

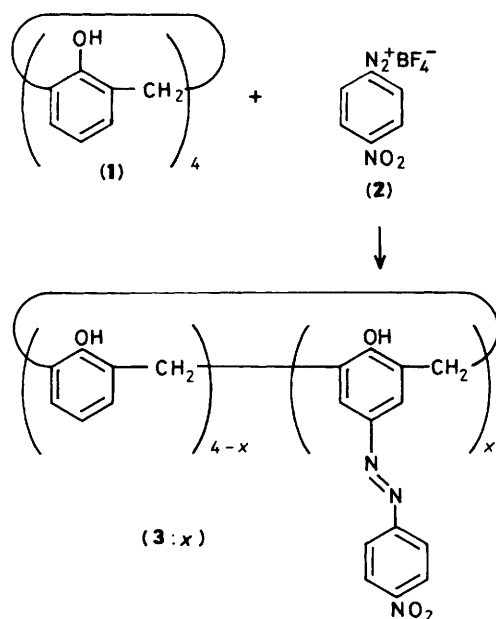
## Autoaccelerative Diazo Coupling with Calix[4]arene: Unusual Co-operativity of the Calixarene Hydroxy Groups

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Diazo coupling between calix[4]arene and *p*-nitrobenzenediazonium ion selectively afforded the tetrasubstituted calix[4]arene and almost no mono-, di-, and tri-substituted calix[4]arenes even in the presence of unchanged calix[4]arene: the unusual all-or-nothing substitution is attributed to the specific hydrogen-bonding effect among the calixarene OH groups.

The chemistry of cyclodextrins and crown ethers has been a focus of interest in host-guest chemistry for the last 2 decades and many functionalised derivatives which can partly mimic the *in vivo* action of enzymes have been exploited.<sup>1-4</sup> More recently, Gutsche and co-workers<sup>5</sup> have reported on a series of new cyclic oligomers called 'calixarenes'. We have currently been interested in the functionalisation of calixarenes which may act as host molecules in solution.<sup>6</sup> It is now known that certain skillfully modified calixarenes are capable of including small molecules in their cavities.<sup>6-10</sup> It thus occurred to us that introduction of chromophoric groups into calixarenes would be of great value for the development of a new class of functionalised calixarenes: one may expect novel association properties and spectroscopic properties for this class of 'chromogenic calixarenes'. The object is readily accomplished by means of the diazo coupling reaction, one of the most well-known substitution reactions in phenol derivatives. We carried out diazo coupling of calix[4]arene and *p*-nitrobenzenediazonium tetrafluoroborate (2) and unexpectedly found that the reaction occurs in an all-or-nothing manner [*i.e.*, in the Scheme (3;



Scheme.

$x = 4$ ) resulted selectively even in the presence of unchanged (1). The unusual autoacceleration behaviour is rationalised in terms of the strong, intramolecular hydrogen-bonding effect among the OH groups.

Compound (1) (0.46 g, 1.09 mmol) and (2) (see Table for the

Table. Product distribution for diazo coupling with calix[4]arene

Molar ratio in feed (2)/(1)	Unchanged (1) (mol %)	Product (mol %)			
		(3; $x = 1$ )	(3; $x = 2$ )	(3; $x = 3$ )	(3; $x = 4$ )
1.00	70.0	5.3	1.2	1.5	22.0
2.00	44.2	5.6	3.4	1.7	45.1
3.00	20.1	6.0	1.6	2.3	70.0
4.00	0	0	0	1.0	99.0

concentration) were dissolved in tetrahydrofuran (THF) (30 ml) at 5 °C and the diazo coupling reaction was completed in 15 min (confirmed by the reaction with 3-hydroxynaphthalene-2,7-disulphonate). The solution was concentrated under reduced pressure and the residual orange powder was analysed by a t.l.c. method [Merck Kieselgel 60F 254, chloroform-methanol-pyridine, 10:1:1 (v/v/v)]. We observed four orange spots for (3;  $x$ ) and one colourless spot for (1); the four orange spots were identified (in the order of  $R_F$ ) to be (3;  $x = 1$ ), (3;  $x = 2$ ), (3;  $x = 3$ ), and (3;  $x = 4$ ), respectively, by elemental analysis. The yields were determined by using a high-speed t.l.c. scanner (Shimadzu CS-920).† The results are summarised in the Table.

Examination of the Table reveals that unchanged (1) decreases with increasing molar ratio (2:1). Very interestingly, with increasing molar ratio only the concentration of (3;  $x = 4$ ) increases and those for (3;  $x = 1$ ), (3;  $x = 2$ ), and (3;  $x = 3$ ) are always low and almost constant (except for the molar ratio = 4.00). They exist only in the level of the steady-state concentration. These findings lead us to a conclusion that the diazo coupling reaction with calix[4]arene occurs autoacceleratively.

What is the origin of the novel autoacceleration effect observed for calix[4]arene? It is known that the OH groups in calix[4]arene interact intramolecularly through hydrogen-bonding.<sup>5,6,11,12</sup> The interaction is so strong that the first dissociation of the OH groups ( $K_{a1}$ ) occurs in the very acidic pH region while the last (fourth) dissociation ( $K_{a4}$ ) occurs in the very basic pH region.<sup>11</sup> Furthermore, introduction of electron-withdrawing groups into the *p*-position would lower the  $pK_a$  of the OH groups not only in the substituted phenol unit but also in the neighbouring phenol units.<sup>12</sup> The first electrophilic attack of (2) occurs towards the phenolate unit dissociated by pyridine. This reaction lowers the  $pK_a$  and dissociates the OH groups in the neighbouring phenol units. Thus, the subsequent electrophilic attack of (2) is considerably facilitated even in the presence of the same amount of pyridine. As a result, the diazo coupling reaction proceeds autoacceleratively. This view was

† We separately synthesized (3;  $x = 4$ ), which was used as a standard sample to prepare the calibration curve. We here assumed that the absorption coefficient for one azobenzene unit is the same in (3;  $x = 1$ ), (3;  $x = 2$ ), (3;  $x = 3$ ), and (3;  $x = 4$ ) [*e.g.*,  $A_{(3;x=4)} = 4 \cdot A_{(3;x=1)}$ ].

also supported by the following preliminary results: (i) the rate constants obtained by the kinetic studies on the successive reaction  $(\mathbf{1}) \xrightarrow{k_1} (\mathbf{3}; x = 1) \xrightarrow{k_2} (\mathbf{3}; x = 2) \xrightarrow{k_3} (\mathbf{3}; x = 3) \rightarrow (\mathbf{3}; x = 4)$  were in the order of  $k_1 \ll k_2 < k_3 < k_4$  and (ii) the concentrations of mono-, di-, and tri-substituted calix[4]-arenes were increased when less electron-withdrawing benzenediazonium salts (e.g., *p*-H or *p*-SO<sub>3</sub><sup>-</sup> instead of *p*-NO<sub>2</sub>) were used.

In conclusion, the autoacceleration effect, unexpectedly discovered for the diazo coupling reaction with calix[4]arene, is closely related to the strong hydrogen-bonding interaction among the OH groups. Since this interaction is quite essential in calixarene chemistry, the similar autoacceleration effect may be generally observed for electrophilic substitution reactions at the calixarene *p*-position.

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