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Structural Analysis

A Reinterpretation of the Crystal Structure Analysis of $[K(crypt\text{-}222)]^+CF_3^-$: No Proof for the Trifluoromethanide Ion

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Abstract: Critically discussing and, if necessary, questioning results presented by other researchers has always been a vitally important process in science. Only through fruitful discourse does science arrive at broadly accepted hypotheses that finally become what we accept as scientific truth. In the spirit of this time-honored tradition, we have examined the crystal structure as well as X-ray diffraction data of the proposed compound $[K(crypt\text{-}222)]^+CF_3^-$, which has recently been published. We arrived at the conclusion that the claim of the authors to have successfully and unambiguously characterized the ionic $[K(crypt\text{-}222)]^+CF_3^-$ through single-crystal X-ray diffraction is not sustainable. Even though it is possible that the original authors have indeed encountered the proposed species, the purpose of this report is to point out that the original authors cannot use the presented crystallographic data and model as proof for the existence of $[K(crypt\text{-}222)]^+CF_3^-$. The reason for our conclusion is twofold: firstly, the crystal structure was not refined to established standards of good crystallographic practice and secondly, even if best practices of structure determination are employed, the submitted diffraction data do not allow establishing conclusively the true nature of the compound at hand. Recognizing that this gives charge unbalance we have not resolved, we nevertheless suggest an alternative molecular model, $[K(crypt\text{-}222)]\cdot CHF_3$, to demonstrate the ambiguity of the diffraction data submitted by the original authors. However, because of this ambiguity, it is important to point out that the purpose of this report is not (and cannot be) the determination of the true nature of the compound at hand; we would merely like to demonstrate that an alternative interpretation of the original diffraction data is possible and, hence, that the conclusion drawn by the original authors is not unambiguously supported by their own data.

Introduction

Without a doubt, single-crystal X-ray diffraction is one of the most important and powerful methods of structure elucidation in modern chemistry and, considering the staggering number of scientific publications that include at least one crystal structure, certainly it is a well-established standard technique. Driven by this broad use of X-ray crystallography, recent decades have seen dramatic improvements with respect to instrumentation and, more recently, especially structure determination software. This development has led to the unfortunate circumstance that even in the absence of formal crystallographic training and with relatively little experience, convincing looking but nevertheless flawed and sometimes simply wrong crystal structures can be obtained by casual users of crystallographic techniques. Carelessly refined crystal structures may be aggravating but often they "merely" negatively influence the precision of the parameter set and do not change the overall conclusion drawn from the structure. Structures that have been determined incorrectly, on the other hand, are highly problematic because they can and do change the overall conclusions and, thus, can have an appreciable negative impact on science in general.[1] The erroneous "bond-stretch isomerism" concept is a good example for a wrong crystal structure leading to an incorrect conclusion.[2] X-ray diffraction is an indirect measurement of electron density and it can be difficult to distinguish between (almost) isoelectronic species such as between an oxygen atom and an N–H function or a formally negatively charged nitrogen atom.[3] Similarly, it can be challenging to accurately detect hydrogen atoms in X-ray structures because there is only one electron per hydrogen atom, which is, on average, located mostly between the hydrogen and its bonding partner.[4] This issue can have a significant impact on conclusions drawn from crystal structures. In coordination chemistry, for example, distinction between coordinated O^{2-}, OH^-, and H_2O is critical for determination of specific molecular properties such as the oxidation state of a metal atom or the charge of a certain moiety. Sometimes, the overall conclusion of a paper hinges on reliably establishing the presence or absence of a single hydrogen atom and, in such cases, it is generally considered good practice to obtain and present additional spectroscopic data supporting the crystallographic

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model because X-ray diffraction alone may not be sufficient for this specific task.

These challenges notwithstanding, X-ray crystallography is of vital importance in many research areas and, in the interest of science in general, structures of potentially groundbreaking molecules deserve a certain amount of scrutiny by experienced crystallographers. A good example is the X-ray structure of the proposed trifluoromethyl anion that has been published recently by Grushin et al. (see Figure 1).[5]

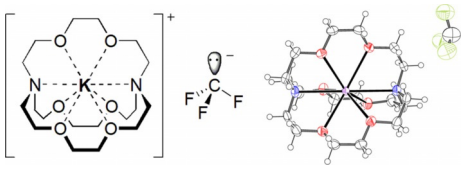

Figure 1. Structure and thermal ellipsoid representation at the 50% probability level of the crystal structure of $[K(crypt\text{-}222)]^+CF_3^-$, as published recently by Grushin et al.,[5] (CCDC 1417273).

Structural characterization of nucleophilic trifluoromethanide-related species is of great interest,[5,6] considering that they are key intermediates in trifluoromethylation reactions.[7–12] The most critical point in the determination of the structure of this compound is the distinction between CF_3^- and CHF_3, that is, the assignment of residual electron density in close proximity to the carbon atom as either a lone pair or a hydrogen atom. For obvious reasons, this distinction is at the limit of the method and, therefore, requires an exceptionally high-quality dataset. (In fact, other methods, such as neutron diffraction, would be more suitable to make the necessary distinction.) Driven by general scientific curiosity, we had a closer look at the structure at hand and found that there is room for serious doubt about the scientific significance of the submitted model. Therefore, we undertook a complete redetermination of the structure and suggest an alternative molecular model as another possible explanation for the diffraction data collected by Grushin et al.[5] This study compares the originally submitted crystallographic model with our alternative one.

Results and Discussion

The description of the X-ray structure determination of $[K(crypt\text{-}222)]^+CF_3^-$ in the paper under discussion already revealed several inconsistencies.[5] It starts with the incorrectly reported crystal system ("hexagonal" for a trigonal space group) and continues to being overly descriptive and unnecessarily verbose about how exactly the crystals were harvested from the crystallization vials, while omitting vital information about data reduction such as absorption correction, the scaling procedure, and resolution ranges. The authors mention technical difficulties in mounting a single crystal: "multiple crystals rather than a single one were mounted on the goniometer head";[5] however, a description of how they proceeded with data reduction is not provided. Did the authors determine individual orientation matrices for each of the "multiple crystals"? If so, were all of those multiple orientation matrices used during data reduction or how else did the authors deal with the problems of exposing several crystals to the X-ray beam at the same time? How were the individual contributions of the "multiple crystals" scaled to one another? Did the authors generate an HKLF5-format data file as well? If so, why was the structure not refined against the HKLF5-format file?

A closer look at the SHELXL instruction file corroborates the initial impression and shows that the submitted structure was, indeed, not refined to established standards of good crystallographic practice.[13] The authors refined the cryptand disorder in a fashion that can only be called chaotic. The authors used unreasonably strong restraints (ISOR 0.01 is ten times the default strength, SIMU 0.005 is eight times the default strength, which is not acceptable), they use direct restraints where relative restraints would have been much preferable (all C–C, C–N, and C–O distances are restrained using DFIX at twice the default strength; SADI or SAME would have been preferable). Their need for FREE statements indicates incorrect disorder parameterization and the use of PART −1 and PART −2 is nonsensical in the way it has been implemented. In addition, two thirds of the hydrogen atoms on the cryptand were introduced incorrectly, that is, ignoring the circumstance that the oxygen positions were refined as disordered to a higher degree than the carbon atoms (see Figure 2 for a comparison of Grushin's disorder model and ours). Grushin and co-workers treated the carbon atoms as ordered, which is, in principle, acceptable, provided the hydrogen atoms on those carbons are still treated as disordered (a detailed description of this issue is provided in reference[14]). Unfortunately, in the published structure, Grushin et al. did not disorder the hydrogen atoms. In our model, the carbon positions of the cryptand are also treated as disordered and the hydrogen atoms are modeled accordingly. This leads to a significantly improved model. All these warning signs prompted us to have a closer look at the submitted diffraction data and subsequently to undertake a complete re-determination of the structure based on Grushin's data set.

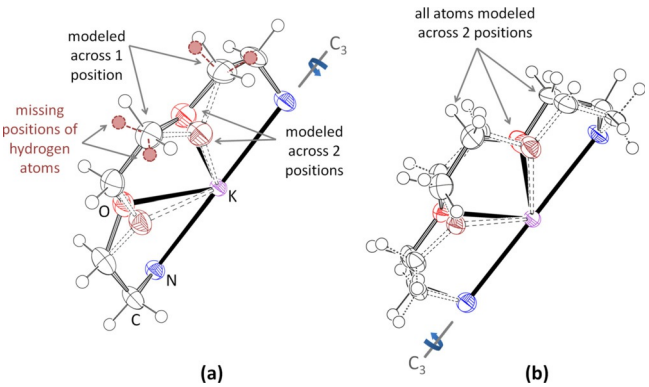

Figure 2. Representations of the disorder model applied by Grushin et al. (a) and the model applied by us (b). For clarity, only the crystallographically independent portion of the cryptand complex is shown (corresponding to 1/3 of the full complex, the remaining two thirds are generated by the crystallographic three-fold axis). Disordered oxygen atoms are shown in dark red. Hydrogen atoms missing in Grushin's model are shown in red for two selected carbon atoms.

Cryptand disorder

We modeled the cryptand as completely disordered over four crystallographically independent positions (see Figures 2b and 3). As is good practice,[13] the disorder was refined with the help of similarity restraints for distances and angles as well as for similar ADP restraints and advanced Hirshfeld restraints[15] (aka rigid-bond restraints) for all atoms involved. Considering the data quality, the disorder is well behaved. All thermal ellipsoids of the major component are of reasonable shape and even most atoms in the lower occupied components refine in a stable fashion. Two pairs of almost overlapping atoms, namely O1B/O1C and C3B/C3C, were pairwise constrained to show identical thermal displacement parameters. The respective occupancies of the four disorder components were refined freely, while restraining their sum to unity within a standard uncertainty of zero, making this effectively a constraint. The occupancy of the main component refined to 45.2(4)%, and the occupancies of the three minor components converged at 21.2(4)%, 20.7(4)%, and 12.9(4)%, respectively (Figure 3).

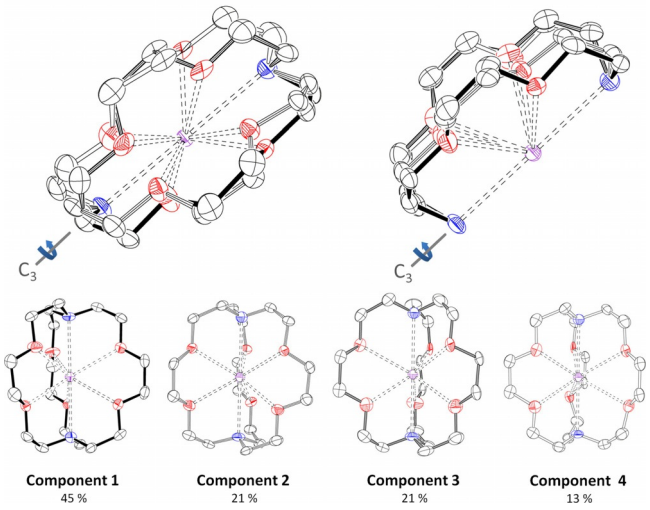

Figure 3. Thermal ellipsoid representation of the four-fold cryptand disorder around the C_3 rotation axes showing only the crystallographically independent portion of the moiety in two different orientations (top) and the four components individually after application of the crystallographic symmetry (bottom). Thermal ellipsoids are rendered at the 50% probability level, hydrogen atoms omitted for clarity.

CF_3 disorder

After applying a technically sound disorder model to the cryptand molecule, we focused on the putative trifluoromethyl anion. The CF_3 unit resides on a crystallographic threefold axis and, hence, the asymmetric unit contains 1/3 of a CF_3 moiety. If there was no disorder, the asymmetric unit would, therefore, contain 1/3 of a carbon atom located on the threefold axis and one fully occupied fluorine atom on a general position. The CF_3 unit is, however, disordered over two positions and both the C and the F atoms are split over two sites. The disorder corresponds to an inversion about a local, non-crystallographic inversion center located near the center of gravity of the CF_3 moiety. This results in a bottom-to-bottom arrangement of the two CF_3 units, as shown in Figure 4. The CF_3 disorder had been modeled more than carelessly by the original authors. In Grushin's model, the two disorder components are not treated as geometrically independent (arguably the very point of disorder) and the two crystallographically independent fluorine atoms are allowed to bind to both independent carbon positions simultaneously, thus leading to distorted bond lengths and angles (Figure 4). Bizarrely, the occupancy ratio for the two alternate F sites was set to 50:50, whereas the ratio for the carbon atom disorder was (arbitrarily?) set to a different ratio, namely 70:30, and Grushin's model required unreasonably strong similar-ADP restraints (SIMU at eight-fold its default strength). Properly parameterizing the CF_3 disorder meant pairwise-assigning the independent F positions to one independent C each and refining the disorder ratio freely (it converged at 63:37 within a standard uncertainty of three percentage points).

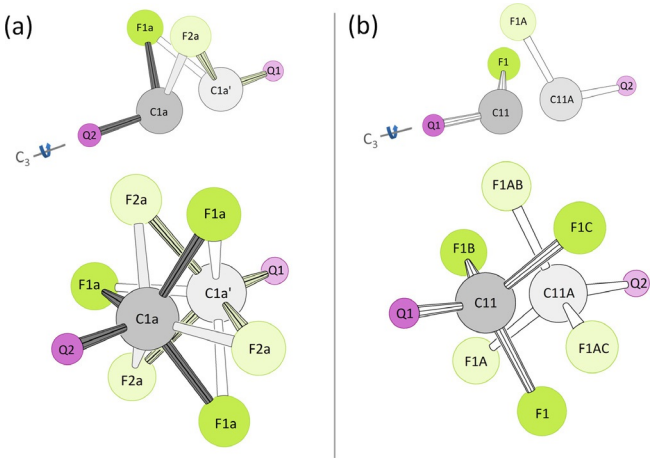

Figure 4. Schematic representation of the arrangement of the disordered CF_3 units on the crystallographic three-fold axis (C_3) axis: (a) Disorder model established by Grushin et al., (b) Our disorder model. The location of the two highest residual density maxima (labeled as Q1 and Q2) are shown in purple.

Residual electron density

In our almost final model, the residual electron density in the difference Fourier synthesis shows two maxima that are significantly higher than all the other electron density peaks: the three top peaks correspond to 0.49, 0.46, and 0.23 electrons, respectively (model ours noh.res, see the Supporting Information), and their location is, indeed, interesting (Figure 4b). The position of the two highest residual density maxima correspond exactly to what one would expect for either hydrogen atoms or the lone pair on the disordered CF_3 unit. It should be pointed out in this context that the submitted structure also contains those two residual density maxima (Figure 4a) and the authors should not have overlooked them. The interpreta-

tion of these maxima is crucial for the determination of the nature of the molecule, that is, CF_3^- or CHF_3. The sum of Q1 and Q2 corresponds to 0.95 electrons per Å^3, which is just about right for a hydrogen atom. For a lone pair on carbon, on the other hand, 0.95 electrons per Å^3 is rather high and the location of the electron density maximum is too far away from the carbon for a lone pair. Therefore, interpretation as lone pairs on a disordered CF_3^- ion is not sensible or, at least, farfetched, especially given the fairly low resolution and poor overall quality of the diffraction data. Yet, Grushin et al. interpreted these maxima as lone pairs, generating a CF_3^- anion and thus professing that "the existence of the free trifluoromethyl anion CF_3^- has been established for the first time".[5]

To determine the nature of the CF_3 unit, Grushin et al. carried out DFT calculations and compared bond distances and angles obtained from their crystal structure to computed geometry parameters for CF_3^- and CHF_3. However, a conclusion "cannot not be drawn because of the limited accuracy of the X-ray data as a result of the above-described disorder in the crystal".[5] Indeed, the bond distances and angles obtained from Grushin's own structural model fall in between the computed geometry parameters of CF_3^- and CHF_3 (Table 1). Interestingly, bonding parameters obtained from our model, which does not suffer from geometrical distortion as a result of incorrectly modeled disorder, clearly agree with the computed geometry parameters for CHF_3 (Table 1), thus supporting an interpretation of the CF_3 species as HCF_3 instead of CF_3^-.

Table 1. Experimentally determined and computed geometry parameters for CF_3^- and CHF_3 as found by Grushin et al. and us. Two values are presented for each parameter because of the two-fold disorder of the CF_3 unit.

Parameter	X-ray structure (Grushin et al.)[a,5]		DFT (Grushin et al.)[5]		Our X-ray structure[b]	
	C1A	C1A′	CF_3^-	CHF_3	C11	C11A
C–F [Å]	1.62(2) 1.35(2)	1.37(3) 1.43(3)	1.43	1.33	1.343(12)	1.311(18)
F-C-F [°]	112(2) 112(2)	99(3) 102(3)	99.6	108.4	107.6(15)	106(2)

[a] Four values are presented for the C–F bond lengths, deriving from the wrongly applied disorder model. [b] C–F bond lengths and F-C-F angles in each CF_3 unit are identical due to crystallographic symmetry.

Encouraged by the strong agreement of our parameters with Grushin's DFT calculations,[5] we included Q1 and Q2 as hydrogen atoms into our model, thus generating CHF_3 instead of CF_3^-. The two CHF_3 hydrogen atoms were refined semi-freely with the help of C–H distance restraints (target distance 1.00(2) Å), while constraining their respective U_{iso} values to 1.2 times the values of the U_{eq} of the corresponding carbon atoms. Those two distance restraints are the only direct restraints employed in the refinement of this structure. When the CHF_3 hydrogen atoms are included into the model, the refinement improves again significantly and the final residual values are $R1 = 0.0413$ for the strong reflections and $wR2 = 0.0970$ for all reflections. This is dramatically better than the residual values of the model submitted by Grushin et al. ($R1 = 0.0638$ for the strong reflections and $wR2 = 0.1815$ for all reflections). The re-determined structure suggests a different conclusion than the one drawn by Grushin et al. Figure 5 shows the new model determined from and based on the originally submitted data.

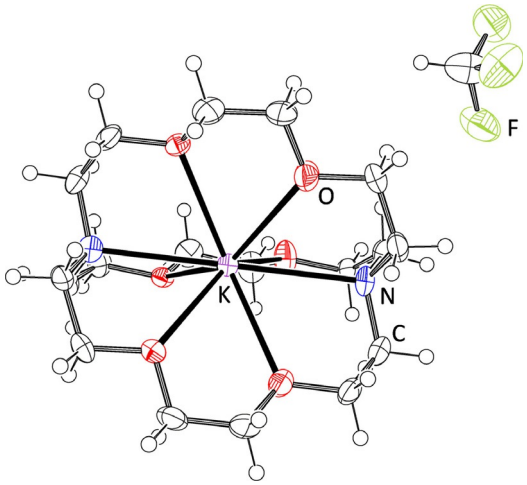

Figure 5. Thermal ellipsoid representation at the 50% probability level of the structure of [K(crypt-222)]·CHF_3. Minor disorder components omitted for clarity. C–F bond length and F-C-F angle in the major disorder component are 1.343(12) Å and 107.5(15), respectively; the corresponding values for the minor disorder component are identical within one to two standard uncertainties. Note that the three C–F bond lengths and the three F-C-F angles in each CHF_3 molecule are identical due to crystallographic symmetry.

Charge balance

A remaining issue of our model is charge balance. Potassium has a positive charge and both the cryptand and the CHF_3 molecule are charge-neutral. One possibility is that the cryptand could be deprotonated and Grushin et al. even suggest as much in their discussion.[5] Although the authors may not have been able to deprotonate the cryptand at −80 °C, this should not be understood as proof that it cannot be done. In addition, it is plausible that Grushin et al. may have let the sample warm up at one point or other during synthesis or, for example, when adding pentane to induce crystallization, which took place at −30 °C, as the authors describe on page S18 of their Supporting Information. Considering the four-fold disorder of the cryptand, it would be impossible to detect a single deprotonation that may well be statistically distributed over all possible hydrogen sites. Consequently, we did not establish a deprotonated cryptand molecule in our model, in full awareness that this leads to a structure that is not charge-balanced. Given the impossibility to locate deprotonation, submission of a non-charge balanced structure is still more reasonable than to deprotonate a random carbon atom. In fact, if the deprotonation is not static but distributed over several carbon atoms, such deprotonation could be the reason for the observed cryptand disorder. Another possibility could be the presence of a disordered OH^- (or DO^-) ion corresponding with and linked to the cryptand disorder.

Restraints

Our structural model of the cryptand and CF_3 unit disorders requires the use of 985 restraints. This is about double the number of restraints utilized by Grushin et al., however (1) only relative restraints were used, which are inherently milder than the direct restraints employed by Grushin et al., (2) no ISOR was needed at all, (3) all restraints were implemented at their default strengths (except for SIMU, which was applied at double the default strength), and (4) only 78 of our restraints are geometry restraints (the remaining restraints are 252 rigid-bond restraints (RIGU), 654 similar-ADP restraints (SIMU), and one restraint to force the sum of the occupancies of the four disorder components to unity), which is almost the same as Grushin's 59 geometry restraints. Considering (a) how much stronger the restrains are that were employed by Grushin et al. (up to ten times default strength!), and (b) that our disorder model is significantly more complex (we refine 326 parameter vs. 214 in the Grushin model), thus requiring a larger number of restraints, it is fair to say that the geometry of our model is restrained much more weakly than the one published by Grushin and co-workers.

Data-to-parameter ratio

The data-to-parameter ratio for our model based on Grushin's data set is poor (2.6:1). The ratio reported by Grushin et al. already had been low (4:1) and introduction of the four-fold cryptand disorder drastically increased the number of parameters. To stabilize the refinement, 985 restraints were used. Restraints should be counted as data and when restraints are included, the (data + restraints)/parameter ratio is (935 + 985)/326 = 5.9, which is still sub-optimal but should be considered acceptable. In addition, we are not merging Friedel pairs for refinement, which further increases the number of data to 1273 and the (data + restraints)/parameter ratio to (1273 + 985)/326 = 6.9.

Conclusion

We have thoroughly examined the submitted crystal structure as well as the X-ray diffraction data of the compound [K(crypt-222)]$^+CF_3^-$ (CCDC 1417273).[5] We demonstrate that the structure at hand was not refined to established standards of good crystallographic practice.[13] Moreover, due to wrongly applied disorder models, important structural parameters such as bond distances and angles had been determined incorrectly by Grushin et al. To evaluate how much usable information was contained in the submitted diffraction data, a complete re-determination of the structure was undertaken and we suggest the alternative model [K(crypt-222)]·CHF_3. It is important to point out that it is beyond the scope of this report to fully establish the true nature of the compound and it is up to the reader to decide whether the evidence as discussed above and provided by Grushin et al. accounts for a CF_3^- species or not. Rather, the purpose of the re-determination of the crystal structure at hand was to suggest an alternative interpretation of the data to emphasize their ambiguity. This alternative interpretation appears to be at least as plausible as the one presented by Grushin et al. and is in many ways even more compelling than the originally published one. Therefore, in our conclusion, the submitted X-ray data are not of sufficient quality to establish the true nature of the compound. Thus, the claim that "ionic [K(crypt-222)]$^+$ CF_3^- has been characterized by single-crystal X-ray diffraction" is not sustainable. Coming full circle, the publication by Grushin et al.[5] is a prime example of the importance of critical, careful, and thorough analysis of diffraction data, especially in the case of potentially groundbreaking molecules.

Experimental Section

The data published by the original authors have been used for the structure refinement at hand. The structure was solved by direct methods using SHELXT[16] and refined against F^2 on all data by full-matrix least squares with SHELXL-2014[17] using established refinement approaches.[13] [K(crypt-222)] hydrogen atoms were incoporated into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the U_{eq} value of the atoms to which they are linked. Coordinates for the hydrogen atoms on the two crystallographically distinct HCF_3 moieties were taken from the difference Fourier synthesis. These hydrogen atoms were subsequently refined semi-freely with the use of a C–H distance restraint (1.00(2) Å), while constraining their U_{iso} values to 1.2 times the U_{eq} of the corresponding carbon atoms.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbanions · structure determination · trifluoromethyl anion · trifluoromethylation · X-ray diffraction

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