Allosteric effects in a tetrapodal imidazolium-derived calix[4]arene anion receptor†

Charlotte E. Willans,[a] Kirsty M. Anderson,[b] Lydia C. Potts[b] and Jonathan W. Steed*[b]

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A ditopic tetrapodal imidazolium-based 1,3-alternate calix[4]arene host binds anions as 1 : 2 complexes *via* a range of CH · · · anion hydrogen bonds. Allosteric enhancement of the affinity for the second chloride anion is observed. X-Ray crystal structures of the chloride, bromide and nitrate complexes suggest that this behaviour is linked to inter-binding site communication mediated by the calixarene framework. The imidazolium groups exist as either *in-out* or *out-out* conformers with respect to the calixarene, with the chloride complex exhibiting conformational isomorphism such that both forms are present in the same crystal structure.

Introduction

The design and synthesis of anion binding and sensing systems continues to be highly topical.[1–5] A key goal in the field is the realisation of inter-anion discrimination in molecular sensors,[6–10] and one route to achieve this outcome is the incorporation of induced-fit anion recognition as a means to signal generation. Hence sensor molecules can be designed that elicit a photophysical, colourimetric or electrochemical response according to the conformational change they induce in the receptor.[11–20] Systems of this type are highly dependent on the way in which the anion binding sites are organised and the way in which their mutual movement is constrained in the receptor—the chemical nature of the anion binding site can be of less importance. Thus there have been a number of recent reports showing that with appropriate preorganisation even relatively weak anion binding sites such as C–H hydrogen bond donors can act as effective anion recognition moieties.[15,21–27] The efficacy of appropriately organised C–H · · · anion hydrogen bonding has been highlighted by tripodal imidazolium,[25,28,29] pyridinium[15] and cryptand based[30] systems. We now report a tetrapodal imidazolium based receptor in which the imidazolium CH binding sites are organised into a ditopic arrangement about a relatively rigid 1,3-alternate calix[4]arene core. During the course of this work a closely related ligand was reported by Hosseini and co-workers.[31]

Results and discussion

The mesityl, hydrocarbon calix[4]arene **1** is readily prepared in one step from α′-chloroisodurene.[32] It is locked into a 1,3-alternate conformation of the aryl rings. This versatile scaffold has been used to support organometallic anion binding groups[33] and, as a nitrile or pyridyl derivative, has been used as a ligand in the formation of coordination arrays.[34,35] Pyridinium type receptors derived from **1** have been shown to display remarkable induced-fit fluorescent anion discrimination.[14] Reaction of **1** with formaldehyde in the presence of Zn–HBr results in facile bromomethylation of the aryl rings.[14,36] The brominated precursor can then be reacted with 1-methyl imidazole followed by metathesis with NH_4PF_6 to give the target tetracation **3** in excellent yield. The 1,3-alternate geometry of **3** means that the imidazolium units are arranged in pairs on opposite faces of the molecule but, subject to that constraint, are free to rotate and adapt the conformation of the molecule in response to the geometry of the bound anion.

Anion binding by **3** was probed by ^{1}H NMR spectroscopic titration of the anion NBu_4^+ salts in MeCN-d_3 solution. These measurements resulted in binding isotherms consistent with the formation of 1 : 1 and 1 : 2 host–guest complexes for all of the anions studied (Cl^-, Br^-, $MeCO_2^-$, NO_3^- and malonate^{2-}). The 1 : 2 stoichiometry was confirmed by Job's method for nitrate and bromide, Fig. 1, although in both cases the plot maximum falls in between 0.5 and 0.33 suggesting that complexes of 1 : 1 and 1 : 2 stoichiometry may coexist in the concentration range studied.

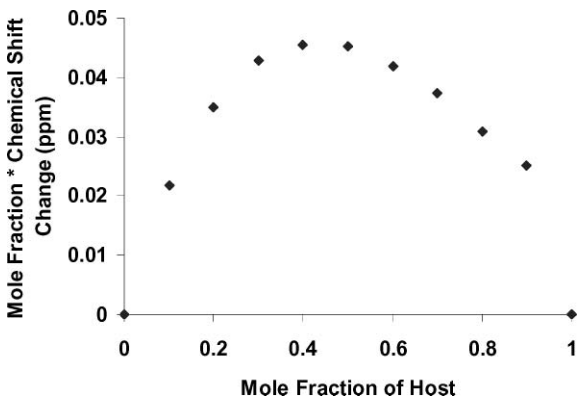


Fig. 1 Job plot in MeCN-d_3 for the interaction of **3** with NBu_4NO_3 showing the 1 : 1 and 1 : 2 stoichiometry.

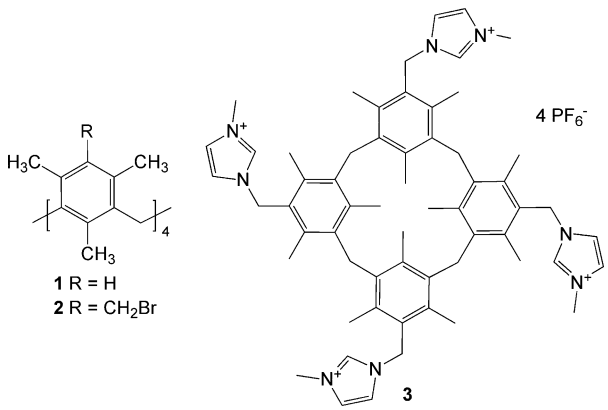
[a]*School of Chemistry, University of Leeds, Leeds, UK LS2 9JT*
[b]*Department of Chemistry, Durham University, South Road, Durham, UK DH1 3LE. E-mail: jon.steed@durham.ac.uk*

† Electronic supplementary information (ESI) available: Crystallographic data in CIF format and details of synthetic procedure and NMR spectroscopic titrations. CCDC reference numbers 722205, 722206 and 722207. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904148f

Table 1 Binding constants for NBu_4^+ anion salts by host **3** in MeCN-d_3

Anion	β_{11}	β_{12}	$\Delta\delta$ at 2 equiv. (ppm)
Cl^-	1.91(3)	5.22(1)	0.52
Br^-	3.40(7)	5.49(7)	0.35
NO_3^-	2.04(7)	3.51(6)	0.22
$MeCO_2^-$	3.90(1)	5.53(1)	0.32
Malonate^{2-}	2.06[a]	3.87[a]	0.16

[a] Manual fit—see ESI.†



Anion binding constants based on a 1 : 1 and 1 : 2 stoichiometry model are given in Table 1. While good fits were obtained to the data in all cases (see ESI†), chemical shift changes continued well beyond the addition of two equivalents of anion and the weaker binding of additional anions to give higher complexes cannot be ruled out. The data show an interesting trend in that while two equivalents of Cl^-, Br^- and $MeCO_2^-$ are bound approximately equally strongly in terms of overall stability constant, there is a lower affinity for the first equivalent of chloride compared to the other two anions with K_{12} being much larger than K_{11} suggesting a positive allosteric effect in which binding of the first chloride anion facilitates binding of the second. Similarly, examination of the titration isotherms (Fig. 2) shows significant sigmoidality in the chloride data, that is absent in the bromide case. The weak binding of nitrate with its diffuse negative charge, high degree of solvation and low basicity is unsurprising, however, the low malonate affinity is more remarkable and may relate to the malonate's being too large to fit between the two imidazolium groups in such a way as to bind *via* both carboxylate residues simultaneously. The low affinity for malonate compared to acetate is also evident in the

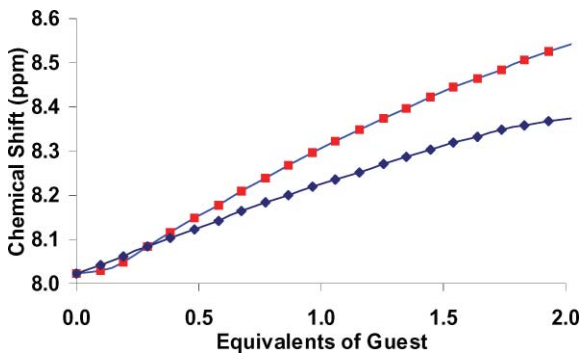


Fig. 2 ^{1}H NMR spectroscopic titration data for binding of Cl^- (■) and Br^- (♦) by **3**.

$\Delta\delta$ values which, although they are highly influenced by intrinsic anion basicity, might be expected to correlate with affinity for two such closely related chemical species.

The structural basis of this interesting solution behaviour was studied further by X-ray crystallography. Crystals of the Cl^-, Br^- and NO_3^- salts of **3** suitable for single crystal X-ray structure determination were obtained by slow evaporation of acetonitrile solutions of the hosts in the presence of excess NBu_4^+ salts of the anions. All three structures showed the expected 1,3-alternate conformation of the calixarene core and all three proved to contain large amounts of enclathrated solvent. In the case of the chloride complex this comprises *ca.* 7 water molecules per calixarene, for bromide 7 water and 2 acetonitrile molecules and for nitrate 1.33 water and 0.67 molecules of acetonitrile. High degrees of hydration/solvation are common in organic ionic crystals.[37] The bromide and nitrate structures exhibit a single crystallographically independent molecule, whereas the chloride exists as a conformational isomorph with two crystallographically independent conformers (*i.e.* $Z' = 2$).[38,39] The three X-ray structures thus contain a total of four unique determinations of the molecular structure of cation **3**. The arrangement of the imidazolium groups in each cation can be described as either *in* or *out* according to whether the imidazolium unit is orientated inwards towards the calixarene *pseudo*-C_4 axis or outwards. The anion binding regions consist of pairs of imidazolium cations, one pair on each face of the calixarene. These imidazolium cation pairs are found to adopt either an *in-out* or an *out-out* arrangement in the structures studied. The *in-in* combination appears to be sterically unfeasible. Across the four unique cations only two conformers are observed; either one of each possibility as in the bromide salt (Fig. 3) or an $(in\text{-}out)_2$ arrangement as in the nitrate salt (Fig. 4).

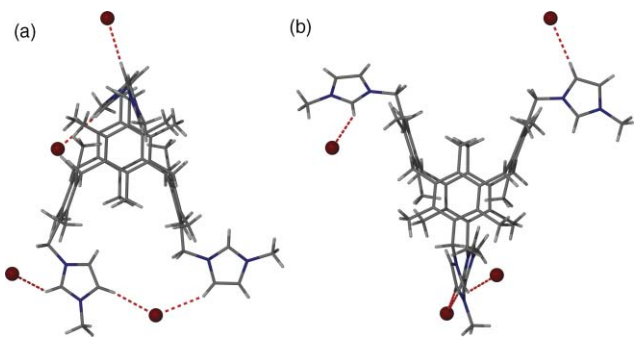


Fig. 3 (a) *In-out* and (b) *out-out* anion binding sites in the X-ray crystal structure of the Br^- salt of **3** (solvent molecules omitted for clarity).

Interestingly the chloride complex exists as both conformers (Fig. 5). The *in-out* arrangement is capable of chelating a single anion in a pincer-like fashion (as in the bromide complex, Fig. 3a) and might thus contribute to enhanced solution-state anion binding, however, this chelation is not observed for chloride (Fig. 5a). In the *out-out* arrangement the imidazolium groups are well separated and bind to different anions or solvent (Fig. 3b and 5b).

The fact that all of the structures contain at least one of the more compact *in-out* pairs leads us to speculate on an anion-dependent basis for communication between the two bis(imidazolium) binding sites. Anion chelation at the *in-out* site could influence the stability of the *in-out* arrangement on the opposite face of

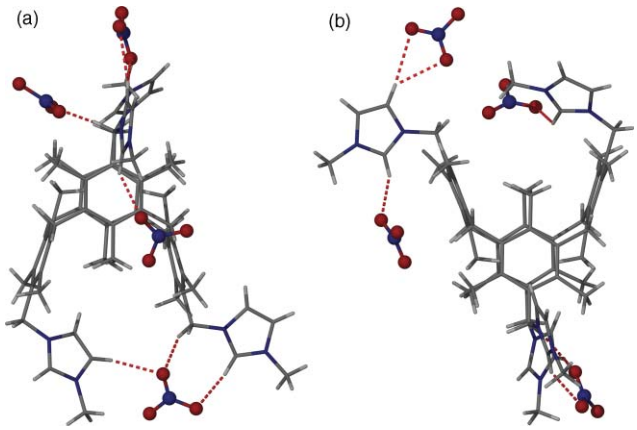


Fig. 4 (a) And (b) the two *in-out* anion binding sites in the X-ray crystal structure of the NO_3^- salt of **3** (solvent molecules omitted for clarity).

the molecule depending on the amount that the anion draws the imidazolium groups together. For example, the calixarene aromatic ring centroid $\cdots$ centroid distance in the bromide salt is marginally shorter for the *in-out* arrangement than for the *out-out* pair (5.94 *vs.* 6.01 Å). Such communication between binding sites, mediated by the calixarene framework, could lead to the observed allosteric effect in solution in the case of chloride in particular.

In addition to these gross conformational details, the X-ray data indicate that these compounds bind to the anions and solvent *via* a very broad range of CH hydrogen bonds involving not just the acidic NCHN unit but also the other sp^2 hybridised imidazolium CH groups and even the methylene and methyl units adjacent to the nitrogen atoms. A final interesting feature is the inclusion of an imidazolium group from an adjacent molecule between an *in-out* pair in one of the chloride complexes (Fig. 5d). This intercalation appears to allow edge-to-face π-interactions at the expense of some distortion of the calixarene framework.

In conclusion, we have shown that imidazolium-based anion receptors are capable of strong anion complexation, however, the plethora of hydrogen bond acidic CH groups leads to low selectivity in solution. Such effects may all be general in this type of compound in the absence of significant binding site

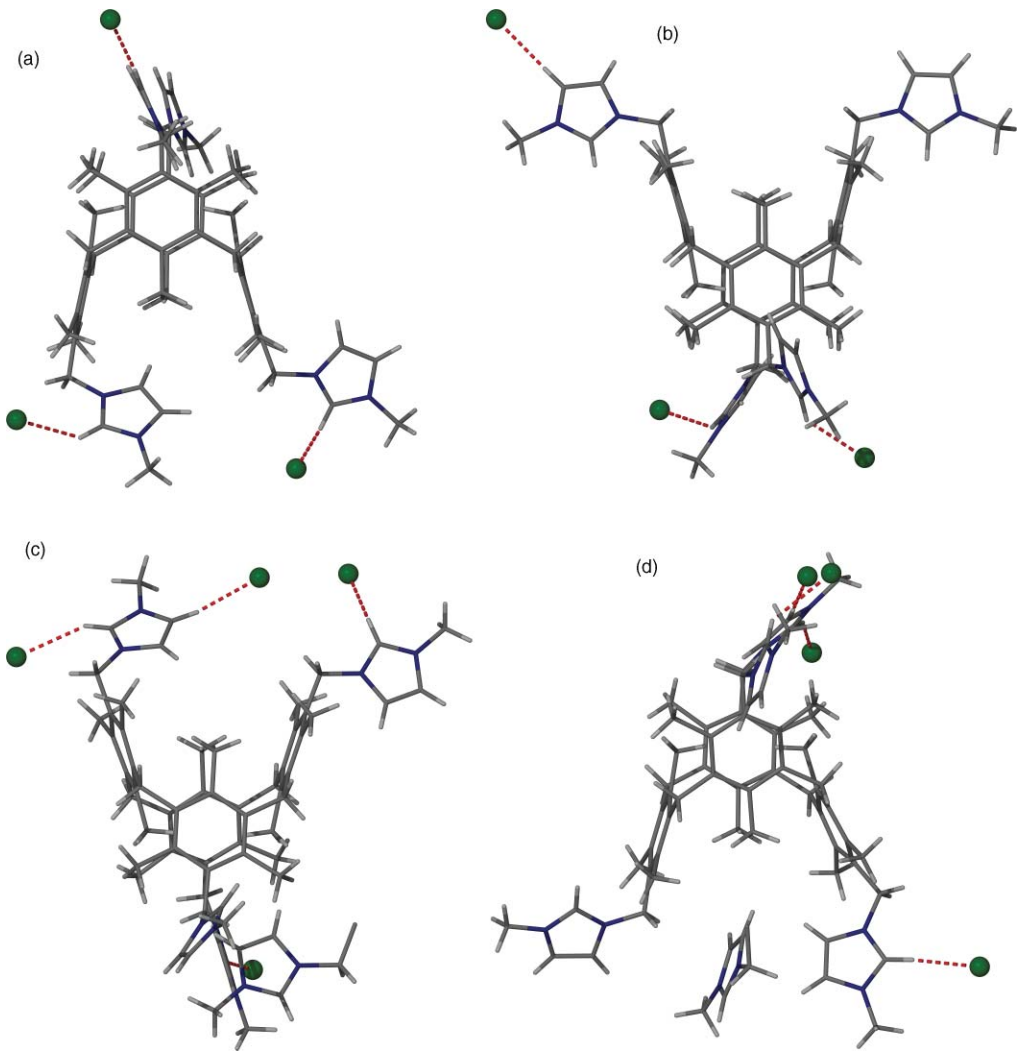


Fig. 5 (a) *In-out* and (b) *out-out* binding regions in molecule **1** in the X-ray crystal structure of the Cl^- salt of **3**; (c) and (d) two views of molecule **2** highlighting the *in-out* geometry and the inclusion of an imidazolium moiety from an adjacent molecule (water molecules omitted for clarity).

preorganisation and highlight that structural data are of key importance in interpreting anion binding by imidazolium-based receptors. The mesitylene-derived calixarene framework based on **1** is a versatile platform for ditopic anion receptors and offers the possibility of interesting allosteric communication between the two binding regions.

Experimental

All reagents were purchased from commercial sources and were used without further purification. Calix[4]arene **1** was prepared from α′-chloroisodurene[32] and reacted with paraformaldehyde in the presence of Zn–HBr to give **2**.[14,36] ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC spectra were obtained from a Varian INOVA 500 spectrometer at a frequency of 500 MHz for ^{1}H and 125 MHz for ^{13}C or from a Bruker Avance 400 at a frequency of 400 MHz for ^{1}H and 100 MHz for ^{13}C. Mass spectrometry data were obtained on a Thermo Finnigan LTQ spectrometer in ES+ and EI mode. C, H and N elemental analysis was performed on an Excitor Analytical Inc CE440 elemental analyser. IR spectroscopic data were obtained from a Perkin Elmer Spectrum 100 FT-IR spectrometer. UV-Vis spectrophotometric titrations were performed on a UNICAM UV-Vis spectrometer (UV2–100) operated under PC-control using Vision software.

Imidazolium calix[4]arene (3)

Compound **2** (2.00 g, 2.22 mmol) and 1-methyl imidazole (0.821 g, 10 mmol) were added to a flask and dissolved in dry dichloromethane (50 mL). The solution was stirred at room temperature for 2 hours resulting in a white precipitate. The precipitate was filtered, washed with dichloromethane (3 × 25 mL) and dried *in vacuo* to give the imidazolium tetrapod as the tetrabromide salt. This bromide salt was dissolved in dry methanol (50 mL) and NH_4PF_6 (1.63 g, 10 mmol) was added resulting in a white precipitate. The mixture was stirred at room temperature for 1 hour and the precipitate was filtered. This was washed with methanol (3 × 25 mL) and dried *in vacuo* to give a hygroscopic white powder. Yield: 3.16 g (95%). ^{1}H NMR (400 MHz, CD_3CN): δ = 8.03 (s, 4H, NCHN), 7.38 (t, 4H, J = 1.8 Hz, NCH), 7.17 (t, 4H, J = 1.8 Hz, NCH), 5.44 (s, 8H, CH_2), 4.10 (s, 8H, CH_2), 3.8 (s, 12H, CH_3), 2.36 (s, 24H, CH_3), 2.17 (s, 12H, CH_3). ^{13}C NMR (400 MHz, CD_3CN): δ = 138.8 (C), 134.5 (C), 127.0 (C), 123.8 (C), 121.3 (CH), 36.1 (CH_2), 18.4 (CH_2), 16.8 (CH_3). Found: C, 47.74; H, 5.12; N, 7.40%. Calc. for $C_{60}H_{76}F_{24}N_8P_4{\cdot}H_2O$: C, 47.81; H, 5.22; N, 7.43%. ES$^+$ (MeCN): 1343.5 $[M - PF_6]^+$ 2%, 599.5 $[M - 2PF_6]^{2+}$ 24%, 351.5 $[M - 3PF_6]^{3+}$ 100%, 227.4 $[M - 4PF_6]^{4+}$ 100%.

^{1}H NMR spectroscopic titration experiments

^{1}H NMR spectroscopic titration experiments were carried out using a Varian Mercury 400 spectrometer running at 400 MHz, at room temperature. All chemical shifts are reported in ppm. A specific concentration of host, typically 0.5–1.5 mM, was made up in a single NMR tube in the desired deuterated solvent (0.5 mL). The anions, as their tetrabutylammonium salts, were made up to 1 mL, 5 times the concentration of the host, with MeCN. 10 μL aliquots of the guest were added to the NMR tube and the spectra were recorded after each addition. Results were analysed using HypNMR 2006.[40,41]

X-Ray crystallography

Crystals suitable for single crystal X-ray analysis were grown from acetonitrile by slow evaporation. For all three structure determinations a single crystal was mounted on a Bruker diffractometer equipped with a SMART 6K CCD area detector and an Oxford Cryostream N_2 cooling device, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å).

Crystal data for **3**(Cl_4): $C_{60}H_{102.50}Cl_4N_8O_{13.25}$, M = 1289.80, colourless block, 0.20 × 0.10 × 0.10 mm^3, triclinic, space group $P\bar{1}$ (no. 2), a = 17.8228(7), b = 18.0014(7), c = 25.5431(10) Å, α = 77.1510(10), β = 82.016(2), γ = 60.6060(10)°, U = 6957.1(5) Å^3, Z = 4, D_c = 1.231 g cm^{-3}, F_{000} = 2770, SMART 6k, Mo-Kα radiation, λ = 0.71073 Å, T = 120(2) K, $2\theta_{max}$ = 58.4°, 118706 reflections collected, 37617 unique (R_{int} = 0.0910). Final *GooF* = 1.251, $R1$ = 0.1233, w$R2$ = 0.3534, R indices based on 17339 reflections with $I>2\sigma(I)$ (refinement on F^2), 1621 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.233 mm^{-1}.

Crystal data for **3**$(Br)_4$: $C_{64}H_{92}Br_4N_{10}O_7$, M = 1433.12, colourless block, 0.20 × 0.20 × 0.20 mm^3, triclinic, space group $P\bar{1}$ (no. 2), a = 12.7428(4), b = 17.2842(6), c = 18.1320(6) Å, α = 117.9510(10), β = 97.0620(10), γ = 99.8510(10)°, U = 3379.69(19) Å^3, Z = 2, D_c = 1.408 g cm^{-3}, F_{000} = 1484, SMART 6k, Mo-Kα radiation, λ = 0.71073 Å, T = 120(2) K, $2\theta_{max}$ = 58.3°, 36796 reflections collected, 18180 unique (R_{int} = 0.0265). Final *GooF* = 1.032, $R1$ = 0.0380, w$R2$ = 0.0913, R indices based on 13552 reflections with $I>2\sigma(I)$ (refinement on F^2), 883 parameters, 12 restraints. Lp and absorption corrections applied, μ = 2.439 mm^{-1}.

Crystal data for **3**$(NO_3)_4$: $C_{61.33}H_{80.68}N_{12.66}O_{13.34}$, M = 1205.98, colourless block, 0.2 × 0.2 × 0.1 mm^3, triclinic, space group $P\bar{1}$ (no. 2), a = 11.2373(3), b = 16.0639(5), c = 19.0982(6) Å, α = 114.2490(10), β = 97.9090(10), γ = 99.5570(10)°, U = 3017.42(16) Å^3, Z = 2, D_c = 1.327 g cm^{-3}, F_{000} = 1283, SMART 6k, Mo-Kα radiation, λ = 0.71073 Å, T = 120(2) K, $2\theta_{max}$ = 58.4°, 51679 reflections collected, 16296 unique (R_{int} = 0.0667). Final *GooF* = 1.029, $R1$ = 0.0784, w$R2$ = 0.2197, R indices based on 7770 reflections with $I>2\sigma(I)$ (refinement on F^2), 848 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.095 mm^{-1}.

One nitrate anion is disordered over two positions. There is also disorder where an acetonitrile and water molecule share a site. No water hydrogen atoms were refined.

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