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Complexation of phthalides and substituted 3-benzylidene phthalides with $Cr(CO)_6$

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Abstract

The acid-catalysed complexation of various substituted phthalides with $Cr(CO)_6$ has been studied. Complexation of substituted 3-benzylidene phthalides takes place at the phenyl ring in most cases, but with di-halogeno-substituted 3-benzylidene phthalides the complexation took place at the phthalide moiety. An explanation of this difference is based on molecular modelling and quantum chemical calculations.

Key words: Chromium; Pthalide; Carbonyl

1. Introduction

In our earlier papers [1–3], we described the complexation of various aromatic derivatives with $Cr(CO)_6$ in the presence of esters, ketones or acids as catalysts. The complexation of benzoic or phenylacetic acid esters proceeded readily without any catalyst. Until now such complexation of lactones, such as phthalides, has been attempted, in spite of the fact that the phthalide moiety is often present in biologically active substances [4,5], and has been used as an intermediate in the synthesis of medicaments [6]. Complexation of phthalides could be of some interest because it is well known that complexation of arenes with $Cr(CO)_6$ considerably changes their properties, including their reactivity [7]. Both Jaouen [8] and Solladie-Cavallo [9,10] have reported that electron-donating substituents on the benzene ring facilitate the complexation, and electron-withrawing substituents hinder it. The main goal of the present work was to find out whether complexation of phthalides and substituted 3-benzylidene phthalides could be achieved. A subsidiary goal was to find out whether the regioselectivity of complexation was dependent on the nature of the substituent on the benzylidene moiety.

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2. Results and discussion

In one of our earlier papers [2], we described the ready complexation of benzoic acid esters with $Cr(CO)_6$ in refluxing decalin without any catalyst. A high yield of η^6-(diethyl phthalate)tricarbonylchromium was achieved by the same method [11]. To our surprise, it was not possible to complex unsubstituted phthalide (A) without a catalyst, but complex I was isolated in 62% yield when acetic acid alone was used as the catalyst. Yields of 3-ethylidenephthalide (II) ranged between 5 and 15% under the same conditions. The attempts to bring about complexation of substituted 3-benzylidenephthalides under these conditions were less satisfactory than those in which a mixture of butanone and acetic acid was used as catalyst. The yields of complexes varied from 6.5 to 90%, depending on the quality of the substituent (Table 1).

The structures of the complexes were confirmed by their ^1H NMR spectra. For that purpose, the H^1 NMR spectra of the free ligands (**A**, **B**, **C**) were also recorded. In the ^1H NMR spectrum of phthalide (**A**), the apparent doublet (a.d.) of H_7 proton at 7.92 ppm is well separated from the signals of H_4–H_6 protons, which form a multiplet at 7.58 ppm; the signal of the $-CH_2-$ group appears as a singlet at 5.32 ppm. In the spectrum of 3-benzylidenephthalide (**B**), the signal of methine proton =CH– is found at 6.36 (s) ppm, and the ph-

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TABLE 1. Results of complexation of phthalide with $Cr(CO)_6$ in boiling decalin

Compound	Catalyst [a]	Reaction time (h)	Yield (%)
I	A	4.5	62
II	A	4	15
III	B	3.5	91
IV	B	7	34
V	B	7.5	51
VI	B	6	12
VII	B	5.5	89
VIII	B	5	84
IX	B	3.5	8.4
X	B	4	9
XI	B	7	6.4

[a] A, 0.1 ml of AcOH for 9 mmol of the starting phthalide; B, 0.1 ml of AcOH and 0.1 ml of butatnone for 9 mmol of the starting phthalide.

thalide protons (H_4–H_7) give a multiplet at 7.78 ppm; the signals of the phenyl group protons ($H_{2'}$–$H_{6'}$) form a well-separated multiplet at 7.38 ppm. In the spectrum of 3-(3,5-difluorobenzylidene)phthalide (**C**), a characteristic feature is the singlet from =CH– at 6.32 ppm, and there is an apparent doublet from the H_7 proton at 7.97 ppm. Signals from the phenyl ring protons were observed as a triplet for H_4 (^3J(H–F) = 8 Hz) at 6.77 ppm, and double doublets of H_2 and H_6 protons at 7.42 and 7.31 ppm (^3J(HF) = 8 Hz and ^5J(HF) = 2 Hz).

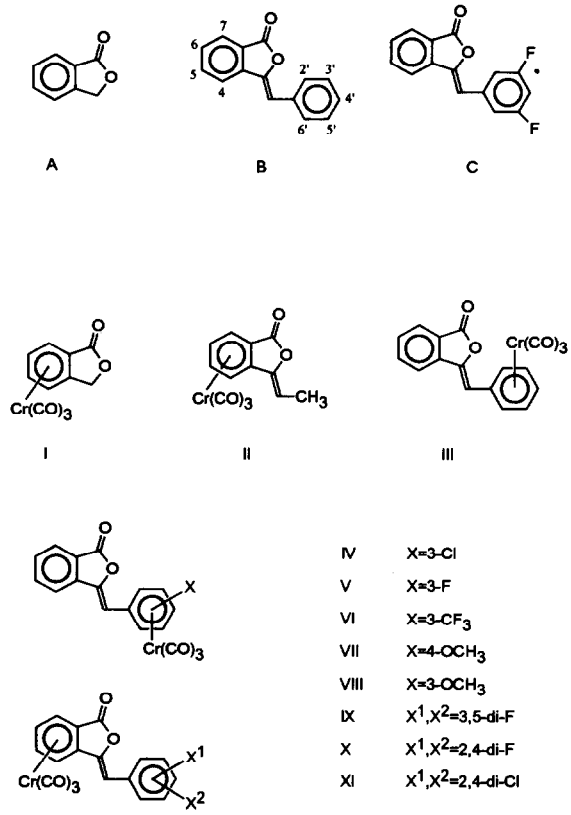

Chart 1.

The CH_2 protons of η^6-phthalidetricarbonylchromium (**I**) are inequivalent, and two doublets at 5.27 and 5.31 (J = 5.7 Hz) ppm are observed in this case. From the shielding of the corresponding signals in the ^{1}H-NMR spectra of benzylidenephthalide complexes **III**–**XI** it can be seen that in the case of the dihalo-substituted derivatives **X**, **XI**, it was the phenyl ring that was complexed.

It is of interest to know whether this regioselectivity is governed by kinetic or thermodynamic control of the complexation. The stabilities (which determine the thermodynamic control) of the complexes were calculated by the Extended Huckel method [12] using the CACAO program [13]. For calculations of geometries, the MMX force field implemented in PC MODEL program [14], parametrized for good reproduction of structures of organometallic complexes [15], was used. The calculated energies ΔE that define the relative stabilities of the benzylidenephthalide bearing the $Cr(CO)_3$ group on the phthalide or the phenyl moiety, respectively, are given by

$$\Delta E = E_{\text{Phthal}} - E_{\text{Phen}} \text{ (in eV mol}^{-1}\text{)}$$

X	H	2,4-diCl	3-F	3-OCH_3
ΔE	1.9	−5.8	5.8	8.7
X	3-Cl	3-CF_3	3,5-diF	2,4-diF
Δ	0.1	1.4	8.4	12.3

It follows from these results that in all cases, except for the 2,4-dichloro derivative, the complex bearing the $Cr(CO)_3$ on the phenyl moiety should be more stable, which is in accord with the experimental observations apart from those the difluoro-derivatives.

The relative tendency to kinetic control of the complexation can be predicted by the molecular electrostatic potential (MEP) of the ligand. MEP represents the interaction energy between the molecule under study and a model electrophilic particle (a point charge). The molecular electrostatic potential was calculated on the basis of atomic charges calculated by the semi-empirical AM1 method [16] for AM1 optimized geometries of phthalides. For MEP calculations and their display on the van der Waals molecular surface, the MGP program [17] was used. The distribution of the MEP on the surface of all molecules under study has a similar character with three minima, one on the phthalide moiety, one on the phenyl moiety, and one on the oxygen of the carbonyl group. Figure 1 shows the distribution of MEP for unsubstituted 3-benzylidene-phthalide, Fig. 2 for its 3-methoxy derivative, and Fig. 3 for its 3,5-difluoro derivative. The dark region represents negative potential (favourable for

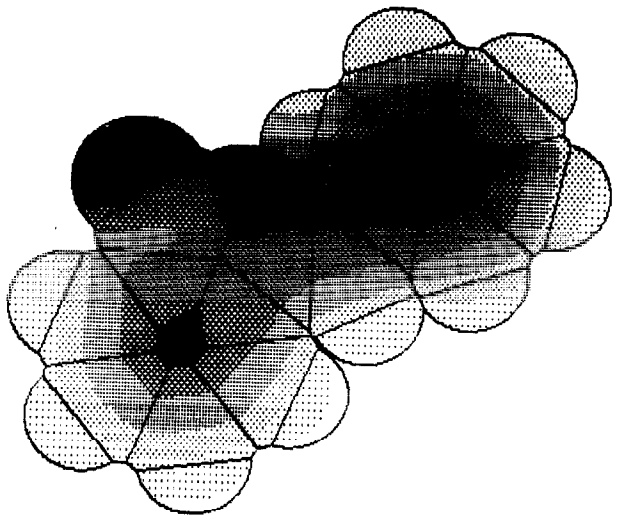

Fig. 1. The map of molecular electrostatic potential of 3-benzylidenephthalide.

interaction with the electrophile) and the light region represents positive potential. The measure of kinetic activity of the above-mentioned regions is given by the value of MEP calculated on the centre of phthalide or phenyl moiety, respectively. The calculated values, in eV, are as follows:

X	H	2,4-diCl	3-F	3-OCH_3
MEP_{Phen}	−2.14	−1.60	−1.59	−1.99
MEP_{Phthal}	−1.50	−1.36	−1.38	−1.48
ΔMEP	−0.64	−0.24	−0.21	−0.51
X	3-Cl	3-CF_3	3,5-diF	2,4-diF
MEP_{Pen}	−1.86	−1.49	−1.05	−1.00
MEP_{Phthal}	−1.40	−1.25	−1.25	−1.35
ΔMEP	−0.46	−0.24	+0.23	+0.35

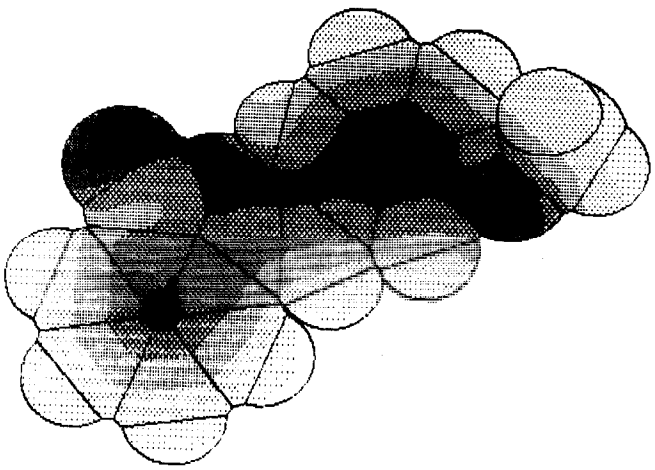

Fig. 2. The map of molecular electrostatic potential of 3-(3-methoxybenzylidene)phthalide.

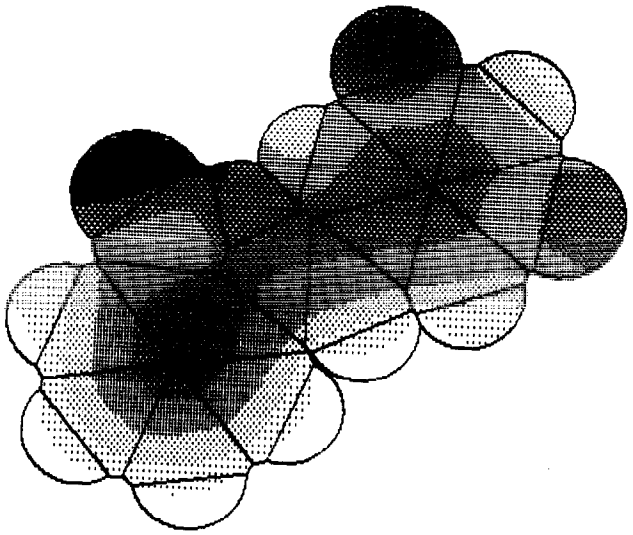

Fig. 3. The map of molecular electrostatic potential of 3-(3,5-difluorbenzylidene)phthalide.

These results are in accord with the experimental facts, except for the 2,4-dichloro derivative, but the errors in predicting electronic distribution in polychloro derivatives are well known. Our results show that even in the substances having two conjugated arene rings, the complexation takes place on the one having the higher electron density, which is in accord with the observed [8–10] relative ease of complexation of substituted benzenes.

3. Conclusions

We have shown that it is possible to prepare $Cr(CO)_3$ complexes of various phthalides providing that the appropriate catalyst is used. Calculations suggest that the complexation under our conditions is probably governed by kinetic control. It thus seems likely that MEP calculations could be widely used for the prediction of regioselectivity of complexation of the aromatic ligands bearing two or more different aromatic moieties.

4. Experimental details

Phthalide was prepared as described in ref. 18, and 3-ethylidenephthalide and most of the substituted 3-benzylidenephthalides as described in refs. 19–21. The ^1H NMR spectra were recorded with $CDCl_3$ solutions on a TESLA BS-587 80 MHz instrument with tetramethylsilane as internal standard.

New compounds were crystallized from a chloroform/ethanol mixture: 3-(3-trifluoromethylbenzylidene)phthalide, m.p. 143–147°C; 3-(2,4-difluoroben-

zylidene(phthalide, m.p. 174–175°C; 3-(3,5-difluorobenzylidene)phthalide, m.p. 201–202°C.

4.1. General procedure for complexation of phthalides

A mixture of 9 mmol of phthalide and 4.5 mmol of $Cr(CO)_6$ in 70 ml of decalin was refluxed in the apparatus described previously [1] for the time specified in each case below. (The apparatus containing the reaction mixture was evacuated and filled with argon several times before immersion into a pre-heated bath.) The catalyst used was 0.1 ml of acetic acid (for phthalide and 3-ethylidenephthalide), or 0.1 ml of acetic acid and 1.4 ml of butanone (for benzylidenephthalides). Heating of the mixture was stopped when the onset of decomposition was observed. The mixture was then cooled to 60°C, filtered through Kieselguhr, and left in the freezer (−30°C) to allow crystallization to take place. Chromatographic separation of the product (SiO_2, isohexane/ethyl acetate) was used when necessary.

η^6-Phthalidetricarbonylchromium (**I**). Reaction time 4.5 h; 1.5 g (62%) of **I**, m.p. 138–139°C, were isolated. For $C_{11}H_6CrO_5$, mol.wt. 269.9. Anal. Found: C, 48.77, H, 2.21. $C_{11}H_6CrO_5$ calc.: C, 48.91; H, 2.22%. ^{1}H NMR: CH_2 δ 5.21 (s, 1 H) and 5.24 (s, 1H), H_7; 6.09 (d, 1H, $^3J = 8$ Hz); H_4 δ 5.07 (d, 1H, $^3J = 8$ Hz); H_5, H_6 δ 5.46 (m, 2H).

η^6-(3-Etylidenphthalide)tricarbonylchromium (**II**). Reaction time 4 h; 0.42 g (15%) of **II**, m.p. 144–147°C, were isolated. For $C_{13}H_8CrO_5$ mol.wt. 296.0. Found: C, 51.96; H, 2.70. $C_{13}H_8CrO_5$ calc.: C, 52.71; H, 2.72%. ^{1}H NMR CH_3: δ 1.99 (d, 2H); H_7: δ 6.08 (d, 1H, $^3J = 8$ Hz), =CH– + H_4–H_6: δ 5.46 (m, 4H).

η^6(3-Benzylidene)tricarbonylchromiumphthalide (III). Reaction time 3.5 h; 2.93 g (91%) of **III**, m.p. 212°C (dec.) were isolated. For $C_{18}H_{10}CrO_5$ mol.wt. 358.3. Anal. Found: C, 60.04; H, 2.71. $C_{18}H_{10}CrO_5$ calc.: C, 60.34; H, 2.82. ^{1}H NMR: H_7: δ 7.96 (d, 1H, $^3J = 8$ Hz); =CH–: δ 5.94 (s, 1H); H_4–H_6: δ 7.72 (m, 3H); $H_{3'}$, $H_{5'}$: δ 5.94 (m, 2H); $H_{2'}$, $H_{4'}$, $H_{6'}$: δ 5.40 (m, 3H).

η^6-(3-(3'-Chlorobenzylidene)tricarbonylchromium-phhthalide (**IV**). Reaction time 7 h; 1.2 g (34%) of **IV**, m.p. 175°C (dec.) were isolated. For $C_{18}H_9CrClO_5$ mol. wt. 392.7. Anal. Found: C, 55.63; H, 2.66. $C_{18}H_9CrClO_5$ calc.: C, 55.11; H, 3.31%. ^{1}H NMR: H_7: δ 7.97 (d, 1H, $^3J = 8$ Hz); =CH–: δ 6.00 (s, 1H); H_4–H_6: δ 7.70 (m, 3H); $H_{2'}$: δ 5.95 (s, 1H); H4'–H6': δ 5.55 (m, 3H).

η^6-(3-(3'-Fluorobenzylidene)tricarbonylchromiumphthalide (**V**). Reaction time 7.5 h; 1.96 g (58%) of **V**, m.p. 184°C (dec.) were isolated. For $C_{18}H_9FCrO_5$ mol.wt. 376.3. Anal. Found: C, 57.31; H, 2.36. $C_{18}H_9FCrO_5$ calc.: C, 57.45; H, 2.41. ^{1}H NMR: H_7: δ 7.96 (app-d, 1H); =CH– δ 5.97 (s, 1H); H_4–H_6: δ 7.71 (m, 3H); $H_{2'}$: δ 5.87 (app. s, 1H); $H_{4'}$–$H_{6'}$: δ 5.45 (m, 3H).

η^6(3-(3'-Trifluoromethylbenzylidene))tricarbonylchromiumphthalide (**VI**). Reaction time 6 h; 0.46 g (12%) of **VI**, m.p. 184°C (dec.) was isolated. For $C_{19}H_9F_3CrO_5$, mol.wt. 426.3. Anal. Found: C, 54.01, H, 2.04. $C_{19}H_9F_3CrO_5$ calc.: C, 53.52; H, 2.13%. ^{1}H NMR: H_7: δ 7.95 (d, 1H, $^3J = 8$ Hz); =CH–: δ 6.05 (s, 1H); H_4–H_7: δ 7.60 (m, 3H); $H_{4'}$: δ 6.20 (d, 1H, $^3J = 8$ Hz); $H_{2'}$: δ 5.90 (s, 1H); H': δ 5.30 (t, 1H), $H_{6'}$: δ 5.65 (d, 1H).

η^6-(3-(4'-Methoxybenzylidene))tricarbonylchromiumphthalide (**VII**). Reaction time 5.5 h; 3.1 g (89%) of **VII**, m.p. 185°C (dec.) were isolated. For $C_{19}H_{12}CrO_6$, mol.wt. 388.3. Anal. Found: C, 58.54; H, 2.99. $C_{19}H_{12}CrO_6$ calc.: C, 58.78; H, 3.12%. ^{1}H NMR: H_7: δ 7.88 (d, 1H, $^3J = 8$ Hz); =CH–: δ 5.88 (s, 1H); H_4–H_6: δ 7.81 (m, 3H); $H_{2'}$, $H_{6'}$: δ 6.16 (d, 2H, $^3J = 8$ Hz); $H_{3'}$, $H_{5'}$: δ 5.21 (d, 2H, $^3J = 8$ Hz).

η^6-(3-(3'-Methoxybenzylidene)tricarbonylchromiumphthalide (**VIII**). Reaction time, 5 h; 2.93 (84%) of **VIII**, m.p. 183°C were isolated. For $C_{19}H_{12}CrO_6$, mol.wt. 388.3. Anal. Found: C, 59.30; H, 3.19. $C_{19}H_{12}CrO_6$ calc.: C, 58.76; H, 3.12%. ^{1}H NMR: H_7: δ 7.96 (d, 1H, $^3J = 8$ Hz); =CH–: δ 6.03 (s, 1H); H_4–H_6: δ 7.69 (m, 3H); $H_{2'}$: δ 5.75 (s, 1H); $H_{4'}$, $H_{6'}$: δ 5.44 (m, 3H).

3-(3',5'-Diflurobenzylidene)(η^6-phthalidetricarbonylchromium) (**IX**). Reaction time 3.5 h; 0.29 g (8.4%) of **IX**, m.p. 178°C was isolated. For $C_{18}H_8F_2CrO_5$, mol.wt. 394.3. Anal. Found: C, 52.77; H, 1.94. $C_{15}H_8F_2CrO_5$ calc.: C, 54.83; H, 2.05%. ^{1}H NMR: δ H_1 + =CH: δ 6.12 (m, 2H); H_2, H_3: δ 5.77 (m, 2H); H_4: δ 5.32 (d, 2H); $H_{4'}$: δ 6.80 (t, 1H); $H_{2'}$: δ 7.20 (app. d, 1H); $H_{6'}$: δ 7.35 (app. d, 1H).

3-(2',4'-Difluorobenzylidene)(η^6-phthalidetricarbonylchromium) (**X**). Reaction time, 4 h; 0.32 g (9%) of **X**, m.p. 184°C (dec.) was isolated. For $C_{18}H_8F_2CrO_5$, mol.wt. 394.3. Anal. Found: C, 52.79; H, 2.03%. $C_{18}H_8F_2CrO_5$ calc.: C, 54.83; H, 2.05%. ^{1}H NMR: H_7: δ 6.12 (d, 1H, $^3J = 8$ Hz); =CH–: δ 6.42 (s, 1H); $H_{2'}$, H_3: δ 5.75 (m, 2H); H_4: δ 5.72 (m, 1H); $H_{3'}$: δ 8.15 (m, 1H); $H_{5'}H_{6'}$: δ 6.89 (m, 2H).

3-(2',4'-Dichlorobenzylidene)(η^6-phthalidetricarbonylchromium) (**XI**). Reaction time, 7 h; and 0.25 g (6.4%) of **XI**, m.p. 168°C (dec.) were isolated. For $C_{18}H_8Cl_2CrO_5$ mol.wt. 427.2. Anal. Found: C, 49.92; H, 2.15%. $C_{18}H_8Cl_2CrO_5$ calc.: C, 50.71; H, 1.89%. ^{1}H NMR: H_7: δ 5.27 (d, 1H, ^{3}J = 8 Hz); =CH–: δ 6.60 (s, 1H); $H_{2'}$, $H_{3'}$: δ 5.80 (m, 2H); H_4: δ 5.27 (d, 1H); $H_{3'}$: δ 7.25 (s, 1H); $H_{5'}$: δ 8.10 (d, 1H, $^3J = 8$ Hz); $H_{6'}$: δ 7.40 (d, 1H, $^3J = 8$ Hz).

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