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A tri-aromatic amide hemicryptophane host: synthesis and acetylcholine binding

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ABSTRACT

Hemicryptophanes have been designed to include endohedral functionalities in the cavity, giving molecular receptors and catalysts. In this study, a tri-aromatic amide hemicryptophane was synthesized. The host–guest interactions with various types of tetraalkylammonium salts were investigated. The structure of the partial inclusion complex in which an acetylcholine molecule was encapsulated within the hemicryptophane was characterized by NMR, X-ray crystal structure, and ESI-MS analysis.

Artificial molecular receptors can mimic biological systems such as enzymes.[1] A large number of bio-inspired compounds have been designed and the recognition of biologically interesting guests has been investigated. Cryptophanes, which have cyclotriveratrylene (CTV) host units, efficiently encapsulate small neutral organic guests, Xe, and tetraalkylammonium salts, are useful molecular receptors.[2] Related hemicryptophanes have been designed to include endohedral functionalities in the cavity, to give molecular receptors and catalysts. The addition of specific binding sites with affinities for metal ions to such structures can give new endohedral metal hemicryptophane complexes. This has been achieved by synthesizing various hemicryptophanes with suitable endohedral functional groups; oxidovanadium,[3] zinc,[4] phosphorus,[5] copper,[6] ruthenium,[7] gallium, and iron[8] endohedral-functionalized hemicryptophanes have been reported, in which the functional atom is located inside the molecular cavity, giving an endohedral complex.

The construction of new catalysts with reaction fields in the hemicryptophane cavity needs additional information on the host–guest interactions of hemicryptophanes. Various guest molecules such as primary alkylammonium salts,[9] carbohydrates,[10] zwitterionic species,[11] carnitine,[12] norephedrine,[13] and tetramethylammonium species[4d,14] have been investigated using NMR spectroscopy and density functional theory calculations. However, the X-ray crystal structures of host–guest interactions are limited to those of simple solvent molecules such as toluene,[8,15] acetonitrile,[4a,4b,5d] dichloromethane,[5b,5d,14a,16] pentane,[16] and water.[11b] Here, we report the synthesis of triaromatic amide hemicryptophane **5**. The host–guest interactions with various tetraalkylammonium salts were clarified. The structure of a partial inclusion complex in which an acetylcholine (ACh) molecule was encapsulated in **5** was determined using ^{1}H NMR spectroscopy, X-ray diffraction, and ESI-MS.

The synthesis of **5** is shown in Scheme 1. Tosylation of **1** gave **2** in 86% yield. Cyclotriguaiacylene **3**[17] was alkylated with **2** to give **4** in 84% yield. Tri-*tert*-butoxycarbonyl (Boc) CTV **4** was deprotected with trifluoroacetic acid (TFA); addition of Et_3N and nitrilotriacetic acid tris(*p*-nitrophenyl ester) in dilute tetrahydrofuran (THF) and chloroform gave **5** in 31% yield (2 steps).[18] The ^{1}H NMR spectrum of **5** has two singlets from the aromatic protons H^b and H^c, a singlet from the OMe group H^d, two doublets from the aromatic protons H^g and H^h, and multiplets from the alkyl protons H^e and H^f (Fig. 1); the spectrum shows that **5** has C_3 symmetry.

Complexation of **5** with anions in $CDCl_3$/MeOD (20/1) was investigated by ^{1}H NMR spectroscopic titrations with tetra-*n*-butylammonium salts (nBu$_4$N$^+$X$^-$). The titration conditions were based on Dutasta and Martinez's report on the complexation of the first triamide hemicryptophane.[14a,16] Only one set of signals was

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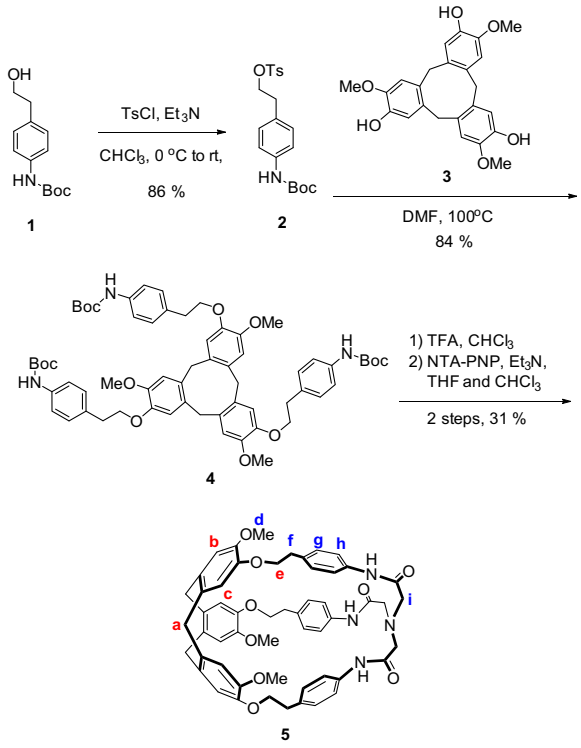

Scheme 1. Synthesis of hemicryptophane **5**.

observed for **5** and nBu$_4$N$^+$X$^-$, indicating that host–guest exchange was fast on the NMR timescale. The complexation-induced shifts of the H^i signal were plotted as a function of the guest/host ratio and modeled using TitrationFit software.[18] Job's plots of **5** and nBu$_4$N$^+$X$^-$ showed 1:1 binding stoichiometry (Figs. S1–S10). No shift was observed in the signals from Bu$_4$N$^+$ or the CTV protons H^b and H^c, indicating that **5** and Bu$_4$N$^+$ did not interact. The binding constants (K_a) of **5** with various anions are listed in Table 1. The results show that order of the affinities of **5** for coordinated anions was $Cl^- < Br^- < I^- < F^- = ClO_4^- < PF_6^-$ (entries 1–6). The binding constant of F$^-$ is stronger than that of other halogen anions because of its hydrogen-bond-accepting ability. The binding constants of other halogen anions and soft anions with lower

Table 1
Binding constants (K_a) at 298 K of **5** with selected anions

Entry	Anion[a]	V_{vdW} (Å^3)[b]	K_a (M^{-1})[c]
1	F^-	3.6	27 ± 2.2
2	Cl^-	13	18 ± 1.0
3	Br^-	17	20 ± 1.5
4	I^-	23	25 ± 2.2
5	ClO_4^-	48	27 ± 3.0
6	PF_6^-	59	53 ± 15

[a] Counter cation: nBu$_4$N$^+$.
[b] Van der Waals volumes were calculated using a reported procedure.[21]
[c] K_a values were determined by fitting ^{1}H NMR titration curves of a H^i proton using TitrationFit.[19]

hydrogen-bond-accepting abilities depend on the anion volume rather than hydrogen-bonding interactions. This is explained by the weak hydrogen-bonding ability of the aromatic amide.

We investigated the binding properties of **5** with tetra-n-alkylammonium cations. The ^{1}H NMR spectra obtained on titrating a solution of **5** with Me$_4$N$^+$Cl$^-$ are shown in Figure 1. Complexation-induced shifts of the phenylene spacer H^g and H^h and alkyl spacer H^f were observed; the CTV-MeO proton H^d and amide-CH$_2$- proton H^i were shifted downfield; CTV-phenylene protons H^b and H^c and CTV-ArCH$_2$ bridge protons H^a were shifted upfield. The Me$_4$N$^+$ proton signals shifted downfield and broadened on

Table 2
Binding constants (K_a) at 298 K of **5** with various tetraalkylammonium salts

Entry	Anion[a]	Proton of **5**	K_a (M^{-1})[b]
1	Me$_4$N$^+$	H^b	$6.5 \pm 1.2 \times 10^4$
		H^c	$6.6 \pm 1.3 \times 10^4$
		H^h	$6.4 \pm 1.1 \times 10^4$
2	Et$_2$Me$_2$N$^+$	H^b	$7.9 \pm 1.3 \times 10^3$
		H^c	$1.2 \pm 0.5 \times 10^4$
		H^h	$9.6 \pm 4.3 \times 10^3$
3	Et$_3$MeN$^+$	H^b	$4.7 \pm 1.4 \times 10^3$
		H^c	$5.7 \pm 1.4 \times 10^3$
		H^h	$6.2 \pm 1.5 \times 10^3$
4	AcOCH$_2$CH$_2$Me$_3$N$^+$ (ACh)	H^b	$1.4 \pm 0.8 \times 10^4$
		H^c	$1.2 \pm 0.6 \times 10^4$
		H^h	$1.2 \pm 0.6 \times 10^4$

[a] Counter anion: Cl$^-$.
[b] K_a values were determined by fitting ^{1}H NMR titration curves of protons using TitrationFit.[19]

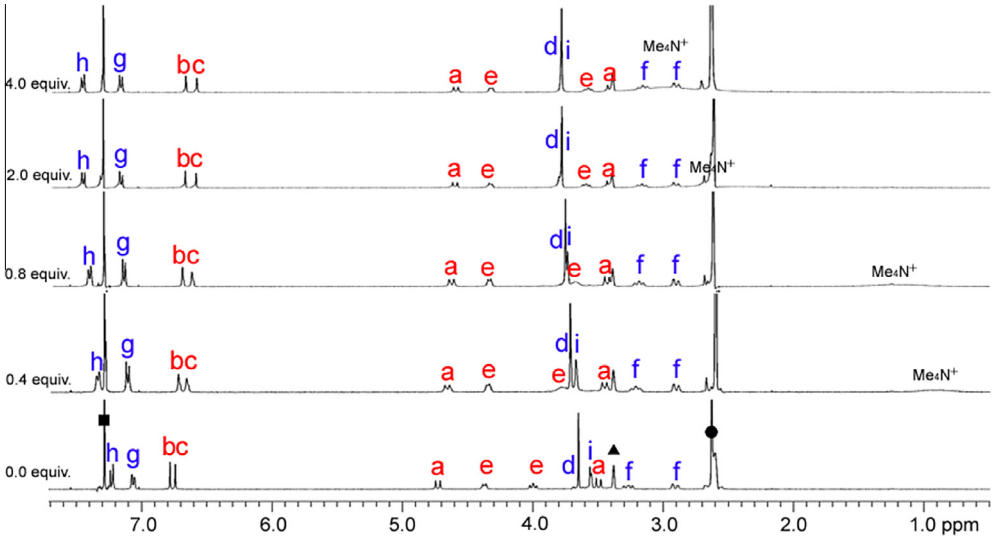

Figure 1. ^{1}H NMR spectra (400 MHz, 298 K in CDCl$_3$/CD$_3$OD, 20/1) for titration of hemicryptophane **5** with Me$_4$N$^+$Cl$^-$; ■ CHCl$_3$, ▲ CD$_2$HOD, ● HOD.

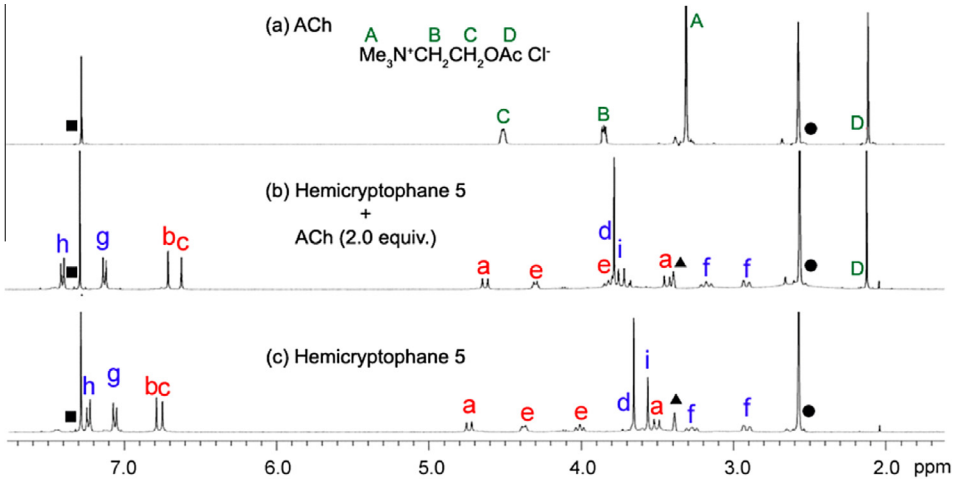

Figure 2. ^{1}H NMR spectra (400 MHz, 298 K in $CDCl_3/CD_3OD$, 20/1) of (a) ACh$^+$Cl$^-$; (b) hemicryptophane **5** with ACh (2.0 equiv); and (c) **5**; ■ $CHCl_3$; ▲ CD_2HOD; ● HOD.

addition of $Me_4N^+Cl^-$. The binding constants for various tetraalkylammonium salts are shown in Table 2. $Et_3MeN^+Cl^-$ and $Et_2Me_2N^+Cl^-$ were also encapsulated in **5** (entries 2 and 3); however, the binding constants were smaller than that with $Me_4N^+Cl^-$.

ACh was encapsulated by **5** (entry 4). Complexation was verified using HR-ESI-MS, which indicated the presence of a 1:1 complex (*m*/*z* calcd for $C_{61}H_{70}N_5O_{11}$ [**5**+ACh+H]$^+$ 1048.5072; found 1048.5071, Fig. S15). The ^{1}H NMR spectra of **5** and ACh are shown in Figure 2. Complexation-induced shifts of phenylene spacers H^g and H^h and alkyl spacer H^f were observed on addition of 2 equiv of ACh. The CTV-MeO proton H^d and amide-CH_2 proton H^i shifted downfield.

The CTV-phenylene protons H^b and H^c and CTV-$ArCH_2$ bridge proton H^a shifted upfield. The trimethyl proton of ACh (H^A) and ethylene protons of H^B and H^C were broadened, similar to the signal corresponding to the tetramethylammonium moiety of $Me_4N^+Cl^-$, although the acetyl proton of H^D remained sharp. This result indicates that the ammonium moiety of ACh entered the cavity, but the acetyl moiety was outside the cavity in solution. These phenomena were also observed in the solid state.

Single crystals of the complex of **5** with ACh were obtained by slow evaporation from $CDCl_3$ and CD_3OD. The X-ray crystal structure (CCDC:1483398), which is shown in Figure 3, indicates that the ammonium unit of ACh is inside the cavity, and the acetyl unit and chloride ions are outside the cavity. The calculated distance between the carbon atom of the trimethylammonium group (C59) and the C15═C16 double bond was 3.56 Å, indicating CH–π interactions between the CTV phenyl unit and ACh H^A protons. The estimated distance between the chloride ion (Cl14) and the amide nitrogen (N2) was 3.17 Å, showing hydrogen-bonding interactions. Intermolecular hydrogen bonding was observed outside the cavity of **5**. Intramolecular hydrogen bonding was observed between the amide nitrogen (N4) and amide oxygen (O4). The solid- and solution-state binding constants between nBu$_4$N$^+$X$^-$ guests and **5** indicate interactions between the tetraalkylammonium salt anions and amide protons outside the cavity of **5**.

In conclusion, we synthesized a triaromatic amide hemicryptophane. The host–guest interactions with various tetraalkylammonium salts were investigated. The ^{1}H NMR spectrum and X-ray crystal structure of the inclusion complex formed between **5** and ACh were obtained. These host–guest interactions of hemicryptophane will help in the design of hemicryptophanes in which the inner cavity can serve as a reaction field. Our next goal is to construct a molybdenum hemicryptophane complex based on **5** toward the Shrock-type catalytic nitrogen-reduction.

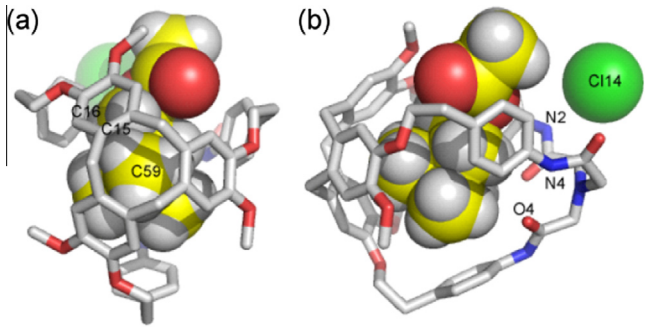

Figure 3. X-ray crystal structure of **5**·ACh$^+$Cl$^-$: (a) top view, (b) side view. Hydrogen atoms of **5** and solvent were omitted for clarity (CCDC: 1483398).[20]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.017.

References and notes

1. (a) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146–153; (b) Kirby, A. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 706–724; (c) Sanders, J. K. M. *Chem.–Eur. J.* **1998**, *4*, 1378–1383; (d) van Leeuwen, P. W. N. M. *Supramolecular Catalysis*; Wiley-VCH: Weinheim, 2008; (e) Raynal, M.; Ballester, P.; van Vidal-Ferran, A.; Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1660–1733.
2. Brotin, T.; Dutasta, J. P. *Chem. Rev.* **2009**, *109*, 88–130.
3. (a) Gautier, A.; Mulatier, J. C.; Crassous, J.; Dutasta, J.-P. *Org. Lett.* **2005**, *7*, 1207–1210; (b) Martinez, A.; Dutasta, J.-P. *J. Catal.* **2009**, *267*, 188–192; (c) Martinez, A.; Guy, L.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2010**, *132*, 16733–16734; (d) Martinez, A.; Robert, V.; Gornitzka, H.; Dutasta, J.-P. *Chem.–Eur. J.* **2010**, *16*, 520–527.
4. (a) Makita, Y.; Sugimoto, K.; Furuyoshi, K.; Ikeda, K.; Fujiwara, S.; Shin-ike, T.; Ogawa, A. *Inorg. Chem.* **2010**, *49*, 7220–7222; (b) Makita, Y.; Sugimoto, K.; Furuyoshi, K.; Ikeda, K.; Fujita, T.; Fujiwara, S.; Ogawa, A. *Supramol. Chem.* **2011**, *23*, 269–272; (c) Makita, Y.; Ikeda, K.; Sugimoto, K.; Fujita, T.; Danno, T.; Bobuatong, K.; Ehara, M.; Fujiwara, S.; Ogawa, A. *J. Organomet. Chem.* **2012**,

706–707, 26–29; (d) Zhang, D.; Gao, G.; Guy, L.; Robert, V.; Dutasta, J.-P.; Martinez, A. *Chem. Commun.* **2015**, 2679–2682.
5. (a) Makita, Y.; Furuyoshi, K.; Ikeda, K.; Fujita, T.; Fujiwara, S.; Ehara, M.; Ogawa, A. *Tetrahedron Lett.* **2011**, *52*, 4129–4131; (b) Raytchev, P. D.; Martinez, A.; Gornitzka, H.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 2157–2159; (c) Payet, E.; Dimitrov-Raytchev, P.; Chatelet, B.; Guy, L.; Grass, S.; Lacour, J.; Dutasta, J.-P.; Martinez, A. *Chirality* **2012**, *24*, 1077–1081; (d) Chatelet, B.; Gornitzka, H.; Dufaud, V.; Jeanneau, E.; Dutasta, J.-P.; Martinez, A. *J. Am. Chem. Soc.* **2013**, *135*, 18659–18664; (e) Chatelet, B.; Dufaud, V.; Dutasta, J.-P.; Martinez, A. *J. Org. Chem.* **2014**, *79*, 8684–8688; (f) Chatelet, B.; Joucla, L.; Dutasta, J.-P.; Martinez, A.; Dufaud, V. *Chem.–Eur. J.* **2014**, *20*, 1–5.
6. (a) Perraud, O.; Sorokin, A. B.; Dutasta, J.-P.; Martinez, A. *Chem. Commun.* **2013**, 1288–1290; (b) Perraud, O.; Tommasino, J.-B.; Robert, V.; Albela, B.; Khrouz, L.; Bonneviot, L.; Dutasta, J.-P.; Martinez, A. *Dalton Trans.* **2013**, *42*, 1530–1535; (c) Schmitt, A.; Collin, S.; Bucher, C.; Maurel, V.; Dutasta, J.-P.; Martinez, A. *Org. Biomol. Chem.* **2015**, *13*, 2157–2161.
7. Makita, Y.; Fujita, T.; Danno, T.; Inoue, M.; Ueshima, M.; Fujiwara, S.; Ogawa, A. *Supramol. Catal.* **2012**, 9–11.
8. Gosse, I.; Robeyns, K.; Bougault, C.; Martinez, A.; Tinant, B.; Dutasta, J.-P. *Inorg. Chem.* **2016**, *55*, 1011–1013.
9. Perraud, O.; Lefevre, S.; Robert, V.; Martinez, A.; Dutasta, J.-P. *Org. Biomol. Chem.* **2012**, *10*, 1056–1059.
10. (a) Perraud, O.; Martinez, A.; Dutasta, J.-P. *Chem. Commun.* **2011**, 5861–5863; (b) Schmitt, A.; Perraud, O.; Payet, E.; Chatelet, B.; Bousquet, B.; Valls, M.; Padula, D.; Di Bari, L.; Dutasta, J.-P.; Martinez, A. *Org. Bioorg. Chem.* **2014**, *12*, 4211–4217; (c) Schmitt, A.; Chatelet, B.; Padula, D.; Di Bari, L.; Dutasta, J.-P.; Martinez, A. *New J. Chem.* **2015**, *39*, 1749–1753.
11. (a) Perraud, O.; Robert, V.; Martinez, A.; Dutasta, J.-P. *Chem.–Eur. J.* **2011**, *17*, 13405–13408; (b) Perraud, O.; Robert, V. H.; Gornitzka; Martinez, A.; Dutasta, J.-P. *Angew. Chem., Int. Ed.* **2012**, *51*, 504–508.
12. Cochrane, J. R.; Schmitt, A.; Wille, U.; Hutton, C. A. *Chem. Commun.* **2013**, 8504–8506.
13. Lefevre, S.; Zhang, D.; Godart, E.; Jean, M.; Vanthuyne, N.; Mulatier, J. C.; Dutasta, J.-P.; Guy, L.; Martinez, A. *Chem.–Eur. J.* **2016**, *22*, 2068–2074.
14. (a) Perraud, O.; Robert, V.; Martinez, A.; Dutasta, J.-P. *Chem.–Eur. J.* **2011**, *17*, 4177–4182; (b) Schmitt, A.; Robert, V.; Dutasta, J.-P.; Martinez, A. *Org. Lett.* **2014**, *16*, 2374–2377.
15. Gosse, I.; Dutasta, J.-P.; Perrin, M.; Thozet, A. *New J. Chem.* **1999**, *23*, 545–548.
16. Raytchev, P. D.; Perraud, O.; Aronica, C.; Martinez, A.; Dutasta, J.-P. *J. Org. Chem.* **2010**, *75*, 2099–2102.
17. Canceill, J.; Gabard, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1983**, 122–123.
18. TFA (1.0 mL) was slowly added into the **4** (414 mg, 0.39 mmol) in chloroform (10.0 mL) at 0 °C. The mixture was turned into at ambient temperature and was stirred at overnight. The reaction mixture was evaporated in vacuo. The residue was dissolved in THF (5.0 mL) and then added chloroform (70 mL). The mixture was suspended. HOBt·H_2O (222.7 mg, 1.45 mmol) and Et_3N (227.4 mg, 2.25 mmol) were added into the suspending solution. The mixture was turned into clear and colorless solution. A solution of NTA–PNP (216 mg, 0.39 mmol) in chloroform (20 mL) was slowly added into the mixture. Then, the reaction mixture was turned into 60 °C for 2 days. The reaction mixture was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 20/1) to obtain 120 mg (0.12 mmol, 31% yield) of **5** as white solid.
19. Akine, S. *TitrationFit, Program for Analyses of Host–guest Complexation*; Kanazawa University: Kanazawa, Japan, 2013.
20. Crystal data of **5**·ACh$^+$Cl$^-$: $C_{66}H_{74}Cl_{13}N_5O_{12}$, Mw = 1680.12, monoclinic, space group $P\,2_1/n$; a = 12.4559(2) Å, b = 21.8943(4) Å, c = 27.3688(5) Å, α = 90.0000, β = 96.056(7), γ = 90.0000; Z = 4; R_1 = 0.0778, wR_2 = 0.2065; goodness-of-fit (GOF) on F^2 = 1.041. CCDC: 1483398.
21. Zhao, Y. H.; Abraham, M. H.; Zissimos, A. M. *J. Org. Chem.* **2003**, *68*, 7368–7373.