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Communications

Podand-Catalyzed Nucleophilic Aromatic Substitutions of Anthraquinones: A Novel Synthetic Approach and a Mechanistic Suggestion from Solid-State Data

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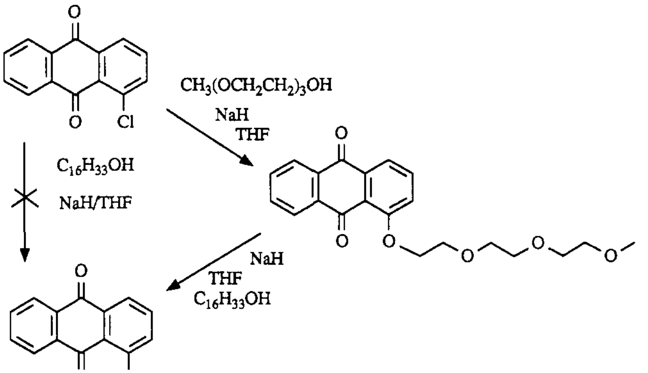
Summary: Haloanthraquinones undergo facile nucleophilic substitution by aliphatic alcohols only when a catalytic amount of oligo(ethylene glycol) derivative is present; the latter serves as both nucleophile and leaving group in the transformation.

The anthraquinone system[1] is increasingly important as its value in electrochemical switching mechanisms becomes more appreciated.[2] Synthetic access to its derivatives has proved limited because the readily available hydroxy derivatives undergo alkylation with difficulty and the halide derivatives are extremely resistant to substitution. We demonstrate in this paper that (1) nucleophilic substitution is efficient so long as a poly(ethyleneoxy) derivative is used as the nucleophile; (2) the poly(ethyleneoxy) side arm, once attached, may be displaced by nucleophiles which do not displace chloride; and (3) the entire process may be made catalytic.



When nucleophilic aromatic substitution of 1-propanol on 1-chloroanthraquinone was attempted (NaH, tetrahydrofuran, reflux, 4 h), no product was obtained and >80% of starting material was recovered. The same result was observed in the attempted reaction with 1-hexadecanol under similar conditions. However, when oligo(ethylene glycol) derivatives such as $CH_3O(CH_2CH_2O)_nH$, where $n = 1$–4 were used, 75 ± 15% yields of anthraquinone ethers were obtained.[3] When displacement of the ethyleneoxy side arm on the anthraquinone podand was attempted with either *n*-propyl oxide or *n*-hexadecyl oxide, substitution was successful even though it has failed when chloride was the leaving group. When 1-chloroanthraquinone was treated with *n*-propyl oxide or *n*-hexadecyl oxide in the presence of *a catalytic amount* (i.e., 0.12–0.24 molar equiv) of $CH_3O(CH_2CH_2O)_3H$, 37% and 80% yields of product, respectively, were obtained. This procedure therefore constitutes a single-step, one-pot, catalytic nucleophilic aromatic substitution reaction on the hitherto intractable anthraquinone series.

The catalytic process has been confirmed for a range of alkoxides from propanol to hexadecanol. The yield of

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Table I. Nucleophilic Aromatic Substitutions of 1-Chloroanthraquinones[a]

nucleophile	yield,[b] %	catalyst added[c]	mp, °C
Leaving Group: Cl^-			
$CH_3CH_2CH_2OH$	0	none	NA[d]
$CH_3(CH_2)_8OH$	0	none	NA
$CH_3(CH_2)_{15}OH$	0	none	NA
1-$CH_3(CH_2)_{15}OH$ + crown[e]	15	none	98.5–99.5
$CH_3CH{=}CHCH_2OH$	0	none	NA
MeOEOH[f]	90	none	147–148
MeOEOEOH	76	none	69–71
MeOEOEOEOH	74[g]	none	55–57
Leaving Group: $O(CH_2CH_2O)_3CH_3$			
$CH_3CH_2CH_2OH$	36	none	150–151
$CH_3(CH_2)_8OH$	75	none	78–79
$CH_3(CH_2)_{15}OH$	83	none	98.5–99.5
$CH_3CH{=}CHCH_2OH$	37	none	105–106
Leaving Group: Cl^-; Catalytic $HO(CH_2CH_2O)_3CH_3$ added[h]			
$CH_3CH_2CH_2OH$	37	0.24	150–151
$CH_3(CH_2)_8OH$	73	0.24	78–79
$CH_3(CH_2)_{15}OH$	77	0.12	98.5–99.5
$CH_3(CH_2)_{15}OH$	80	0.24	98.5–99.5
$CH_3CH{=}CHCH_2OH$	0	0.24	NA
$(CH_3)_2CHCH_2CH_2OH$	40	0.24	92–93
$(CH_3)_2CHOH$	0	0.24	NA
cyclohexanol	0	0.24	NA
$CH_3(CH_2)_{15}OH$ + $CH_3OCH_2CH_2OH$	76	0.24	98–99

[a] The reactions were conducted as described in ref 2. [b] Isolated yield for compounds having the expected spectral (^1H NMR, IR) characteristics. All new compounds gave satisfactory (±0.4%) combustion analyses. [c] Catalyst added simultaneous with alcohol and base. [d] NA means not applicable. [e] 18-Crown-6. [f] *E* in this context means ethylene, CH_2CH_2. [g] We reported a yield of 61% for each of these reactions in an earlier study. We believe that those yields reflect product loss during recrystallization. [h] Quantity added: ca. 0.12–0.24 molar equiv (see Supplementary Material).

product when propanol is the nucleophile was lower than in the other cases and likely reflects a difference in solubility for the alkoxide compared to the more lipophilic species. In the hexadecanol case, yields were excellent at different catalyst concentrations, but hexadecanol substituted effectively even when crown was added externally. This suggests that coordination plays a role in enhancing nucleophilicity. The fact that the podands are more effective suggests that a more tightly coordinated nucleophile or nucleofuge is required. It is interesting to note that 2-butenol did not afford product in the catalytic reaction although 37% of product was obtained when $(OCH_2CH_2)_3OCH_3$ was the leaving group. Yields for the catalytic process were slightly lower for branched-chain alcohols, and the secondary alcohols 2-propanol and cyclohexanol failed to yield product. Finally, 2-methoxyethanol was used successfully as catalyst in a reaction with hexadecanol, an observation which suggests considerable generality.

Color changes observed during the reaction suggested the possibility of an electron-transfer reaction, but we failed to confirm this possibility by EPR analysis.[3] It seemed reasonable to assume that the oligo(oxyethylene) chain was complexed during both its roles as nucleophile and nucleofuge. Although we lack definitive evidence on this point, we have obtained the X-ray crystal structure of a unique (bis)podand complex which is highly suggestive. The structure of 1,5-bis(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)anthracene-9,10-dione·$2Na^+$ is shown in Figure 1.[4]

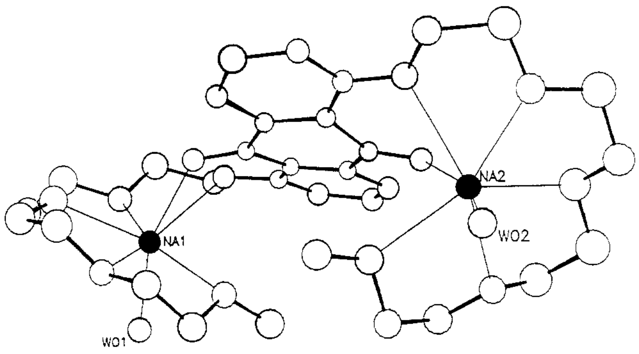
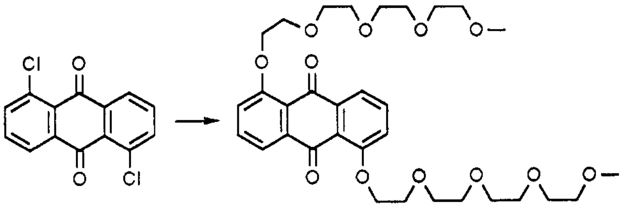


Figure 1. ORTEP plot of the bis(NaI) complex of 1,5-bis(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)anthracene-9,10-dione.

The anti two-armed anthraquinone derivative shown below was prepared by heating 1,5-dichloroanthraquinone for 5 h in a dry THF solution containing tetraethylene glycol monomethyl ether and NaH. The product, a yellow oil, was obtained after chromatography (silica, 2% MeOH–CH_2Cl_2) in 72% yield. The NaI complex was crystallized (45%) from a CH_2Cl_2 solution containing NaI (10 equiv) and 1,5-bis(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)anthracene-9,10-dione. Recrystallization from anhydrous EtOH gave yellow crystals, mp 173–174 °C. Anal. Calcd for $C_{32}H_{44}O_{12}\cdot 2NaI\cdot 2H_2O$: C, 40.18; H, 5.07. Found: C, 40.49; H, 5.29.



Complexation of two sodium cations as reported herein is not unexpected. We have previously shown by EPR spectroscopy in THF solution that 1,5-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)anthracene-9,10-dione, when reduced to the radical anion, stoichiometrically complexes two Na^+ cations. Evidence obtained by similar EPR experiments showed that the syn or 1,8-analogue also bound two sodium cations, a result that is more difficult to envisage structurally.[5]

The solid state structure,[4] refined to a final *R* value of 7.5%, shows the 1,5-disubstituted anthraquinone residue to be at the center of the complex and each Na^+ cation is heptacoordinated. The central anthraquinone ring distorts to achieve solvation of Na^+ from one axis and the other axial solvation is provided by a water of hydration on each side. An ORTEP plot of the structure is illustrated in Figure 1.

The two-cation complex structure is strongly suggestive of an associative nucleophilic aromatic substitution in which a cation plays a key role both in coordination of the nucleophile and the nucleofuge. Even so, interesting mechanistic questions remain to be answered. Experiments to answer such questions are currently underway.

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Supplementary Material Available: Experimental data for (1-hexadecyloxy)anthracene-9,10-dione (6 pages). Ordering information is given on any current masthead page.

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[4] Crystal data: $C_{32}H_{44}O_{12}\cdot 2NaI\cdot 2H_2O$, FW 959.59, space group *Cc*, $a = 11.429$ (5) Å, $b = 16.153$ (6) Å, $c = 22.472$ (6) Å, $Z = 4$, $d_c = 1.57$ g cm^{-1}, Mo Kα ($\mu = 16.14$ cm^{-1}), $R = 0.060$ for 1836 unique reflections with $I > 2\sigma(I)$ (of 2803 unique data) measured by an Enraf-Nonius CAD4 X-ray spectrometer by ω–2θ scans, $2° < \theta < 42°$.

[5] Gustowski, D. A.; Delgado, M.; Gattto, V. J.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 7553.