

Solid-State Hierarchical Cyclodextrin-Based Supramolecular Polymer Constructed by Primary, Secondary, and Tertiary Azido Interactions**

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Abstract: The crystallization of a di-azido- α -cyclodextrin revealed a polymeric self-assembly involving a variety of azido-type interactions. The crystal arrangement relies on the cooperativity of a primary azido inclusion, a secondary azido-azido interaction involving an unprecedented distribution of canonical forms, and a tertiary azido-groove interaction. The second azido group brings in a major contribution to the supramolecular structure illustrating the benefit of a difunctionalization for the generation of hierarchy.

Organic azides are versatile functional groups,^[1] which are involved in a wide variety of chemical transformations, the flagship of these being the well-established catalyzed or thermal Huisgen reaction.^[2,3] The tolerance, orthogonality, and specific reactivity of this ligation have contributed to its development in several fields ranging from materials science to biological conjugates.^[4] The organic azide function itself has also attracted attention because of its explosive character,^[5–7] which stands in a striking contrast to its relative inertness in biological media providing an efficient bio-orthogonal labeling site.^[8,9] The biological inertness of the azido group is also the basic principle of the well-known azidothymidine (AZT) anti-HIV drug that acts as a DNA chain terminator and an HIV reverse transcriptase (RT) inhibitor.^[10] Furthermore, weak interactions involving the azido group are also key to the recognition of AZT by RT and their nature and strength appear to change in the resistant mutants.^[11] This recognition seems to involve a combination of hydrogen bonding and hydrophobic interactions. Hydrogen-bonded organic azides are well-known in the solid state

and are often engaged in one or multiple hydrogen bonds.^[12] Azido groups involved in hydrophobic interactions are less common, but they have been described in an intermolecular inclusion complex. This interaction appeared to be strong enough to provide a primary interaction in the supramolecular polymerization of monofunctionalized cyclodextrins (CDs),^[13] which are usually built up by larger hydrophobic groups^[14–16] (adamantyl,^[17] aryl derivatives,^[18–20] cinnamoyl derivatives,^[21] etc.).

Here we report an original collection of azido interactions serving as basis for the solid-state hierarchical polymerization of a difunctionalized CD bearing two distant azido groups. In contrast to monofunctionalized CDs, difunctionalized ones can bring additional cooperative intra- and interstrand interactions. In the present case, the first azido group is engaged in the polymeric strand and the second one either stabilizes the strand itself or interacts with neighboring strands to stabilize the whole assembly (Figure 1). The azido groups are engaged in an unexpected variety of interactions organized in distinct primary (hydrophobic inclusion), secondary (azido-azido dipole-induced dipole interaction involving a unique distribution of canonical forms), and tertiary (azido-hydrogen bonding array) azido-type interactions to build the hierarchical assembly. This system represents a unique example of a difunctionalized CD-based supramolecular polymer involving an unprecedented cooperative role of the second function.

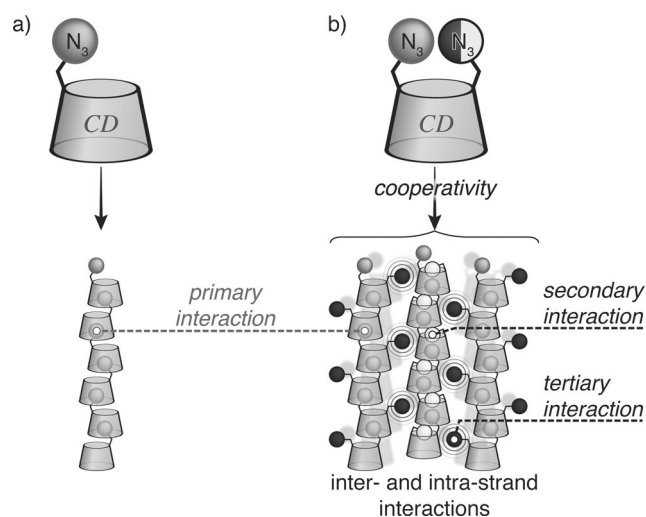


Figure 1. Schematic representations of a) monoazido-CD- and b) diazido-CD-based supramolecular polymers with emphasis on the interactions brought by the second azido group described herein.

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The 6^A,6^D-diazido-6^A,6^D-dideoxy- α -cyclodextrin^[22] (**1**) (Figure 2a) was efficiently synthesized from native α -CD in five steps with 74 % overall yield following a procedure we have previously described.^[23] Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a saturated aqueous solution of **1**.^[24,25]

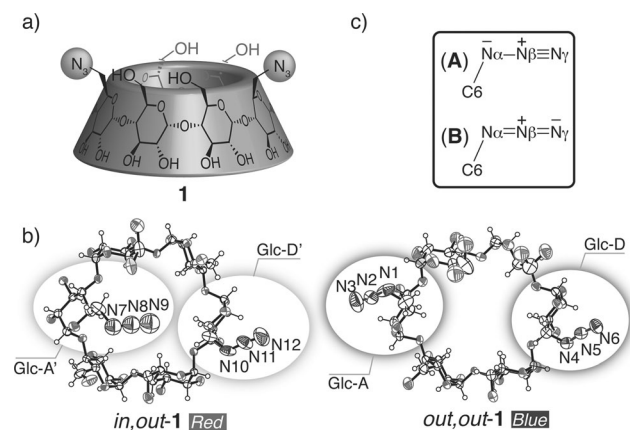


Figure 2. a) Schematic representation of **1**. b) X-ray structure of the *in,out*-1 and *out,out*-1 conformers. c) Canonical forms of the azido group.

Analysis of the crystal showed two conformationally different diazido- α -CDs in the unit cell with some disorder of the O-6 oxygen atoms (Figure 2b). Both conformers orient one of their azido groups outward the torus of the CD while the other azido group is either directed inward (*in,out*-1) or outward (*out,out*-1) the CD macrocycle. While the ⁴C₁ chair conformation of every glucose unit is preserved, the macrocyclic torus of the conformer *in,out*-1 undergoes a minor distortion due to the introverted position of the azido group resulting in a slight tilt of the A' glucose unit (Glc-A'). Each conformer arranges in the crystal lattice into distinct left-handed helices (Figure 3a,b). The helical arrangements involve four repeating CDs that define a screw pitch of 21.95 Å for both helices. The supramolecular polymerization of each conformer is based on a primary interaction involving the inclusion of one “out” azido group (N₃^{GlcA} for *out,out*-1 or N₃^{GlcD} for *in,out*-1) in the cavity of the next CD affording a linear helical assembly (Figures 3b and 4a), which is efficiently assisted by numerous intrastrand hydrogen bonds of the hydroxy groups.

Interestingly, the 4₁ screw axes of these assemblies differ from the reported 2₁ organization of the monoazido- α -CD.^[13] Such a variation results from the presence of the second azido function that induces another level of organization. The inward-oriented azido group on the *in,out*-1 conformer induces a secondary interaction. The geometric analysis of the azido groups revealed some discrepancies in the charge repartition along the nitrogen atoms depending on the azido group.^[26–28] In particular, measurement of C₆–N α , N α –N β , and N β –N γ bonds (Figure 2c and Table 1) showed significant length variations for the introverted azido group compared to typical ones.^[1,12] Longer distances for C₆–N α and N β –N γ bonds (1.51 Å and 1.25 Å) and a shorter one for N α –N β

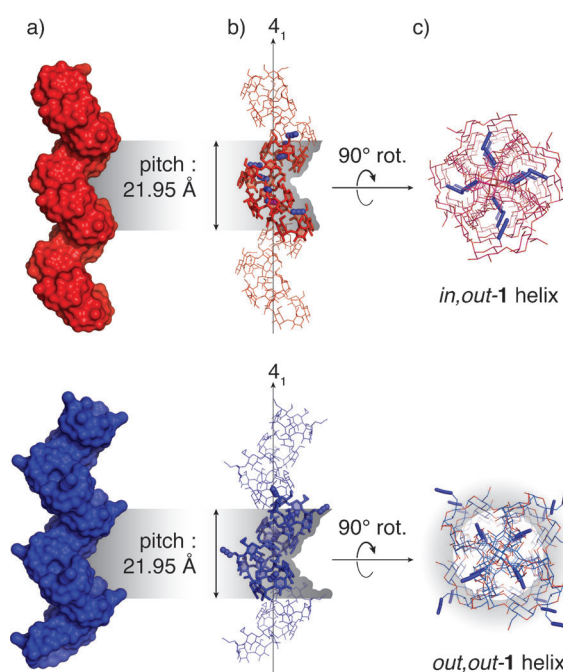


Figure 3. a) Surface representation of the helical arrangements of the *in,out*-1 and *out,out*-1 helices. b) Wireframe representation of the same helices with emphasis on the four CDs composing the pitch. c) View along the screw axis of the two helices showing the inner azido groups and the peripheral ones (bottom).

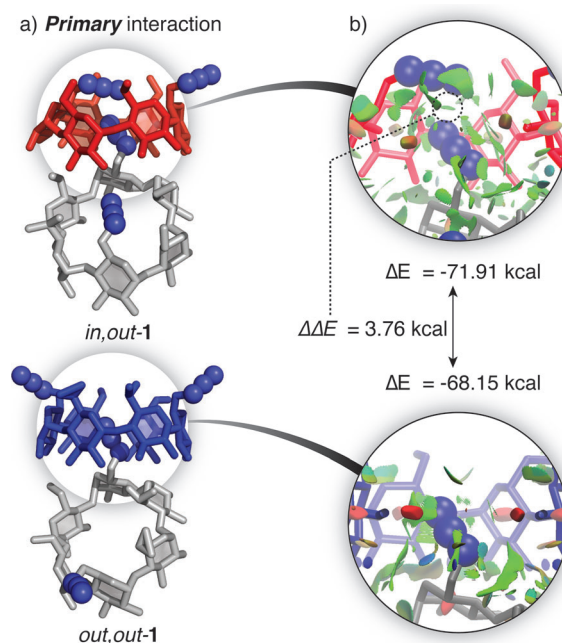


Figure 4. Primary interaction. a) Azido group inclusion complex for *in,out*-1 (top) and *out,out*-1 (bottom). b) Circular insets: calculated DFT structures showing NCI surfaces (green layer) and energies of interactions.

(1.16 Å) are measured for this inner azido group that contrasts with the other three azido groups displaying more homogeneous values for N α –N β (1.18 to 1.23 Å) and N β –N γ (1.09 to 1.14 Å) in accordance to previously reported mono-

Table 1: Bond lengths [Å] of the azido groups.

Cyclodextrin	Azido group	C6–N α	N α –N β	N β –N γ
<i>out,out</i> -1	C6A–N1–N2–N3	1.50(1)	1.19(1)	1.09(1)
<i>out,out</i> -1	C6D–N4–N5–N6	1.45(1)	1.23(1)	1.14(1)
<i>in,out</i> -1	C6A'–N7–N8–N9	1.51(1)	1.16(1)	1.25(2)
<i>in,out</i> -1	C6D'–N10–N11–N12	1.49(1)	1.18(1)	1.14(1)

azido- α -CD.^[13] This length variation is in agreement with a charge redistribution for which the shortening of the N α –N β bond corresponds to an increased double bond character and the lengthening of the N β –N γ bond to a decreased triple bond character. Thus the introverted azido group would adopt a charge distribution closer to the B resonance form rather than to the A resonance form adopted by the three other azido groups (Figure 2c). The interactions involved in the inclusion were identified performing NCI analysis (non-covalent interaction)^[29,30] on the extracted elementary dimeric complexes from their corresponding helical assembly and optimized using DFT at the B3LYP-D3/SV(P) level.^[24] The NCI analysis (Figure 4b) revealed numerous stabilizing isosurfaces illustrating the van der Waals interactions between the included azido group and the hydrogen atoms covering the interior of the CD's cavity ($\Delta E_{in,out-1} = -71.91$ kcal and $\Delta E_{out,out-1} = -68.15$ kcal). The slight difference in energy between the two dimeric conformers ($\Delta\Delta E = 3.76$ kcal) indicates an additional contribution to the stability of the *in,out*-1 assembly, hence sustaining a secondary azido interaction stabilizing the structure.

The nature of this secondary azido interaction was further examined. The introverted azido group is located above the primary rim of its CD, thereby positioning the terminal nitrogen N9 near the center of the torus and just above the included interresidual azido guest ($d_{N9-N12} = 2.94(2)$ Å, Figure 5a). The N9...N12 distance is shorter than the sum of the two van der Waals radii of the nitrogen atoms ($r = 1.55$ Å, $2r = 3.10$ Å),^[31] hence delineating an attractive interaction also seen in the NCI plot (Figure S1).^[24] To evaluate the strength of such an original azido–azido interaction, we performed a potential of mean force (PMF) analysis (at the B3LYP-D3/def2-TZVP level) with a model interaction involving two azidomethane units (Figure 5c).^[24] The analysis showed a significant gain in energy for short N γ ...N γ' distances (ca. 2.9 to 3.3 Å) with 2.76 kcal for a distance of 2.94 Å. Hence, the observed gain in energy for the *in,out*-1 assembly arises from a secondary azido–azido interaction. The natural bond orbital (NBO) analysis done in addition to DFT calculations (at the B97D/TZVP level, NBO version 3.1)^[24] gave further information on the nature of this interaction. The electronic distribution confirmed the observed tendency of the included azido group toward the A-type resonance form displaying a terminal triple bond while the introverted azido group adopts a B-type resonance form with an allene-like bonding pattern (Figure 5b). Therefore, the bonding arrangement of the canonical forms suggests that the secondary azido–azido interaction operates in a dipole-induced dipole fashion cooperatively strengthening the primary inclusion.

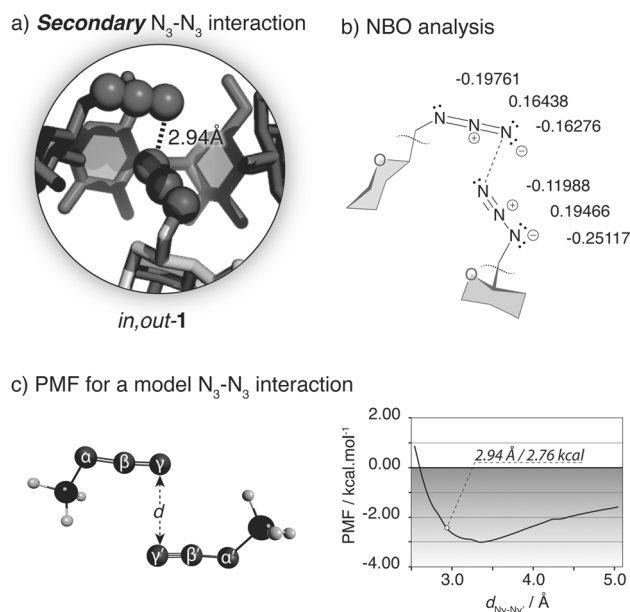


Figure 5. Secondary interaction. a) X-Ray structure of the azido–azido interaction in the *in,out*-1 helix. b) Lewis-like bonding structure of the azide functions obtained through NBO analysis (Mulliken charges are depicted for each nitrogen atoms). c) Potential of mean force analysis of the N γ –N γ' distance for a model azidomethane dimeric complex.

While the first and second azido-based interactions concentrate the azido groups inside the *in,out*-1 helix, the *out,out*-1 conformer orients its second azido group on the periphery of the polymeric helix to operate a third level of interaction that introduces hierarchy into the whole assembly (Figure 3c). Indeed, the crystal organization reveals a strong complementarity between the *out,out*-1 peripheral azido groups with the helix formed by the *in,out*-1 conformer (Figure 6). Each peripheral azido function is surrounded by three glucose units (GlcC', GlcD', and GlcE') belonging to three different assembled CDs defining the groove of the *in,out*-1 helix (Figure 6a). The orientation of the glucose units concentrates the secondary hydroxy groups in the middle of the groove affording a network of weak hydrogen bonds focusing on the housed azido group. Moreover, the hydrogen bonds participating in the recognition of the azido group are specific as the N α binds the OH-3s (N4–O3C' 3.75 Å, N4–O3D' 3.31 Å, and N4–O3E' 3.38 Å) while the N γ binds the OH-2s (N6–O2C' 3.32 Å, N6–O2D' 3.32 Å, and N6–O2E' 3.20 Å). The fact that the peripheral azido groups fill the groove of the *in,out*-1 red helix results in a coaxially intertwined helix that wraps the first one and adopts the same screw pitch (Figure 6b,c). The CDs bearing these peripheral azido groups and surrounding the central helix are engaged in four distinct *out,out*-1 helices staggered with the *in,out*-1 helix (Figure 6c,d), thereby arranging their primary/secondary rim-termini in an opposite fashion (Figure 6e).

The binding of the peripheral azido groups within the groove allows the two different helices to get close enough to create additional cooperative interstrand hydrogen bonds between the secondary hydroxy groups. These dense inter-

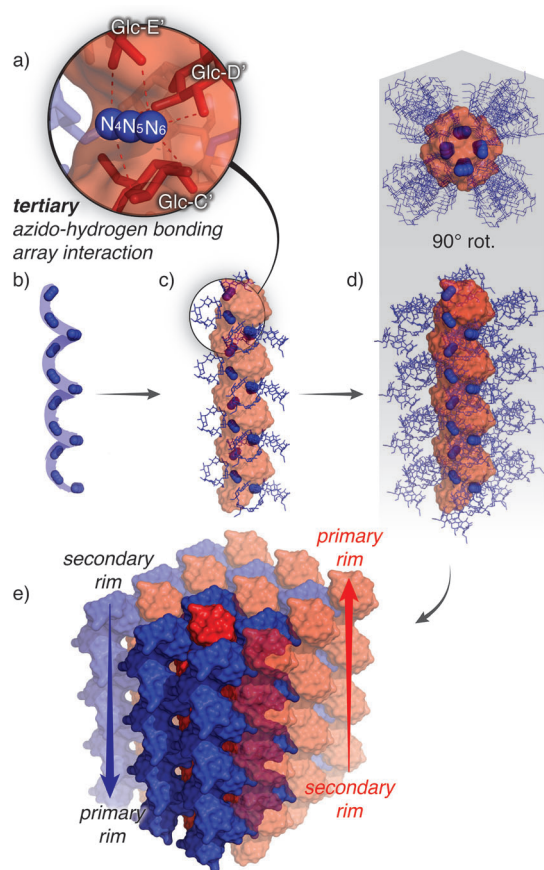


Figure 6. Tertiary interaction. a) Stick and surface representations of the azide–hydrogen bonding array located in the groove of the *in,out*-1 helix. b) Helical arrangement of the *out,out*-1 interacting peripheral azido groups. c) Surface representation of *in,out*-1 helix surrounded by the interacting *out,out*-1 CDs, and d) by the four *out,out*-1 helices (top and side view). e) Surface representation of the interacting helices showing the alternate orientation.

actions give rise to an arrangement different to the one observed in the case of the 6^A-monoazido- α -CD where the strands are isolated by residual water molecules.^[13,24] The complementarity between the peripheral azido groups embedded in the groove of the *in,out*-1 helix provides a tertiary interaction, which stabilizes both helix types and consequently the whole hierarchical assembly.

In conclusion, we have shown that the combination of two azido groups diametrically disposed on the primary rim of an α -CD results in cooperative primary, secondary, and tertiary interactions in a hierarchical supramolecular polymerization. The azido hydrophobic inclusion, which is the primary interaction responsible for the supramolecular polymer, is efficiently assisted by an unprecedented secondary azido–azido dipolar interaction. The latter involves two different canonical forms of the azido group creating a dipole-induced dipole interaction, which is strengthening the main helical assembly. Finally, the helix groove delineated by the cyclodextrins piling offers a hydrogen bonding network able to accommodate the peripheral azido groups of the surrounding helices through a tertiary azido–hydrogen bonding array interaction. The sum and complementarity of the azido–

driven interactions afford a CD-based hierarchical supramolecular polymer. This original set of azido interactions sheds light on the variety and significance of such interactions.

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- [1] S. Patai, *The Chemistry of the Azido Group*, Interscience Publishers, London, **1971**.
- [2] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320–5374; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.
- [3] S. Bräse, K. Banert, *Organic Azides*, Wiley, **2010**.
- [4] J. Lahann, *Click Chemistry for Biotechnology and Materials Science*, Wiley, Hoboken, **2009**.
- [5] J. Evers, M. Göbel, B. Krumm, F. Martin, S. Medvedev, G. Oehlinger, F. X. Steemann, I. Troyan, T. M. Klapötke, M. I. Eremets, *J. Am. Chem. Soc.* **2011**, *133*, 12100–12105.
- [6] T. M. Klapötke, F. A. Martin, J. Stierstorfer, *Angew. Chem. Int. Ed.* **2011**, *50*, 4227–4229; *Angew. Chem.* **2011**, *123*, 4313–4316.
- [7] X. Zeng, E. Bernhardt, H. Beckers, K. Banert, M. Hagedorn, H. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 3503–3506; *Angew. Chem.* **2013**, *125*, 3587–3591.
- [8] J. A. Prescher, C. R. Bertozzi, *Nat. Chem. Biol.* **2005**, *1*, 13–21.
- [9] K. Fauster, M. Hartl, T. Santner, M. Aigner, C. Kreutz, K. Bister, E. Ennifar, R. Micura, *ACS Chem. Biol.* **2012**, *7*, 581–589.
- [10] O. A. Olivero, *Environ. Mol. Mutagen.* **2007**, *48*, 215–223.
- [11] X. Tu, K. Das, Q. Han, J. D. Bauman, A. D. Clark, X. Hou, Y. V. Frenkel, B. L. Gaffney, R. A. Jones, P. L. Boyer et al., *Nat. Struct. Mol. Biol.* **2010**, *17*, 1202–1209.
- [12] L. Tchertanov, *Acta Crystallogr. Sect. B* **1999**, *55*, 807–809.
- [13] S. Hanessian, A. Benalil, M. Simard, F. Bélanger-Gariépy, *Tetrahedron* **1995**, *51*, 10149–10158.
- [14] K. Hirotsu, T. Higushi, K. Fujita, T. Ueda, A. Shinoda, T. Imoto, I. Tabushi, *J. Org. Chem.* **1982**, *47*, 1143–1144.
- [15] a) A. Harada, Y. Takashima, H. Yamaguchi, *Chem. Soc. Rev.* **2009**, *38*, 875–882; b) A. Harada, A. Hashidzume, *Aust. J. Chem.* **2010**, *63*, 599–610.
- [16] A. Harada, A. Hashidzume, Y. Takashima, *Supramolecular Polymers/Polymeric Betains/Oligomers in Advances in Polymer Science, Vol. 201*, Springer, Berlin, **2006**, pp. 1–43.
- [17] V. H. S. Tellini, A. Jover, L. Galantini, F. Meijide, J. V. Tato, *Acta Crystallogr. Sect. B* **2004**, *60*, 204–210.
- [18] Y. Liu, Y. L. Zhao, H. Y. Zhang, E. C. Yang, X. D. Guan, *J. Org. Chem.* **2004**, *69*, 3383–3390.
- [19] Y. Liu, Z. Fan, H.-Y. Zhang, C.-H. Diao, *Org. Lett.* **2003**, *5*, 251–254.
- [20] Y. Liu, C.-C. You, M. Zhang, L.-H. Weng, T. Wada, Y. Inoue, *Org. Lett.* **2000**, *2*, 2761–2763.
- [21] M. Miyauchi, Y. Takashima, H. Yamaguchi, A. Harada, *J. Am. Chem. Soc.* **2005**, *127*, 2984–2989.
- [22] S. Hanessian, A. Benalil, C. Laferrière, *J. Org. Chem.* **1995**, *60*, 4786–4797.
- [23] M. Guitet, F. Marcelo, S. Adam de Beaumais, Y. Zhang, J. Jiménez Barbero, S. Tilloy, E. Monflier, M. Ménand, M. Sollogoub, *Eur. J. Org. Chem.* **2013**, 3691–3699.
- [24] See the Supporting Information.
- [25] Crystal data for **1**: colorless stick-like crystals: C₃₆H₅₈N₆O₂₈·8H₂O, tetragonal, *P*₄, *a* = 21.7457(5), *c* = 21.9544(6) Å, *V* = 10381.7(6) Å³, *Z* = 8, *T* = 200(2) K, λ = 1.54178 Å, μ = 1.176 mm^{−1}, 101044 reflections measured, 18460 independent (*R*_{int} = 0.0316), 17202 observed [*I* ≥ 2 σ (*I*)], 1259

parameters, final R indices $R_1 [I \geq 2\sigma(I)] = 0.0495$ and wR_2 (all data) = 0.1392, GOF on $F^2 = 1.036$, max/min residual electron density = 0.62/−0.35 e Å^{−3}. CCDC 990388 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

- [26] L. Pauling, L. O. Brockway, J. Y. Beach, *J. Am. Chem. Soc.* **1935**, 57, 2705–2709.
- [27] L. Pauling, L. O. Brockway, *J. Am. Chem. Soc.* **1937**, 59, 13–20.
- [28] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, **1960**.
- [29] E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, 132, 6498–6506.
- [30] J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, *J. Chem. Theory Comput.* **2011**, 7, 625–632.
- [31] A. Bondi, *J. Phys. Chem.* **1964**, 68, 441–451.