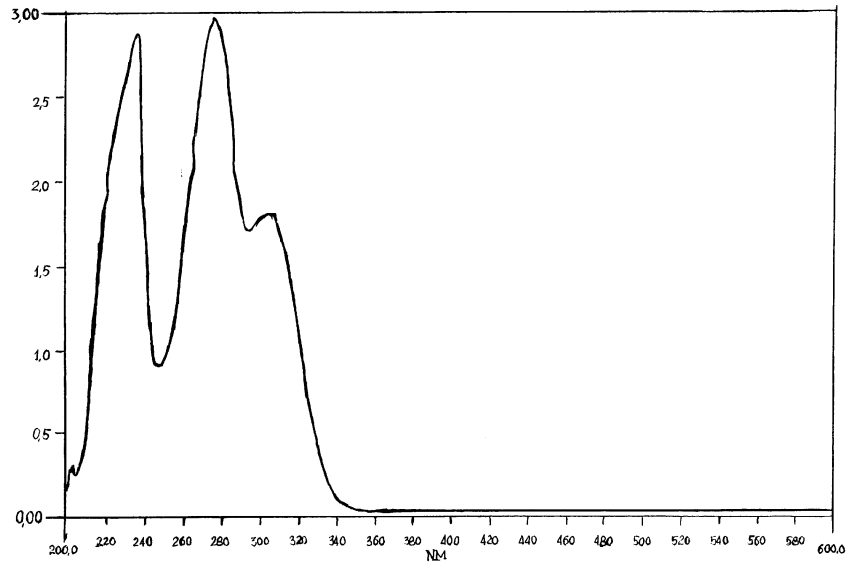
In other words, the electron-acceptor substituent passivates the unsubstituted benzene ring and orients the second group mainly in the 4″-position. That is why the main acylation product is 4′,4″-diacyl–DB18C6 [1]. The activating and orienting influence of an electron-donor substituent was less manifest as was to be expected.

And how is this influence exerted? In the literature it has been stated that the DB18C6 molecule can have several conformations. If the cation size is equal to the size of the macrocyclic cavity, the molecule DB18C6 adopts a 'nest' conformation, in which all oxygens are situated in one plane. If the size of the macrocyclic cavity is less than the cation size, or it bonds with the large anion, the DB18C6 molecule adopts a 'tripod' or 'roost' conformation, in which three oxygens (through 1) are in one plane and three other oxygens are in a parallel plane.

In Ref. [5] we showed that 4″- and 5″-positions are inequivalent in 4′-acetyl-DB18C6. However, these differences disappear in the complex of 4′-acetyl-DB18C6 with KI or $La(ClO_4)_3$ because the 'nest' conformation is formed. By contrast, the 4″- and 5″-positions are equivalent in 4′-acetyl-DB24C8. They are equivalent in its complex with CsI, forming the 'nest' conformation, but they are inequivalent in its complex with KI, forming the other conformation, like a double 'tripod'.

Our experimental data show that in acylation in PPA the 4′-acetyl-DB18C6 molecule assumes a conformation where differences in the 4″- and 5″-positions are intensified. We think that in PPA the 4′-acetyl-DB18C6 molecule is predominantly in the 'tripod' conformation, which is distorted by the quinonic-like structure of the acyl-substituted benzene ring. The so-called 'guest' favours its stability. The role of 'guest' might be played by a solvent proton. Our experimental data show that PPA is not only an acylation catalyst; PPA remains fixed by a carbonyl group like $AlCl_3$ in the classic Friedel–Crafts acylation. As a result of interaction between the acyl group and PPA an oxonium cation is formed which is able to form the quinonic-like structure (Figure 2).

Its presence is confirmed by UV spectra of 4′-acetyl-DB18C6, taken in alcohol and PPA. The comparison of the UV-spectra of 4′-acetyl-DB18C6 in alcohol (Figure 3) and in PPA (Figure 4) confirmed our assumption that the electronic structure



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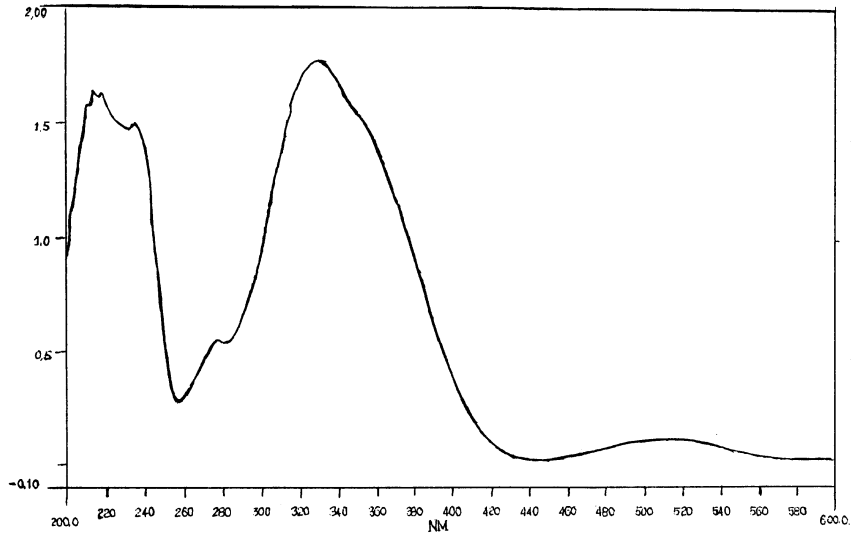
ETK002.SP	401	600.00	200.00	0.015	2.975	2.00	A	1

302.0	1.807	292.0	1.702	274.0	2.975	246.0	0.885	234.0	2.885
206.0	0.230	203.0	0.302	202.0	0.154				

Figure 3. UV spectrum of 4′-acetyl-dibenzo-18-crown-6 in alcohol.



Filename	#pts	start	end	min	max	res	ord	acc
POLK003.SP	401	600.00	200.00	0.012	1.767	2.00	A	1

514.0	0.106	446.0	0.012	330.0	1.767	281.0	0.525	277.0	0.540
256.0	0.266	235.0	1.485	232.0	1.463	219.0	1.624	217.0	1.603
214.0	1.629	212.0	1.568	211.0	1.580				

Figure 4. UV spectrum of 4′-acetyl-dibenzo-18-crown-6 in polyphosphoric acid.

of 4′-acetyl-DB18C6 in PPA differs greatly from its electronic structure in other solvents. The appearance of an absorption line at 514 nm and a bathochromic shift of the absorption line from 302 nm (in alcohol) to 330 nm (in PPA) confirms the presence of a quinonic structure.

Because of the formation of the quinonic like structure, O^4 will not interact with a 'guest'. Therefore, the 'guest' will interact only with O^{10} and O^{16}, situated in the same plane as the O^4, whereas the other 'guest' is bound to all three O^1, O^7 and O^{13}, situated on the parallel plane. This causes the considerable shift of free electron pairs from O^{10} in comparison with O^{13} towards the 'guest'. This in turn leads to a decrease of electron density in the 5″- position of the benzene ring, situated in the *para*-position to O^{10}. In addition, the breaking of the O^4 bond with the 'guest' leads to greater lability of O^{10} and O^{16} in comparison with that of O^1, O^7 and O^{13}. Therefore, the O^{10} couples with the benzene ring more readily than O^{13}. This leads also to a decrease of electron density in the 5″-position. The 4″-position is less depleted by electrons and electrophilic attack goes mainly towards this position. Therefore 4′,4″- or '*trans*'-isomer is mainly formed during acylation.

Thus, we have revealed the previously unknown effect of transmission of the substituent influence on the reactivity of an aromatic ring separated from an R-substituted benzene ring by a chain consisting of 7 atoms and having no coupled bond system. We have called this effect 'transannular transmission' in analogy to the well-known transannular interaction.

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