Medium-sized cyclophanes. Part 66.[1] Through-space electronic interactions on acylation of 8,16-disubstituted [2.2]metacyclophanes

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Depending on the substituents at the 5-position of 8,16-dimethyl[2.2]metacyclophanes different reactivities to acylation at the 13-position were observed due to the through-space electronic interaction with the other benzene ring.

Keywords: cyclophanes, strained molecules, acylation, through-space electronic interaction

Maquestiau *et al.*[2] reported formylation of [2.2]metacyclophane (MCP= metacyclophane) with dichloromethyl *n*-butyl ether in the presence of $TiCl_4$ according to the Rieche procedure[3] to give 4-formyl[2.2]MCP. This result was different from other electrophilic aromatic substitutions of [2.2]MCP; *e.g.* bromination, iodination, and nitration, which afforded the corresponding 2-substituted 4,5,9,10-tetrahydropyrenes *via* an addition elimination mechanism.[4] The relatively late transition state in the formylation of [2.2]MCP compared to other electrophilic aromatic substitution might be proposed to be involved. However, there is no report concerning the acylation of internally substituted [2.2]MCPs. We undertook the present work in order to obtain further information about the chemical behaviour of 5-substituted 8,16-dimethyl[2.2]MCPs. These might forced to form the acylation product because the formation of the 4,5,9,10-tetrahydropyrene by transannular cyclisation is prevented by the 8- and 16- methyl groups. We report here on the acylation reactions of 8,16-disubstituted [2.2]MCPs **1** with acylation reagents.

Results and discussion

When acetylation of 8,16-dimethyl[2.2]MCP (**1a**)[5] with acetic anhydride in the presence of $TiCl_4$ as a catalyst was carried out at 0°C for 5 min, 5-acetyl-8,16-dimethyl[2.2]MCP (**2a**) and 5,13-diacetyl-8,16-dimethyl[2.2]MCP (**3a**) were obtained in 96% and 4% yield, respectively. Prolonging the reaction time of **1a** with acetic anhydride at 0°C increased the yield of the diacetyl compound **3a** or reacting at room temperature for 90 min gave 96% yield.

Thus, the extent of acetylation of **1a** was strongly affected by the reaction conditions used. The present acetylation behaviour of [2.2]MCP **1a** can be explained by the stability of the cationic intermediates, which could arise from through-space electronic interaction with the benzene ring located on the opposite side. Thus, a first σ-complex intermediate (**A**) would be stabilized by the through-space electronic intraannular interaction through the 8,16-positions with the opposing benzene ring, thus accelerating the reaction. However, the second electrophilic substitution with the acetyl group can be strongly suppressed in intermediate (**B**) because of deactivation of the second aromatic ring by the acetyl group like in the nitration of 8,16-dimethyl[2.2]MCP (**1a**), which only afforded a mono-nitration product even under drastic nitration conditions.[6]

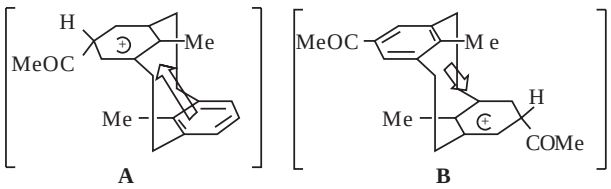
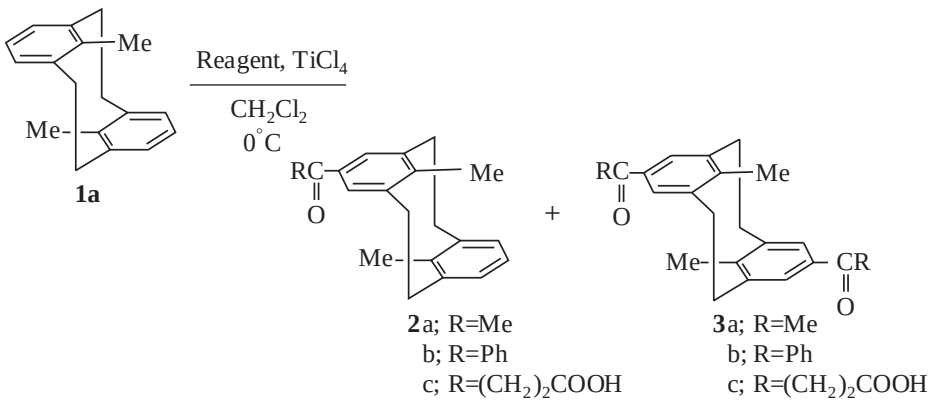


Fig.1 The through-space electronic interaction of σ-complex intermediates.

A similar tendency was observed in the acetylation of **1a** with acetyl chloride in the presence of $TiCl_4$ which afforded the monoacylation product **2a** in 86% yield along with the diacylation product **3a** in 12% yield. Interestingly, acylation of **1a** with benzoyl chloride or succinic anhydride in the presence of $TiCl_4$ as a catalyst was carried out at 0°C for 90 min, also giving mono-acylation products **2b–c** in 98 and 96% yields, respectively. No two-fold acylation product was also observed even under the conditions of $AlCl_3$–$MeNO_2$. In contrast, it is shown that in the case of 8,16-dimethoxy[2.2]MCP (**1b**) with acetyl chloride and benzoyl chloride the bis-acylated products



Scheme 1

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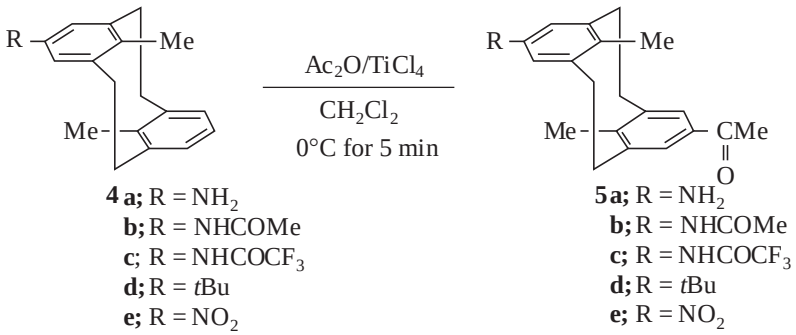

4 a; R = NH_2
b; R = NHCOMe
c; R = $NHCOCF_3$
d; R = *t*Bu
e; R = NO_2

5 a; R = NH_2
b; R = NHCOMe
c; R = $NHCOCF_3$
d; R = *t*Bu
e; R = NO_2

Scheme 2

were obtained in quantitative yields due to the increased π-basicity caused by introduction of two methoxy groups.

In order to study the substituent effects on the present acylation reaction by through-space electronic interactions in more detail, we have chosen to investigate the acylation of the 5-substituted 8,16-dimethyl[2.2]MCPs **4** and **2a** (see Scheme 2). In fact, the presently developed procedure was extended to the acetylation of the 8,16-dimethyl[2.2]MCPs **4a**–**e**.[6a] The reaction was carried out under the same conditions as described above and the results are summarised in Table 2.

Acetylation of 5-amino-8,16-dimethyl[2.2]MCP (**4a**) with acetic anhydride in the presence of $TiCl_4$ at 0°C resulted in almost complete acetylation at the 13-position within 5 min to afford 5-acetylamino-13-acetyl-8,16-dimethyl[2.2]MCP (**5b**), which was obtained via *N*-acetylation of **5a** under the reaction conditions used. Complete monoacetylation was also observed in the acetylation of the 5-acetylamino- (**4b**) and 5-trifluoroacetylamino- (**4c**) derivatives. A similar result was obtained in the case of the 5-*tert*-butyl derivative **4d** to afford **5d** in 98% yield. In contrast, compound **2a** which has an electron-withdrawing group (acetyl) afforded the mono-acetylation product **3a** only in 12% yield along with recovery of the starting compound **2a** under the conditions used. However, in the case of the 5-nitro derivative **4e**, the desired mono-acetylated product **5e** could not be isolated due to the formation of a mixture of intractable products.

In conclusion we have found that the substituent effect at the 5-position on the reactivities to acylation at the 13-position does exist in 8,16-dimethyl[2.2]MCPs due to the through-space electronic interaction with the other benzene ring. Further studies on electrophilic substitution of 8,16-disubstituted [2.2]MCPs are currently in progress in our laboratory.

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Table 1 Acylation of 8,16-dimethyl[2.2]MCPs (**1a**)[a]

Run	Reagent	Time/min	Product/%[b,c]	
1	Ac_2O	5	**2a** (96) [77]	**3a** (4)
2	Ac_2O	30	**2a** (79)	**3a** (21)
3	Ac_2O	90	**2a** (69)	**3a** (31)
4[d]	Ac_2O	90	**2a** (4)	**3a** (96) [78]
5	AcCl	90	**2a** (86) [70]	**3a** (12)
6	C_6H_5COCl	90	**2b** (100) [98]	**3b** (0)
7	Succinic anhydride	90	2c (100) [96]	**3c** (0)

[a]Reagent/**1a** = 3.8 mol/1 mol, $TiCl_4$/Reagent = 3.6 mol/1 mol. [b]Yields are determined by GLC analysis. [c]Isolated yields are shown in square brackets. [d]Reaction temperature was 20°C.

Table 2 Acetylation of 5-substituted 8,16-dimethyl[2.2]MCPs (**4**) and (**2a**)[a]

Run	R	Substrate	Product/%[b,c]	Recovered/%[b]
1	NH_2	**4a**	**5b** (98.6) [83]	**4a** (1.4)
2	NHCOMe	**4b**	**5b** (97.8) [92]	**4b** (2.2)
3	$NHCOCF_3$	**4c**	**5c** (98.4) [93]	**4c** (1.6)
4	*t*Bu	**4d**	**5d** (97.5) [90]	**4d** (2.5)
5	COMe	**2a**	**3a** (12.0)	**2a** (88.0) [80]
6	NO_2	**4e**	Complex mixture[d]	**4e** (0)

[a]Ac_2O/**4** = 3.8 mol/1 mol, $TiCl_4$/Ac_2O = 3.6 mol/1 mol. [b]Yields are determined by GLC analysis. [c]Isolated yields are shown in square brackets. [d]A large amount of resinous materials and unidentified compounds as formed.

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