Alkaline earth metal-sensing anthracene fluorophore-hosts

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Novel anthracene fluorophore-hosts 1–4, bonding through an ester or ether linkage to a crown ether or polyether side-arm, have been synthesized. Addition of an alkaline earth metal cation to a host solution causes a unique fluorescence intensity change. That is, the hosts bonding through an ester linkage, compounds 1 and 3, give fluorescence quenching, whereas the hosts bonding through an ether linkage, compounds 2 and 4, give fluorescence enhancement. The host having a crown ether side-arm, compound 2, recognises calcium cations more strongly than barium cations, in contrast to the host having a polyether side-arm, compound 4, which prefers barium cations to calcium cations.

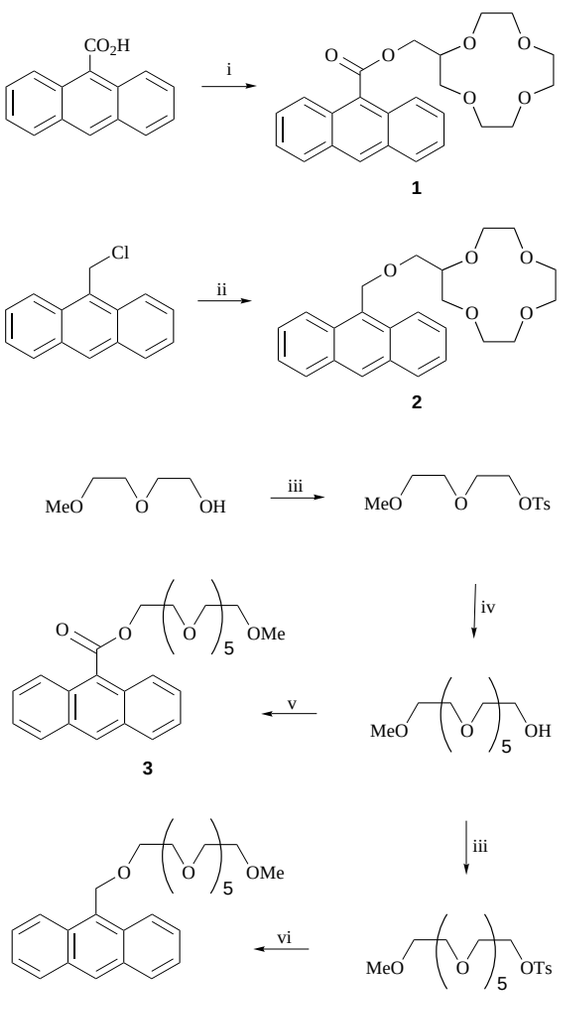
Introduction

Fluorescence sensing in molecular recognition systems is very useful in biomimetic research, since the resulting fluorescence can be highly sensitive so as to permit analysis. Recently, many fluorophore-hosts were reported to sense a number of guests such as alkali metals, alkaline earth metals, protons, transition metals and sugar derivatives.[1–5] Moreover, de Silva *et al*. created a logical recognition system operated by changes in fluorescence intensity.[6] In our previous paper, we reported a crown ether-armed fluorophore, pyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazine (PIP), which was able to logically recognise two input signals, alkaline earth metal cations *and* thiocyanate anions, to give a fluorescence-quenching output. This quenching character is explained by the photoinduced electron transfer (PET) from the thiocyanate anion to the PIP ring. Here we describe the metal-sensing ability of simple anthracene hosts bonding through an ester or ether linkage to a crown ether or polyether side-arm, as in structures **1**–**4**.

Results and discussion

Novel anthracene hosts **1**–**4** were synthesized by the following routes (Scheme 1). The ester linked hosts **1** and **3** were prepared from anthracene-9-carboxylic acid and the corresponding alcohols by 2-chloro-1,3-dimethylimidazolinium chloride (DMC) dehydration, respectively. The ether linked hosts **2** and **4** were prepared by usual etherification methods.

The UV–visible and fluorescence spectra of the crown ether hosts **1** and **2** are shown in Figs. 1–4. The UV–visible spectra of both compounds **1** and **2** indicate that there is little change in absorption pattern and intensity by the addition of calcium or sodium thiocyanate (Figs. 1 and 3). On the other hand, the fluorescence intensity of the host is remarkably changed in the presence of calcium thiocyanate; that is, fluorescence of the ester linked host **1** was nearly quenched (Fig. 2); however, that of the ether linked host **2** was substantially enhanced (Fig. 4). The fluorescence intensity change caused by the addition of alkaline earth metal and alkali metal thiocyanates, perchlorates, iodides and nitrates is summarised in Table 1. The negative value shows fluorescence enhancement by the addition of a salt, the positive value showing the fluorescence quenching. These results indicate the following features. (a) All hosts **1**–**4** recognise alkaline earth metal salts more effectively than alkali metal salts, bringing about the substantial fluorescence quenching or enhancement. (b) Fluorescence of the ester linked hosts **1** and **3** is quenched by alkaline earth metal salts while, on the other hand, that of the ether linked hosts **2** and **4** is enhanced by the corresponding salts. (c) One of the ether linked hosts, **2**, recognises calcium salts preferentially in the presence of barium salts and, conversely the other host, **4**, prefers barium salts to calcium salts.



Scheme 1 *Reagents:* i, hydroxymethyl-12-crown-4, DMC, pyridine, CH_2Cl_2; ii, hydroxymethyl-12-crown-4, NaH, THF; iii, TsCl, Et_3N, CH_2Cl_2; iv, tetraethylene glycol, Bu^{t}OK, THF; v, anthracene-9-carboxylic acid, DMC, pyridine, CH_2Cl_2; vi, 9-(hydroxymethyl)-anthracene, Bu^{t}OK, THF

From the fact that sodium and potassium salts don't affect the fluorescence quenching, it is suggested that the quenching of the hosts **1** and **3** is caused by the calcium and barium cations trapped by the 12-crown-4 ether or polyether side-arm.

Table 1 Fluorescence intensity change $(F_0 - F)/F_0$ by addition of salt[a]

	SCN^-				ClO_4^-			I^-		NO_3^-	
Host	Ca^{2+}	Ba^{2+}	Na^+	K^+	Ca^{2+}	Ba^{2+}	Na^+	Ca^{2+}	Ba^{2+}	Ca^{2+}	Ba^{2+}
1	0.40	0.48	0.03	0.02	0.29	0.26	0.02	0.15	0.19	0.00	0.06
2	−1.49	−0.91	−0.03	−0.03	−1.52	−0.80	−0.07	−2.40	−0.62	−1.05	−0.05
3	0.53	0.78	0.05	0.05	0.56	0.79	0.05	0.79	0.72	0.37	0.19
4	−1.10	−1.36	−0.13	−0.17	−1.06	−2.16	−0.14	−0.22	−0.49	−0.56	−1.48

[a] [Host] = 2×10^{-6} mol dm^{-3} in acetonitrile at 25 °C; F_0 stands for fluorescence intensity without salt, F for fluorescence intensity with salt. [Salt] = 2×10^{-4} mol dm^{-3}; $\lambda_{ex} = 350$ nm, $\lambda_{em} = 457$ nm.

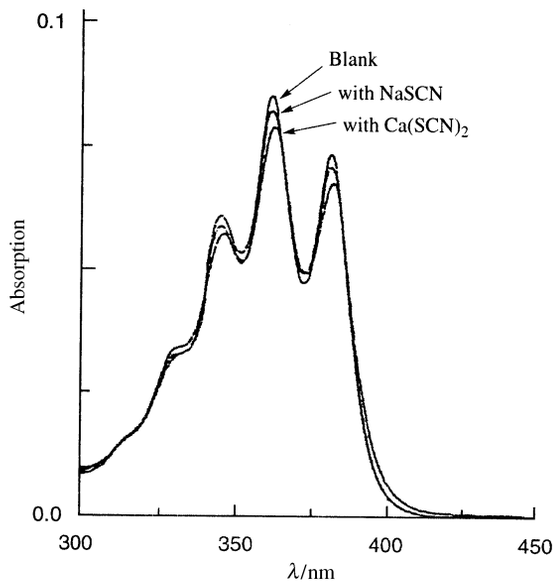


Fig. 1 Absorption of compound **1** ([**1**] = 1.4×10^{-5} mol dm^{-3}) in UV–visible spectrum

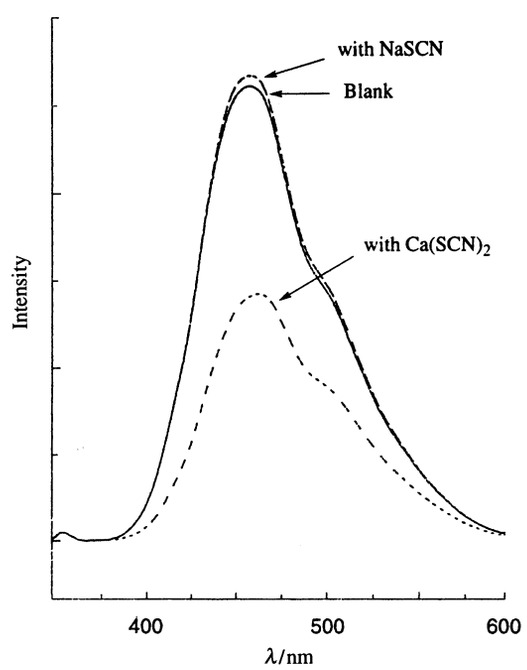


Fig. 2 Intensity of fluorescence of compound **1** in fluorescence spectrum ($\lambda_{ex} = 350$ nm)

Moreover, it should be added that the fluorescene quenching is dependent on the counter anion and, in both hosts **1** and **3**, the nitrate anion relaxed the quenching. In host **1**, the quenching effect of the thiocyanate anion is notable and this is due to PET occurring from the thiocyanate anion to the anthracene ring, as discussed in the case of the PIP-host in our previous paper.[7]

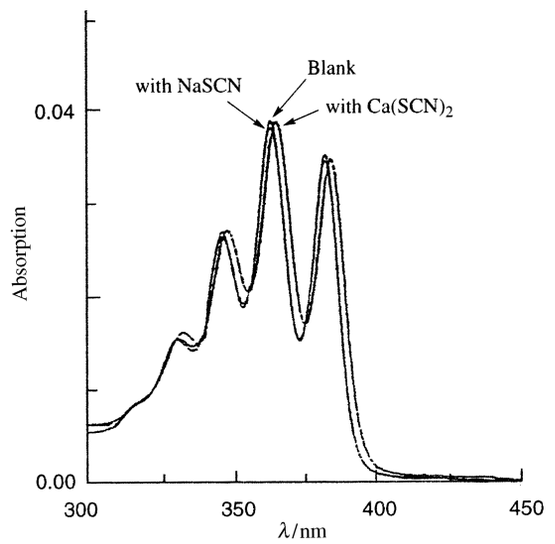


Fig. 3 Absorption of compound **2** ([**2**] = 8.0×10^{-6} mol dm^{-3}) in UV–visible spectrum

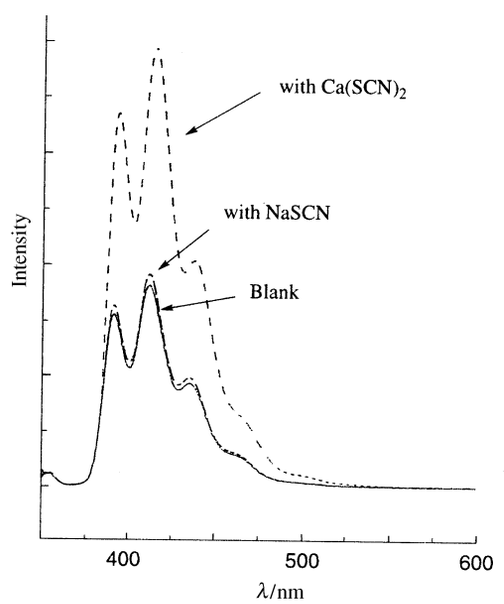


Fig. 4 Intensity of fluorescence of compound **2** in fluorescence spectrum ($\lambda_{ex} = 350$ nm)

Czarnik and de Silva reported that the fluorescence enhancement in the anthracene hosts having an aza-crown ether or an alkylamino group was caused by the metal chelating to the nitrogen atom.[5,8] The metal chelation decreases the reducing ability of the nitrogen lone pair, which retards the electron transfer to the anthracene photoexcited state. Therefore the fluorescence enhancement effect of the ether linked hosts **2** and **4** could be ascribed to the weakened reducing ability of the benzylic oxygen by the calcium or barium cation. To clarify these relationships, quantum yields of some related anthracene-

Table 2 Fluorescence quantum yields of 9-substituted anthracene derivatives[a]

Substituent 9-R	CH_2OMe	CH_2OCH_2-12-Crown-4 **2**	CH_2OH	CH_2OAc	H[b]	CO_2Me	CO_2CH_2-12-Crown-4 **1**	CH_2CO_2Me
Quantum yield	0.10[c]	0.10	0.15	0.21	0.23	0.26	0.26	0.29

[a] In acetonitrile at 25 °C, λ_{ex} = 260 nm. [b] $\Phi_{standard}$ (calculated value on the basis of quantum yield Φ = 0.30 in ethanol). [c] Φ = 0.08 (methylcyclohexane), see ref. 9.

9-carboxylic acid and -methanol derivatives were measured (Table 2). The quantum yields were found to be fairly dependent on the electronic effects of the 9-substituent. Electron-withdrawing groups such as ester groups and ester-substituted methyl groups increased the quantum yields. In contrast, hydroxy- and alkoxy-methyl groups decreased the quantum yields, the degree of which is determined by the electronic effects of the substituent attaching to the alcohol oxygen; that is, the electron-withdrawing acetyl group increases the quantum yield whereas the electron-donating methyl group decreases it. A 12-crown-4-ether-substituted methyl group should have an effect equal to that of the methyl group.† These results confirm that the quenching of anthracenemethanol derivatives is proportional to the electron density of the benzylic oxygen. On the other hand, according to computer-aided modelling, the ether linked hosts **2** and **4** are holding calcium or barium cations not only by the crown ether or polyether oxygen atoms but also the linkage oxygen atom. Therefore, in the hosts **2** and **4**, chelation of calcium or barium cations decreases the reducing ability of the linkage oxygen and brings about the fluorescence enhancement.

The ether linked host **2** recognised calcium cations preferentially in the presence of barium cations, in contrast to the host **4** which prefered barium cations to calcium cations; these preferences were not affected by the kind of counter anion. These results may therefore be attributed to the size of cation. Thus the calcium cation fits better in the holding cavity constructed by the 12-crown-4 ether and the linkage oxygen atom and, conversely, the holding cavity in the host **4**, which is constructed with a flexible pseudo-crown ether of the polyether moiety, prefers the barium cation, resulting in substantial fluorescence enhancement.

In conclusion, the anthracene hosts bonding through an ester or ether linkage to 12-crown-4 ether or polyether side-arm **1**–**4** recognised calcium and barium cations, and the fluorescence of the ester bonding hosts **1** and **3** or the ether bonding hosts **2** and **4** were quenched or enhanced, respectively, in the presence of these cations. Calcium or barium cations were strongly recognised by the 12-crown-4 ether or polyether side-armed host **2** or **4**, respectively. These results are very useful for helping us build a new type of host having a fluorescence output signal.

Experimental

Mps were measured on a MEL-TEMP II apparatus and are uncorrected. IR Spectra were recorded on a JASCO Report-100 spectrometer. ^{1}H NMR Spectra were taken on a JEOL JNM-GX270 (270 MHz) spectrometer for solutions in $CDCl_3$. The chemical shifts are given in δ_H (ppm) downfield from tetramethylsilane as the internal standard; *J* values are given in Hz. The elemental analyses were measured with a Yanaco MT-3 instrument. The fluorescence spectra and quantum yields were measured with a JASCO FP-777 spectrophotometer. UV–Visible spectra were recorded with a JASCO Ubest-50 spectrophotometer. The liquid chromatography purification was carried out by LC-908 (Japan Analytical Industry, Co., Ltd.) using JAI gel 1H (eluent, $CHCl_3$). Acetonitrile for spectoscopy was the highest quality from KOKUSAN Chemical Co. and was used without purification.

† For the low fluorescence of methoxymethylanthracene, consult ref. 9.

Synthesis of (anthracen-9-ylcarboxymethyl)-12-crown-4 ether 1

To a suspension of dichloromethane (10 ml) containing anthracene-9-carboxylic acid (0.69 g, 3.1 mmol) were added hydroxymethyl-12-crown-4 ether (0.50 g, 2.4 mmol) and DMC (0.53 g, 3.1 mmol). After the mixture had been stirred for 15 min at room temperature, pyridine (0.50 g, 6.3 mmol) was added dropwise, and the mixture was stirred for 24 h at room temperature. The solid was filtered off, and washed with dichloromethane. The combined filtrates were washed successively with 1 M hydrochloric acid, water and brine, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated off, and the residue was chromatographed on silica gel (eluent, ethyl acetate) to give 0.16 g (16%) of *ester* **1** as a yellowish oil; ν_{max}(neat)/cm^{-1} 3050 (CH of Ar), 1720 (C=O), 1205 and 1135 (C–O); δ_H 8.54 (1 H, s, 10-ArH), 8.14 (2 H, d, *J* 8.5, 1- and 8-ArH), 8.11 (2 H, d, *J* 7.3, 4- and 5-ArH), 7.57–7.46 (4 H, m, 2-, 3-, 6- and 7-ArH), 4.72 (1 H, dd, *J* 4.4 and 11.7, C*H*$_2$CH), 4.60 (1 H, dd, *J* 6.2 and 11.7, C*H*$_2$CH), 4.08 (1 H, m, CH) and 3.94–3.85 (14 H, m, OCH_2); λ_{max}(MeCN)/nm 382, 362, 346 and 252 (log ε/dm^3 mol^{-1} cm^{-1} 3.68, 3.75, 3.60 and 4.95) (Found: C, 69.9; H, 6.4. $C_{24}H_{26}O_6$ requires C, 70.2; H, 6.4%).

Synthesis of (anthracen-9-ylmethoxymethyl)-12-crown-4 ether 2

To a tetrahydrofuran (THF) solution of hydroxymethyl-12-crown-4 ether (0.50 g, 2.4 mmol) and sodium hydride (0.18 g) was added 9-(chloromethyl)anthracene (0.55 g, 2.4 mmol). After being stirred for 6 h at room temperature, the reaction mixture was extracted with ethyl acetate, and the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (3:1)] to give 0.70 g (73%) of *ether* **2** as a yellowish oil; ν_{max}(neat)/cm^{-1} 3050 (CH of Ar), 2860 (CH_2), 1620 and 1520 (Ar) and 1100 (C–O); δ_H 8.40 (1 H, s, 10-ArH), 8.37 (2 H, d, *J* 10.0, 1- and 8-ArH), 7.95 (2 H, d, *J* 8.3, 4- and 5-ArH), 7.52–7.40 (4 H, m, 2-, 3-, 6- and 7-ArH), 5.46 (2 H, s, CH_2) and 3.74–3.42 (17 H, m, OCH_2 and CH); λ_{max}(MeCN)/nm 384, 364, 346, 331 and 253 (log ε/dm^3 mol^{-1} cm^{-1} 3.67, 3.72, 3.55, 3.26 and 4.91) (Found: C, 72.8; H, 7.0. $C_{24}H_{28}O_5$ requires C, 72.7; H, 7.1%).

Preparation of 1-tosyloxy-3,6-dioxaheptane

To a dichloromethane (200 ml) solution of diethylene glycol monomethyl ether (15.0 g, 0.13 mol) and toluene-*p*-sulfonyl chloride (20.2 g, 0.11 mol) in an ice-bath was added triethylamine (15.2 g, 0.15 mol) dropwise slowly over a 20 min period. After the mixture had been stirred for 3 h, the solid was filtered off, and washed with dichloromethane. The combined filtrates were washed successively with water and brine, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed to give 13.5 g (47%) of 1-tosyloxy-3,5-dioxaheptane as an oil and this product was used for the next reaction without further purification.

Preparation of hexaethylene glycol monomethyl ether

To a THF (50 ml) solution of 1-tosyloxy-3,6-dioxaheptane

(2.00 g, 7.3 mmol) and tetraethylene glycol (1.42 g, 7.3 mmol) was added potassium *tert*-butoxide (0.82 g, 7.3 mmol). After being refluxed for 17 h, the reaction mixture was cooled to room temperature and the solid was filtered off, and washed with THF. The combined filtrates were evaporated to give 2.24 g of the crude hexaethylene glycol monomethyl ether, which was used for the next reaction without further purification.

Synthesis of 1-(anthracen-9-ylcarboxy)-3,6,9,12,15,18-hexaoxanonadecane 3

Hexaethylene glycol monomethyl ether (1.0 g) was dissolved in dichloromethane (6 ml), and anthracene-9-carboxylic acid (0.75 g, 3.4 mmol) and DMC (0.57 g, 3.4 mmol) were added to the solution. After the mixture had been stirred for 20 min, pyridine (0.53 g, 6.7 mmol) was added to the mixture in an ice-bath. After the mixture had been stirred at room temperature for 24 h, the solid was filtered off, and washed with dichloromethane. The combined filtrates were evaporated to leave a residue, which was chromatographed on silica gel (eluent, ethyl acetate). The crude product was further purified with liquid chromatography to give 0.18 g (12%) of *polyether ester* **3** as a yellowish oil; ν_{max}(neat)/cm^{-1} 3050 (CH of Ar), 2870 (CH_2), 1720 (C=O), 1520 (Ar), 1445 (OMe), 1205 and 1105 (C–O); δ_H 8.52 (1 H, s, 10-ArH), 8.12 (2 H, d, *J* 8.8, 1- and 8-ArH), 8.01 (2 H, d, *J* 7.6, 4- and 5-ArH), 7.56–7.45 (4 H, m, 2-, 3-, 6- and 7-ArH), 4.78 (2 H, t, *J* 4.9, 1-H_2), 3.93 (2 H, t, *J* 4.9, 2-H_2), 3.72–3.50 (20 H, m, OCH_2) and 3.35 (3 H, s, OCH_3); λ_{max}(MeCN)/nm 382, 362, 346 and 252 (log ε/dm^3 mol^{-1} cm^{-1} 3.88, 3.94, 3.80 and 5.15) (Found: C, 67.6; H, 7.0. $C_{28}H_{36}O_8$ requires C, 67.2; H, 7.25%).

Preparation of 1-tosyloxy-3,6,9,12,15,18-hexaoxanonadecane

To a dichloromethane (3 ml) solution of the crude hexaethylene glycol monomethyl ether (1.06 g) and toluene-*p*-sulfonyl chloride (0.68 g, 3.6 mmol) in an ice-bath was added triethylamine (0.54 g, 5.4 mmol) slowly. After the mixture had been refluxed for 2.5 h, the solid was filtered off, and washed with dichloromethane. The obtained filtrates were washed successively with water and brine, and the organic layer was dried over anhydrous magnesium sulfate and evaporated. The obtained crude product was used for the next reaction without further purification.

Synthesis of 1-(anthracen-9-ylmethoxy)-3,6,9,12,15,18-hexaoxanonadecane 4

To a THF (4 ml) solution of 1-tosyloxy-3,6,9,12,15,18-hexaoxanonadecane (0.58 g) and 9-(hydroxymethyl)anthracene (0.27 g, 1.3 mmol) was added potassium *tert*-butoxide (0.14 g, 1.3 mmol). After reflux of the mixture for 4 h, the solid was filtered off, and washed with THF. The combined filtrates were evaporated, the residue was chromatographed on silica gel (eluent, ethyl acetate), and the crude product was further purified by liquid chromatography to give 0.10 g (16%) of *polyether* **4** as a yellowish oil; ν_{max}(neat)/cm^{-1} 3050 (CH of Ar), 2860 (CH_2), 1620 and 1520 (C=C and Ar), 1445 (OCH_3) and 1100 (C–O); δ_H 8.44 (1 H, s, 10-ArH), 8.41 (2 H, d, *J* 8.8, 1- and 8-ArH), 7.99 (2 H, d, *J* 8.3, 4- and 5-ArH), 7.55–7.42 (4 H, m, 2-, 3-, 6- and 7-ArH), 5.53 (2 H, s, CH_2), 3.79–3.51 (24 H, m, OCH_2) and 3.35 (3 H, s, OCH_3); λ_{max}(MeCN)/nm 384, 364, 346, 331 and 253 (log ε/dm^3 mol^{-1} cm^{-1} 3.81, 3.85, 3.69, 3.45 and 5.04) (Found: C, 68.8; H, 7.4. $C_{28}H_{38}O_7$ requires C, 69.1; H, 7.9%).

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