



Isohexide Dinitriles: A Versatile Family of Renewable Platform Chemicals

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Building blocks of isohexides extended by one carbon atom at the 2- or 5-positions are now synthetically accessible by a convenient, selective, base-catalyzed epimerization of the corresponding dinitriles. Kinetic experiments using the strong organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) show that all three possible isohexide dinitrile isomers exist within a dy-

namic equilibrium. An epimerization mechanism based on density functional theory (DFT) calculations is proposed. Structural identification of all three possible isomers is based on NMR analysis and single crystal x-ray crystallography. DFT calculations confirm that the observed crystal structures are indeed the lowest energy conformers of these isohexide derivatives.

Introduction

The transformation of readily available, yet structurally-complex biomass into simple molecules with high added-value is currently one of the central topics for both academia and industry. Isohexides (1,4:3,6-dianhydrohexitols) are a family of rigid bicyclic diols, which can be derived from cellulose or starch. Three different isomeric isohexides are known (Figure 1), namely isosorbide (IS; 1,4:3,6-dianhydro-D-mannitol), isomannide (IM; 1,4:3,6-dianhydro-D-glucitol), and isoidide (II; 1,4:3,6-d-dianhydro-L-iditol). These bio-based molecules are

highly interesting owing to several key features: all three isomers are non-toxic, chiral, aliphatic, bifunctional, and have rigid structures.^[1]

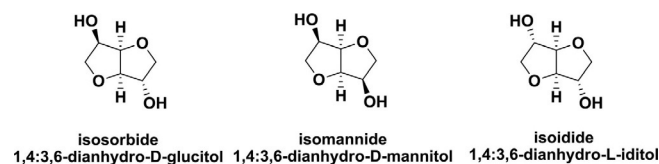


Figure 1. Three isomeric isohexides (1,4:3,6-dianhydrohexitols).

The current expansion of papers and patents on isohexide chemistry is indicative of the broad scope of potential applications for these molecules.^[1] Besides the direct use of the parent isohexides in, for example, polyester and polycarbonate syntheses, a number of derivatives have also been synthesized for various purposes.^[1] This is accomplished by modification of the hydroxy groups at the 2- and 5-positions of the bicyclic ring. One approach is chain extension on the oxygen atoms of the original hydroxy groups. For instance, reacting isosorbide with ethylene carbonate in the presence of potassium carbonate yields a 2,5-bis(2-hydroxyethyl)isosorbide.^[2] Alternatively, the direct replacement of the original hydroxy groups by new functional groups (e.g. $-\text{NH}_2$, $-\text{NCO}$, $-\text{COOH}$, $-\text{CH}_2\text{OH}$, and $-\text{CH}_2\text{NH}_2$) has also been reported.^[3] Hence, the application window of the parent isohexides can be significantly broadened. Current applications include the use of isosorbide dinitrate as a vasodilator for treating cardiac or vascular diseases.^[4] Furthermore, isosorbide alkyl derivatives have been proposed as green solvents for pharmaceutical or cosmetic compositions,^[1f,5] and isosorbide diesters are excellent plasticizers for poly(vinyl chloride) (PVC).^[6] In the field of synthetic organic chemistry, the chirality of isohexides and derivatives has been exploited in the synthesis of a variety of sophisticated mole-

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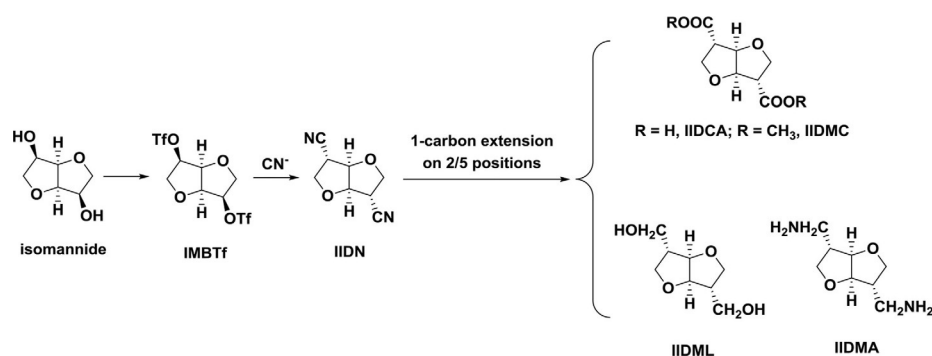
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Scheme 1. Synthesis of 1-carbon-extended isohexides from isomannide. R = H or CH₃.^[3d,10a,11]

cules, such as chiral ionic liquids,^[7] phase-transfer catalysts,^[8] and ligands for asymmetric catalysis (amino alcohols, amines, mono- and diphosphines, diphosphites, bis-diaminophosphites, etc.).^[9] Difunctional isohexide derivatives are also interesting building blocks for various step-growth polymers with potential applications ranging from performance polymers to biodegradable/biocompatible materials and optical materials.^[1]

As we are interested in developing value-added, bio-based materials, we have been involved in the development of novel synthetic routes for isohexide-based building blocks,^[3a,b] as well as new polymers based on these monomers.^[10] Recently, we reported the synthesis of a new family of 2,5-deoxy 1-carbon-extended isohexides.^[3c,d,11] The aim of the research is to overcome some of the drawbacks associated with the use of the parent isohexides in the synthesis of step-growth polymers, such as low reactivity and moderate thermal stability (Scheme 1).^[3c,d,12]

Our synthetic approach (Scheme 1) is based on a stereo-specific conversion of the *endo-endo*-configured isomannide-2,5-bistriflate (IMBTf) to the *exo-exo*-configured isoidide-2,5-dinitrile (IIDN) via Walden inversion in the presence of a cyanide anion. IIDN then serves as a key intermediate for the subsequent transformations into a family of bi-functional building blocks, including isoidide-2,5-dicarboxylic acid (IIDCA), isoidide-2,5-dimethyl ester (IIDMC), isoidide-2,5-dimethanol (IIDML), and isoidide-2,5-dimethylene amine (IIDMA; Scheme 1).^[3d,11] We have successfully shown that IIDCA and IIDMC, as well as IIDML are rigid AA-type monomers from which novel polyesters have been obtained.^[12] Furthermore, these new molecules can have various additional applications, including catalysis, pharmaceuticals, and liquid-crystalline materials.

Unfortunately the current synthetic strategy only gives access to the *exo-exo*-configured isohexide derivatives. Derivatives with the *exo-endo* or *endo-endo* configurations cannot be synthesized using the same protocol, since Walden inversion of an *exo*-triflate group is sterically unfavorable.^[3i,13] As the orientation of the substituents at the 2- and 5-positions in isohexides can have a dramatic influence on physical and chemical properties, investigation of the effects of the substituent orientation in the new 1-carbon-extended isohexides is important in order to unlock their full potential. Hence, an alternative synthetic route toward the *exo-endo* and *endo-endo* isomers is highly desired. Catalytic epimerization of readily avail-

able isohexide derivatives has been an attractive strategy to obtain the synthetically less-accessible isomers. In the 1960s, Wright and Brandner reported a catalytic epimerization protocol to obtain isoidide and isomannide from isosorbide by using a nickel catalyst under a hydrogen atmosphere.^[14] Recently, Le Nôtre et al. showed that all three parent isohexide isomers can be obtained by catalytic epimerization of isosorbide, giving access to separate epimers by simple distillation.^[15] This prompted us to explore the potential of catalytic epimerization of IIDN to obtain the other epimers.

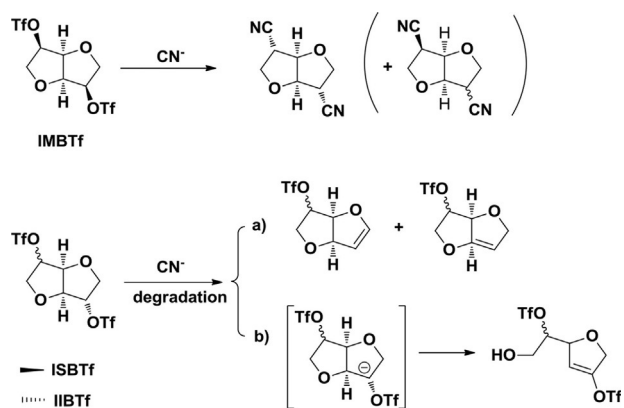
Herein, we describe the laboratory-scale synthesis of isosorbide-2,5-dinitrile (ISDN) and isomannide-2,5-dinitrile (IMDN) by a convenient base-catalyzed epimerization protocol, starting from the previously developed isoidide-2,5-dinitrile (IIDN). A reaction mechanism for the epimerization reaction is proposed based on experimental data and density functional theory (DFT) calculations. The molecular structures of three dinitrile isomers were analyzed by 1D and 2D NMR spectroscopy, single crystal X-ray diffraction, and DFT calculations.

Results and Discussion

Synthesis of isohexide isomers

IIDN can be efficiently synthesized from isomannide-2,5-bistriflate (IIBTf) via an S_N2 substitution by cyanide anions, affording IIDN in approximately 80% isolated yield after column chromatography.^[3d] When the same cyanation conditions [IIBTf/KCN/18-crown-6/tetrahydrofuran (THF); -10–0 °C] were applied to either isosorbide-2,5-bistriflate (ISBTf) or isoidide-2,5-bistriflate (IIBTf), severe degradation of the starting material was observed and no significant amounts of the desired product could be isolated (Scheme 2). S_N2 substitution of *exo*-leaving groups in isohexides has been known to be unfavorable owing to steric hindrance.^[16] As shown in Scheme 2, E2 elimination under basic conditions can give unstable vinyl ethers,^[17] whereas α -deprotonation can result in ring-opened side products.^[16a-c]

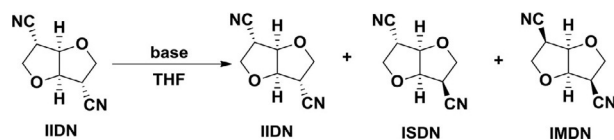
Interestingly, small amounts of the dinitrile epimers ISDN and IMDN were occasionally observed during the synthesis of IIDN, depending on reaction time and temperature, as well as on the excess of KCN/18-crown-6 used. Regarding the mechanism of such an epimerization side reaction, the possibility of



Scheme 2. Synthetic and degradation pathways of isohexide dinitrile isomers from isohexide bistriflate intermediates via S_N2 substitution by cyanide anions. Possible degradation pathways for ISBTf and IIBTf are: a) elimination of the *exo*-triflate groups generating reactive vinyl ethers^[17] and b) ring-opening reactions caused by α -deprotonation.^[16a-c] ISBTf and IIBTf are distinguished by the configuration of one OTf group.

free-radical-induced epimerization was first investigated. A radical mechanism could be excluded based on the results of the cyanation reactions conducted in THF solution in the presence of radical scavengers, for example, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxytoluene (BHT). Both of the experiments with radical scavengers showed the formation of isomers. Given that potassium cyanide is a relatively strong base (pK_b in water = 2.9) and the basicity in THF will increase in the presence of a phase-transfer catalyst such as a crown ether, we concluded that base-induced epimerization was the most likely mechanism. Catalytic epimerization of readily available isohexide derivatives has been an attractive strategy to obtain the synthetically less-accessible isomers. As mentioned above, catalytic epimerization of isosorbide to isoidide and isomannide has been demonstrated by Wright and Brandner, and Le Nôtre et al. in 1964 and 2013, respectively.^[14,15] This prompted us to explore the potential of catalytic epimerization of isosorbide to obtain the other epimers. Based on our previous results, starting from isomannide, high-purity IIDN (>99.9%) can be readily obtained in 80% yield in two steps. We decided to explore the viability of a base-catalyzed epimerization reaction of IIDN to obtain ISDN and IMDN.

To investigate the viability of the epimerization reaction as a synthetic procedure, IIDN was treated with inorganic and organic bases of various strengths in THF at room temperature (Scheme 3). 18-Crown-6 was added to increase the solubility of the potassium salts. The reaction conditions and the corresponding ratios of the three isohexide isomers produced are shown in Table 1. Relatively strong bases such as potassium *tert*-butoxide ($pK_b = -3$), potassium hydroxide ($pK_b = 0.5$) and potassium cyanide ($pK_b = 0.5$) gave swift epimerization (entries 1–3). At the same time, severe discoloration of the reaction mixtures indicated that significant degradation occurred. To examine the molar ratio of three isohexide epimers, aliquots of the reaction mixtures were extracted with ethyl acetate/water. After separation of the organic layer and drying over $MgSO_4$, the ethyl acetate layer was subjected to GLC analysis.



Scheme 3. Base-induced epimerization reactions of IIDN in THF solutions.

Table 1. Epimerization results using various bases.^[a]

Entry	Base	<i>t</i> [h]	Color	Isohexide ratio [%] ^[b]		
				IIDN	ISDN	IMDN
1	(CH_3) ₃ COK	0.5	brown	38.7	51.6	9.7
2	KOH	0.5	brown	39.1	48.0	12.9
3	KCN	0.5	brown	45.2	44.3	10.5
4	CH_3CO_2K	24	colorless	86.6	13.4	trace
5	DBU ^[c]	26	colorless	39.6	50.1	10.3

[a] All reactions performed at room temperature. The reactant molar ratio is: IIDN/18-crown-6/base = 1:0.1:0.2. [b] Data derived from the GLC analysis of the extracted sample. For the procedure, see the Experimental Section. [c] No 18-crown-6 was used. Reaction was performed at 50 °C with 0.5 equiv of DBU.

It should be noted that some ethyl acetate/water-insoluble by-products or compounds that are undetectable by GLC analysis are not included in the analysis. The molar ratios as shown in Table 1 only reflect the relative molar ratios of the three isohexide epimers, rather than the actual yields of all possible epimerization products. The approximate molar ratio of isohexides IIDN/ISDN/IMDN is 4:5:1 as obtained by GLC analysis. In contrast, the weak base potassium acetate demonstrated low epimerization activity (entry 4); only 13% of ISDN and almost no IMDN were observed after 24 h. However, no discoloration occurred over this extended time-span, indicating that these mild conditions are highly selective. Although the combination of potassium salts with 18-crown-6 can effectively induce epimerization, the results were unsatisfactory in terms of selectivity or reactivity. Moreover, rather tedious isolation/purification procedures were required owing to the complex composition of the crude product mixtures. We therefore explored the potential of using a fully soluble, strong, and non-nucleophilic organic base that does not require the presence of 18-crown-6. Initial experiments with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, $pK_b = 2.0$) showed that DBU effectively induces epimerization, affording a similar equilibrium molar ratio of IIDN/ISDN/IMDN = 4:5:1 after 26 h (entry 5). The DBU-induced epimerization reaction also exhibited good selectivity toward epimerized products, given the absence of the aforementioned discoloration as observed for the strong potassium bases. Although potassium acetate has a low activity compared to DBU, the high selectivity of potassium acetate (no discoloration of the reaction mixture and ISDN as the sole observed product) warrants further research, yet this falls outside of the scope of the present study.

Concerning the possible reactions of isohexide dinitriles in the presence of different bases, we speculated that either 1) base-induced epimerization resulting from deprotonation/reprotonation of the α -proton, and/or 2) nucleophilic attack on

the polarized nitrile groups to initiate an anionic polymerization could occur. The epimerization mechanism will be explained in detail in a later section. According to Wöhrle et al., strong, nucleophilic bases (e.g. NaOMe, *t*-BuOK or dimethylsodium) can initiate anionic polymerizations of dinitriles by nucleophilic attack on the polarized nitrile groups, giving an $R^1-C(R^2)=N^-$ anion.^[18b-e] Further propagation of the reaction leads to the formation of brown-to-black insoluble polymers. Moreover, intramolecular anionic polymerization is efficient especially for 1,4-dinitriles (e.g. succinonitrile and fumaronitrile). For dinitriles with longer chain lengths, such as adiponitrile, polymerization is much less efficient owing to a larger ring size and to lower stability of the formed cyclic anions.^[18a] As isohexide dinitriles are conformationally restricted adiponitrile analogues, Wöhrle-type polymerization is estimated to be only possible for the *endo-endo*-configured dinitrile, yielding a 7-membered ring. Given the low concentration of the IMDN isomer in solution, efficient intermolecular propagation is not very likely. The brown-to-black degradation mixtures observed in our systems when using strong inorganic bases are thus expected to be the products of intermolecular anionic polymerization. The utility of DBU as a non-nucleophilic base has been widely promoted owing to its sterically hindered ring structure.^[19] Given that discoloration was not observed for the DBU reactions, we conclude that DBU is essentially non-nucleophilic under our reaction conditions and hence the epimerization pathways are highly favored.

The pure dinitrile isomers (IIDN, ISDN, and IMDN) were separated by performing column chromatography (ethyl acetate/petroleum ether; 1:8 v/v) on the crude reaction mixtures obtained using DBU. On a scale of 5.0 g, each of the three isomers were obtained in excellent purity (>99.0%) and the combined total isolated yield exceeded 90%, confirming that this procedure is highly selective toward the targeted products. The molecular structures of the three isomers were fully characterized by NMR, FTIR, GC-MS and high resolution MS (see the Supporting Information).

NMR spectroscopy is a powerful technique for characterizing the molecular structures of isohexides, as the different isomers give rise to very distinct spectra. The 1H and ^{13}C NMR spectra of the three isohexidedinitrile isomers are presented in Figure 2. The stereo-configurations of the three isomers can be distinguished by several typical features. The bridgehead protons H3/4 appear as a singlet at around 5.0 ppm for the *exo-exo*-configured IIDN. This is mainly attributable to effects of symmetry and a dihedral angle of approximately 90° , thereby inducing negligible vicinal coupling between the adjacent protons H2-H3, as well as between the protons H4-H5, respectively.^[20] For the *endo-endo*-configured IMDN, the magnetically inequivalent signals of the bridge protons H3/4 are shifted upfield to a doublet centered around 4.85 ppm.^[20] In the case of structurally asymmetrical ISDN, the coupling constants differ between the bridge protons H3/4 and the neighboring protons H2/5, respectively. The bridge protons H3/4 appear as a quasi-doublet (H4) and a triplet (H3) at 4.96 and 4.91 ppm, respectively.^[20] The symmetry (or asymmetry) of the three isomers is also reflected in the respective ^{13}C NMR spectra. For

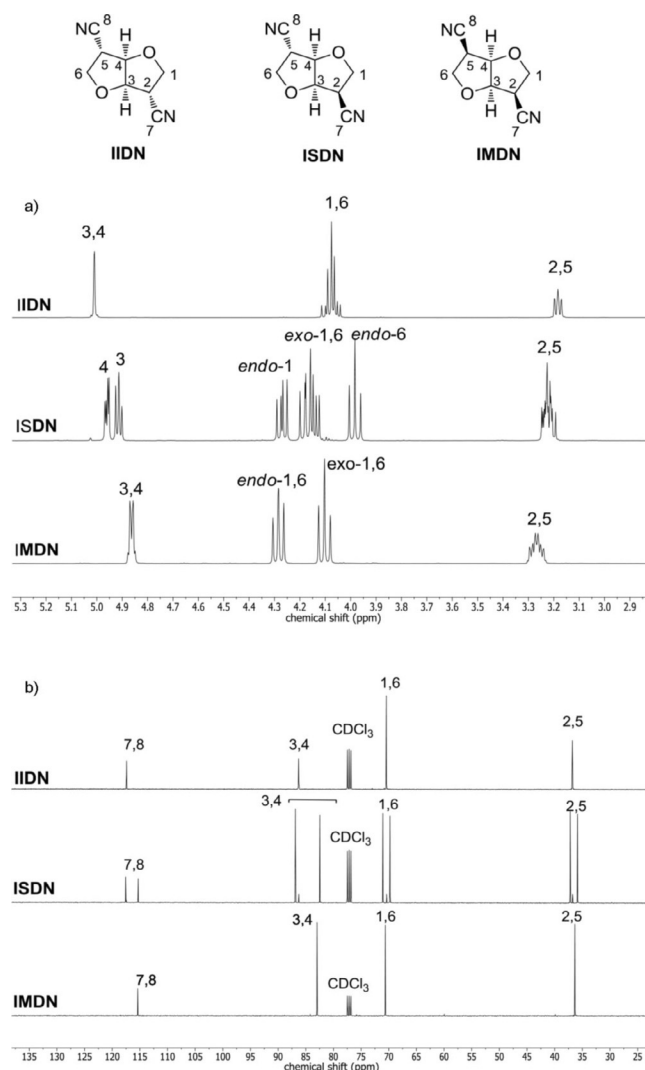


Figure 2. 1H NMR a) and ^{13}C NMR b) spectra of isohexide dinitriles recorded in $CDCl_3$ at room temperature; note that the ISDN sample contains a small amount of IIDN.

the asymmetrical ISDN, eight signals are found whereas only four signals are found for each of the symmetrical IIDN and IMDN compounds.^[20] The nitrile groups exhibit very distinctive signals at approximately 115 ppm. Overall, both the 1H and ^{13}C NMR spectra of the asymmetrical *exo-endo*-configured ISDN appear as a combination of signals comprising the symmetrical isomers on the NMR timescale. 2D COSY NMR spectra of the three isomers confirm the assignments based on the 1D spectra (see the Supporting Information).

Epimerization kinetics and mechanistic study

To improve the efficacy of the epimerization reaction as a synthetic tool, as well as to elucidate the epimerization mechanism, a kinetic study was performed. Epimerization reactions were carried out on all three purified isohexide dinitriles in THF solution at $50^\circ C$ in the presence of DBU. Samples were taken at specific time intervals and the ratio of isomers was analyzed by gas chromatography with a flame ionization detector (GC-

FID). To avoid thermally induced epimerization during the GC analysis, special care was taken to remove all DBU from the samples prior to GC analysis. This was accomplished by ethyl acetate/water extraction, followed by rapid filtration over silica gel. Figure 3 shows the mole fractions obtained of the three dinitrile isomers versus reaction time for the epimerization reactions. When starting from IIDN (Figure 3a), a dynamic equilibrium is reached in approximately 26 h. The final isomer molar ratio is IIDN/ISDN/IMDN = 35:50:15. The formation of ISDN is rapid within the first 10 h, whereas the amount of IMDN formed is almost negligible. When starting from pure ISDN, equilibrium is reached in 20 h, eventually giving the same isohexide ratio. In the case of IMDN, it is clear that the initial epimerization rates are significantly higher than those of IIDN and ISDN, as indicated by the steeper slopes of the kinetic curves and especially during the initial 5–7 h. Again, the same final equilibrium molar ratio is obtained. In each case the steady-state concentration of ISDN is around 50% within 25 h, whereas the fractions of IIDN and IMDN become stable in 48 h with final concentrations of approximately 35% and 15%, respectively. The trends in Figure 3 conclusively show that a dynamic epimerization equilibrium exists for all three isomers. The apparent preference for the *exo-endo* ISDN contrasts with the data reported for the catalytic epimerization of the parent isohexide diols. A molar ratio of isoidide/isosorbide/isomanide = 60:30:10 was observed for the catalytic epimerization of isohexides by means of dehydrogenation-rehydrogenation.^[14, 15] The isomer ratio was observed to be independent of the configuration of the starting material as well.

To understand this difference in selectivity, we performed density functional theory (DFT) calculations on the three isohexide isomers both in the form of neutral molecules and anions modelled in both the gas phase and in THF. As strong electron-withdrawing groups like nitriles increase the acidity of α -protons, we assume that the base abstracts a proton at C2 or C5 generating a carbanion (Scheme 4). Previous work by Paolucci and Rosini has shown that an unstabilized negative charge at C2/C5 results in ring-opening of the isohexide skeleton, forming a reactive 2,5-dihydrofuran species. This reaction has been shown to proceed at temperatures as low as -78°C .^[16d] Given that the DBU-catalyzed epimerization at 50°C described above did not promote any ring-opening side-reactions, charge stabilization/delocalization by the nitrile group appears to be very efficient.

All DFT calculations were performed using the Amsterdam Density Functional (ADF) program at the BP86/TZ2P level for geometry optimization and energies.^[21] This level of theory has been benchmarked and widely used in organic chemistry.^[22] Solvation in THF was simulated using the conductor-like screening model (COSMO).^[23] All stationary points were verified to be minima through vibrational analysis.

The relative energies between the molecules and anions are given in Table 1. The two *cis*-fused tetrahydrofuran rings of the three isohexide dinitriles have the possibility to pucker on C1 and C6. This can result in different conformations (up-up, up-down, down-up and down-down). The computations show that in the gas phase, the *exo-exo*-IIDN is the most stable

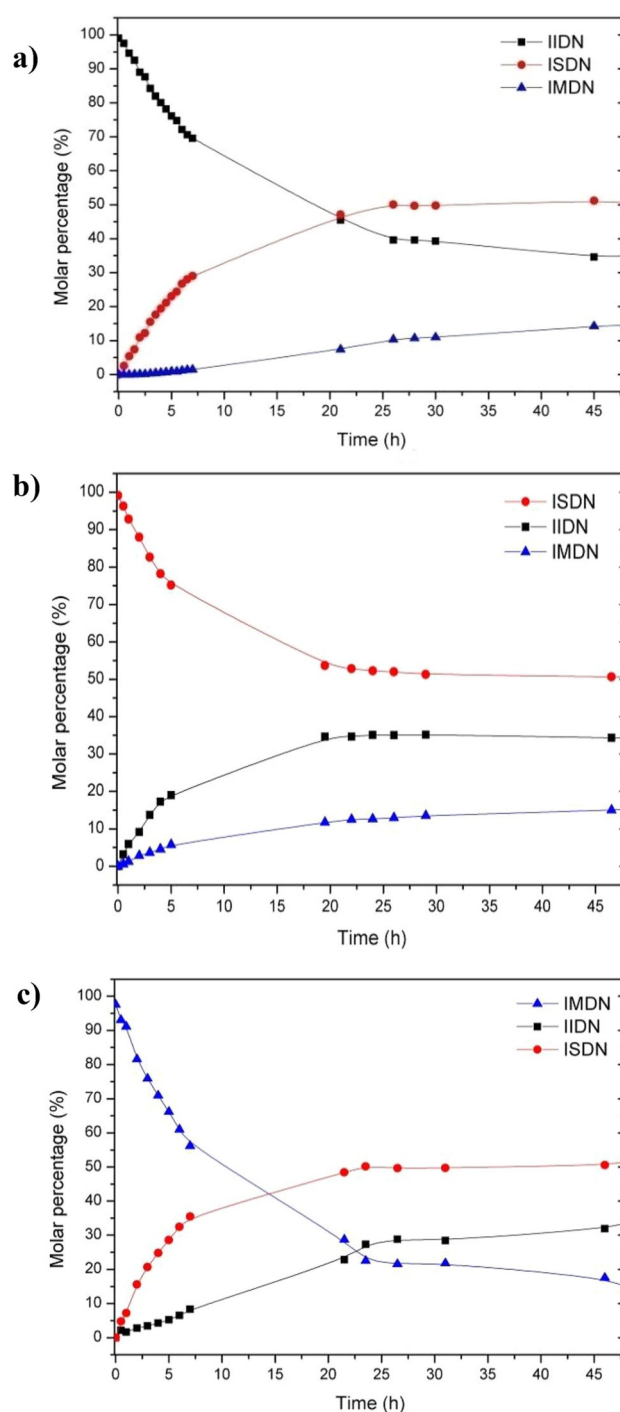
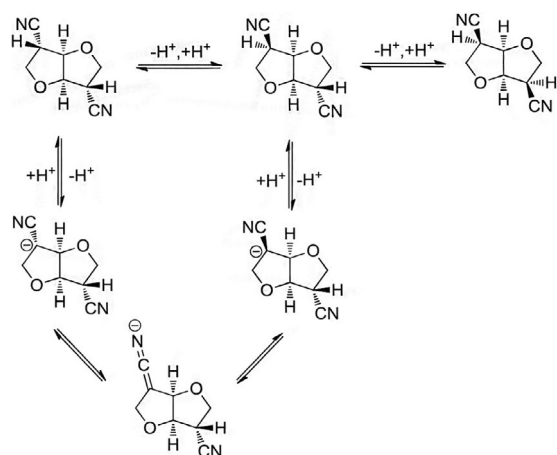


Figure 3. Epimerization kinetic curves of the molar percentage of isomers (%) versus reaction time (h): a) epimerization of IIDN; b) epimerization of ISDN; c) epimerization of IMDN. A typical epimerization experiment is performed in THF (25 mL), the presence of isohexide dinitriles (1.0 mmol), and DBU (0.5 mmol) at 50°C under a nitrogen atmosphere. Samples for GLC analysis were taken at intervals over a period of 48 h.

form, whereas in THF the energy difference among the three conformers is negligible. For the corresponding anions, the same trend is encountered. As indicated by the energy values in Table 1, the up-down conformations of IIDN and ISDN, as well as the up-up conformation of ISDN appear to be the most stable configurations with the lowest energy minima



Scheme 4. Deprotonation–reprotonation epimerization pathway of isohexide dinitriles through stabilization of the carbanion by the nitrile group.

(Figure 4). Notably, they are the same types of conformations as found in the crystal structures (see Figure 5, below).

Under basic conditions, deprotonation of the sp^3 -hybridized 2/5 carbon atoms of isohexide dinitrile is expected to initially give an sp^3 -hybridized α -nitrile carbanion with a tetrahedral conformation (Scheme 4). For epimerization to occur, conformational inversion of this carbanion is required to enable reprotonation from the opposite side. The dihedral angle formed by the planes C1–C2–C3 and C4–C2–C3 (see Figure S1, Supporting Information) serves as a measure for the degree of pyr-

amidalization of the carbanion. According to the DFT calculations, the (monoanionic) isohexide dinitrile carbanions have almost planar configurations in the gas phase with dihedral angles of nearly 180° , and slightly pyramidal configurations in THF solution with dihedral angles in the range of 150 – 160° (Table 2). In contrast, the corresponding dihedral angle of the fully pyramidal methylene anion is 110° (Table 2). The distances between the carbanion atom and the neighboring carbon atoms of the sp^2 -hybridized carbanion, with respect to the C1–C2 and C2–C3 bond lengths, were also shortened by up to 0.08 \AA (Figure 4). In THF, the calculated barrier for sp^3 – sp^2 rehybridization is virtually negligible at only $0.4 \text{ kcal mol}^{-1}$. Thus, rehybridization of the tetrahedral carbanion to a planar sp^2 hybrid is believed to be a feasible route.

It is known that substituents at a carbanion, particularly nitrile groups, stabilize a planar structure.^[25] In our case, the stabilization is accomplished by donation of charge from the isohexide dinitrile carbanion into the π^* orbitals of the neighboring cyano group. During this transformation, a dynamic equilibrium develops between the original nitrile group and imine anion (Scheme 4), resulting in elongation of the C–N bond by 0.03 \AA (Figure 4). The planar- sp^2 -hybridized carbanion allows H^+ to attack from both sides giving a mixture of these three structures as a result. In the case of catalytic epimerization of isosorbide under hydrogen pressure using a dehydrogenation–hydrogenation catalyst, an sp^2 -hybridized ketone intermediate was postulated.^[14–15] A preference for *exo*-substitution (75%) was favored, which resulted in an overall preference for isoi-

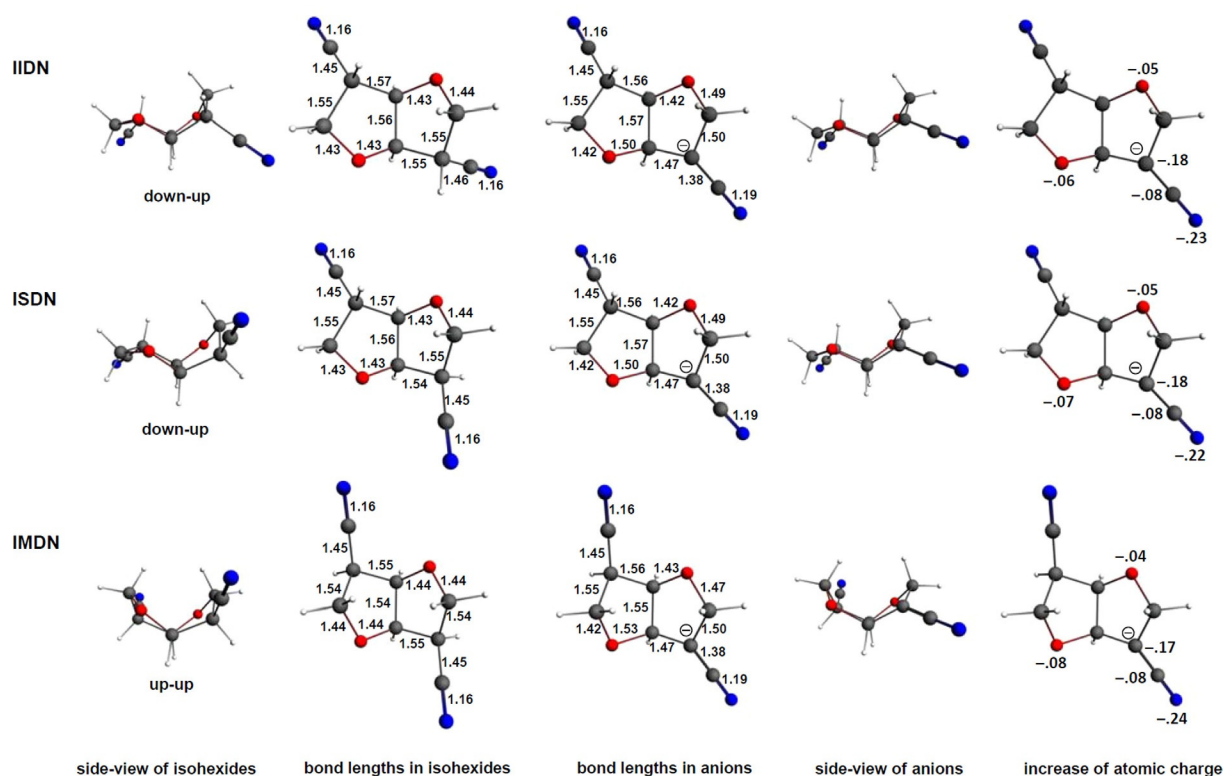


Figure 4. Bond lengths (\AA) for IIDN, ISDN and IMDN and anions thereof. Computations conducted at the BP86/TZ2P level of theory using COSMO to estimate the solvent effects by THF (top and side view are presented), and the increase in atomic Voronoi Deformation Density charges (VDD; only charge increments larger than 0.04 electrons are shown).^[24]

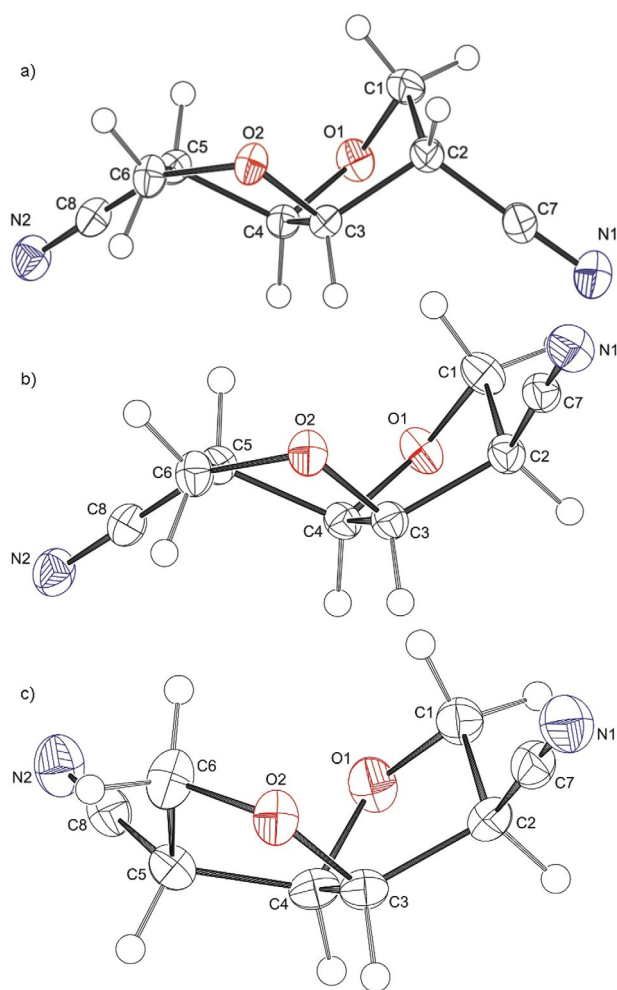


Figure 5. Molecular structures of three isohexide dinitrile isomers in the crystal; thermal ellipsoids set at 50% probability. a) Isoidide dinitrile (IIDN);^[3d] b) isosorbide dinitrile (ISDN); c) isomannide dinitrile (IMDN).

Table 2. Relative energies (in kcal mol⁻¹) and dihedral angles of three isohexide isomers in the forms of molecules and anions in the gas phase and THF solution.^[a]

Species	C1/C6 pucker ^[b]	Gas phase			THF solution		
		Molecule	Anion	Dihedral angle ^[c]	Molecule	Anion	Dihedral angle ^[c]
IIDN	D/U	0.0	0.0	171.4	0.0	0.0	150.1
	U/U	0.7	1.2	174.3	0.6	0.6	157.0
	D/D	0.4	0.0	171.4	1.2	0.0	150.2
ISDN	U/U	1.2	1.2	174.7	0.2	0.6	161.5
	D/U	0.5	0.0	171.5	-0.2	0.0	150.2
	U/D	1.4	1.2	174.3	0.8	0.7	157.3
IMDN	D/D	3.0	0.0	171.5	1.9	0.0	150.3
	U/U	1.8	1.2	177.3	-0.2	0.6	161.3
	D/U	2.5	1.2	177.1	0.5	0.6	160.9
	D/D	1.8	4.3	172.8	2.2	1.2	149.2
CH ₃ ⁻	-	-	-	110.0	-	-	-

[a] Computed at the BP86/TZ2P level of theory using COSMO to estimate the solvent effects by THF. Entries in bold face indicate the conformers with lowest energy minima. [b] Conformers with different puckering directions of C1 and C6. U=up; D=down. [c] Dihedral angle (°) between the planes defined by C1–C2–C3 and C4–C2–C3; see Figure S1 in the Supporting Information.

dide isomer formation (57%). In the case of the isohexide dinitriles, the observed isohexide ratio infers a 60% preference for *exo*-substitution and hence a preference for ISDN formation (50%). Given the large differences in reaction temperature between the isohexide epimerization and our reaction conditions (220–240 °C versus 50 °C, respectively), care should be taken in comparing the epimeric molar ratio values. Moreover, as shown in Figure 4, carbanion formation under basic conditions results in elongation of CO (ether) bonds, in particular the C3–O2 bond, by up to 0.09 Å. This is thought to be an effect of the lone-pair-charge donation from C2 or C5 into the neighboring σ^* orbital of the ether bonds (note the increase of atomic charges shown in Table S1 in the Supporting Information). Without the presence of electron-stabilizing groups such as nitrile on C2 or C5, an elongation of the C–O bond can result in a ring-opening side reaction, as reported by Paolucci and Rosini.^[16d]

X-ray crystal structures

The orientation of the functional groups in isohexides has a profound influence on both physical and chemical properties such as reactivity and thermal stability.^[1d,f,3d] When used as building blocks for step-growth polymer synthesis, factors such as rigidity, symmetry and linearity can have dramatic effects on molecular weight build-up, thermal properties, degree of crystallization, and crystallization rates of the polymers. We have recently reported a number of studies which focused on the structural characterization of the building blocks and the important structure–property relationships in the ensuing polymers. Studies on isohexide-based polyamides and polyesters showed that the glass transition temperature and crystallinity were influenced by the orientation and type of substituents at the 2- and 5-positions.^[3c,d,10a,12,26]

Our previous single crystal X-ray diffraction study and DFT calculations have shown that isoidide-2,5-dicarboxylic acid (IIDCA; Scheme 1) can adopt different conformations enabled by puckering of the five-membered rings.^[3d] Significant differences were observed for selected structural parameters, including the planarity of the rings, and the symmetry and linearity of the molecules among different conformers. DFT results showed that the free energies of these conformers are very similar and only differ by approximately 1 kcal mol⁻¹. The existence of three types of conformers suggests that the flexibility of the bicyclic skeleton is higher than expected. To expand our understanding of the structural properties of isohexide derivatives, we conducted an in-depth analysis of the three dinitrile isomers by X-ray crystal structure determinations and DFT calculations.

Single crystals of all three dinitriles were obtained by crystallization of high-purity isomers from ethyl acetate/*n*-hexane, and subsequently analyzed by single-crystal X-ray diffraction techniques (Figure 5). Analysis of the crystal structures shows that the tetrahydrofuran rings of each isomer are non-planar through ring puckering on C1 and C6 (Figure 5). C1 is puckered upward in all three isomers, whereas C6 points downward in IIDN and ISDN and upward in IMDN (Table 3). The corre-

sponding Cremer–Pople puckering parameters (Q , Φ)^[27] based on X-ray crystal structure data tabulated in Table 3 quantitatively describe the degree of puckering of each ring. It should be noted that the description on puckering up/down directions is only meaningful when the rings take on an envelope conformation. In ISDN, ring *b* is twisted, thus an up/down comparison is not applicable. In IMDN, both rings are in envelope conformation, but the pivot atoms (C2, C5) are different from IIDN (C1, C6). A simple up/down analysis is not warranted in this situation.

Analysis of the torsion angles defined by $\angle O1-C4-C3-C2$ and $\angle O2-C3-C4-C5$ (Table 3) shows that transitioning from IIDN ($0^\circ/5^\circ$, or virtually co-planar), via ISDN ($5^\circ/9^\circ$) to IMDN ($24^\circ/25^\circ$), the two 5-membered rings become severely twisted. Since the two *cis*-fused tetrahydrofuran rings are not planar, the interplanar angles, namely the V-shape-opening angles, cannot be determined precisely. Alternative methods could use alternative metrics of various planes through sets of three or four atoms, or in terms of selected torsion angles. According to the angle formed by the two least-square planes intersecting $O1-C4-C3-C2$ and $O2-C3-C4-C5$, the V-shape angles of

the three isomers are comparable with the previously described 120° opening of the isohexide skeleton.^[1d-f] Nevertheless, a significant difference of 50° between the two torsion angles $\angle O1-C4-C3-C2$ and $\angle C2-C3-C4-C5$ was observed for the highly deformed IMDN (Table 3). It is widely accepted that the bicyclic isohexide skeleton is a rigid moiety.^[1] However, based on the above observations, it is clear that this skeleton can deform to a large extent. A similar phenomenon has been observed in the case of isoidide-2,5-dicarboxylic acid (IIDCA).^[3d]

The degree of linearity and symmetry of the molecules is governed by the orientation of the nitrile groups. Interestingly, in all three isomers the nitrile groups adopt an equatorial conformation (Figure 5). The distances between carbon atoms on the two nitrile groups (defined as D , Table 3) are comparable (ca. 5.8 Å) for all three isomers. Therefore, the relative positions of C2 and C5 are mainly not affected by the different degrees of deformation of the bicyclic skeletons. The angle α , defined as the $\angle C8-C5-C2/\angle C7-C2-C5$ angle pair, is a measure for the (non)linearity of the nitrile groups. Since α angles of 180° are not encountered for any of the three isomers, all three dinitriles are non-linear. A further distinct feature is expressed by the angle β , defined as the $\angle C8-C5-C2-C7$ torsion angle. In the case of IIDN, both nitrile groups are located virtually in the same plane as evidenced by a β angle of almost 0° , while the angle increases progressing to ISDN (25°), and to IMDN (62°). These observations on β angles suggest that the two nitrile groups are virtually coplanar for IIDN and gradually separate to planes that are almost perpendicular for IMDN. The last parameter describing the relative positions of the two nitrile groups is defined as γ , which represents the projected angles between the two nitrile groups of the three isomers. Owing to a more “stretched” *exo-exo* structure, IIDN displays an apparently higher γ angle than for the other two isomers

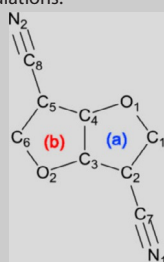
According to these X-ray diffraction data, the three dinitriles display varying degrees of deformation and all show a lack of symmetry. The energy barriers for conformational changes within the 5-membered-rings of the isomers differ by less than 2 kcal mol⁻¹ in THF and by less than 3 kcal mol⁻¹ in the gas phase (Table 2). This is supported by the room-temperature NMR spectra for IIDN and IMDN, where single symmetrical conformers are visible on the NMR timescale.

Based on the comprehensive structural comparisons above, the deformations and differences in all of the investigated structural parameters point to deviations from symmetry as well as to flexibility of the bicyclic ring structure. The apparent dynamic equilibrium between the isohexide ring conformers at room temperature shows that isohexides are more flexible than previously thought, given the significant differences in the angles between the substituents for the various ring conformations.

Conclusions

A novel, mild, base-catalyzed epimerization procedure was developed for isohexide dinitriles, giving access to all possible 1-C-extended isohexide derivatives. Although various bases are effective, the strong organic base DBU was most suitable:

Table 3. Structural characteristics and values of structural parameters of isohexide dinitrile isomers derived from single crystal X-ray structure determinations and DFT calculations.^[a]



Parameter	IIDN ^[10a]	ISDN	IMDN
C1/C6 PD ^[a]	U/D	–	–
2-CN/5-CN	eq./eq.	eq./eq.	eq./eq.
Q_a [Å]	0.3944(13)	0.4039(13)	0.3596(17)
Φ_a [°]	217.31(19)	224.75(19)	256.6(3)
Q_b [Å]	0.3659(12)	0.3940(13)	0.3558(17)
Φ_b [°]	30.0(2)	24.36(19)	259.3(3)
$Tors_{O1-C4-C3-C2}$ [°]	0.09(12)	–5.32(12)	–23.86(15)
$Tors_{O2-C3-C4-C5}$ [°]	–4.99(11)	–9.36(12)	–24.87(14)
A [°] ^[b]	62.83(8)	61.81(8)	63.86(11)
$Tors_{C2-C3-C4-C5}$ [°]	–119.40(9)	–125.08(10)	–141.22(12)
$Tors_{O1-C4-C3-O2}$ [°]	114.49(10)	110.40(11)	92.50(13)
D_{C7-C8} [Å] ^[c]	5.7287(18)	5.8869(19)	5.720(2)
α [°] ^[d]	151.14(8)/ 132.41(8)	149.46(9)/ 123.84(8)	127.88(10)/ 128.01(10)
β [°] ^[e]	–2.8(2)	–154.99(18)	117.92(19)
γ [°] ^[f]	76.43	30.45	47.99

[a] Abbreviations: PD=puckering direction; U=up; D=down; eq.=equatorial; Q =Cremer–Pople ring puckering amplitude of a or b ring; Φ =Cremer–Pople ring puckering phase angle of a or b ring. $Tors$ =torsion angle; [b] Dihedral angle between the two least-square planes defined by $O1-C4-C3-C2$ and $O2-C3-C4-C5$; [c] The distance between two nitrile groups, defined by the interatomic distance of C7–C8; [d] $\angle C8-C5-C2/\angle C7-C2-C5$; [e] Improper torsion angle $\angle C8-C5-C2-C7$; [f] Actual or projected angle between the C8–C5 bond and the C2–C7 bond.

combining high selectivity with high reactivity under mild conditions. A detailed structural analysis of all three possible dinitrile isomers by single-crystal X-ray diffraction and DFT calculations shows that several structural parameters, such as dihedral angles and torsion angles, can vary over a wide range. Hence, the supposedly rigid bicyclic isohexide skeleton is significantly more flexible than previously thought. Our convenient synthetic procedure gives access to a unique family of bio-based building blocks, and allows the substituent orientation effects in C2/C5-extended isohexides for polymer chemistry and polymer properties to be systematically investigated.

Experimental Section

Epimerization procedure

Isohexide dinitrile (250 mg, 1.52 mmol), a base, and anhydrous THF (25 mL) were placed into a two-necked round-bottom flask. An additional portion of 18-crown-6 (0.2 equiv with respect to isohexide dinitrile) is required in the case of a potassium base. After initiation of the reaction, a GLC sample was taken at a certain time interval to monitor the epimerization conversion. To prepare the GLC samples, 1 mL of the reaction mixture was taken from the flask. After partitioning in a mixture of an aqueous HCl solution (1.0 mL, 1.5 N) and chloroform (2 mL), the water layer was removed with a Pasteur pipette. The remaining organic layer was dried over MgSO_4 and filtered. The filtrate was injected into the GC-FID.

X-ray crystal structure determination

Reflections were measured on a Bruker Kappa Apex II diffractometer with sealed tube source and Triumph monochromator ($\lambda = 0.71073 \text{ \AA}$) at a temperature of 150(2) K. Intensity data were integrated with the SAINT software.^[28] Absorption corrections and scaling were performed based on multiple measured reflections with SADABS.^[29] The structures were solved by Direct Methods using the programs SHELXS-97.^[30] Least-squares refinement was performed with SHELXL-97^[30] against F^2 of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. Hydrogen atoms were located in difference Fourier maps and refined with a riding model. Geometry calculations and checking for higher symmetry were performed with the PLATON program.^[31]

CCDC 890377 (IMDN) and 890378 (ISDN) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

IMDN: $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$, Fw = 164.16, colorless plate, $0.64 \times 0.46 \times 0.08 \text{ mm}^3$, monoclinic, $P2_1$ (no. 4), $a = 5.6599(3)$, $b = 9.1663(5)$, $c = 7.8939(5) \text{ \AA}$, $\beta = 106.0095(16)^\circ$, $V = 393.65(4) \text{ \AA}^3$, $Z = 2$, $D_x = 1.385 \text{ g cm}^{-3}$, $\mu = 0.10 \text{ mm}^{-1}$. 7873 Reflections were measured up to a resolution of $(\sin \theta/\lambda)_{\text{max}} = 0.65 \text{ \AA}^{-1}$. Friedel pairs were merged. 956 Reflections were unique ($R_{\text{int}} = 0.018$), of which 936 were observed [$I > 2\sigma(I)$]. The absolute structure was assigned according to the synthesis. 109 parameters were refined with one restraint. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0304/ 0.0803. $R1/wR2$ [all refl.]: 0.0309/ 0.0809. $S = 1.055$. Residual electron density between -0.16 and 0.29 e \AA^{-3} .

ISDN: $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$, Fw = 164.16, colorless block, $0.70 \times 0.48 \times 0.44 \text{ mm}^3$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 6.7519(4)$, $b = 8.3266(5)$, $c = 13.4595(8) \text{ \AA}$, $V = 756.70(8) \text{ \AA}^3$, $Z = 4$, $D_x = 1.441 \text{ g cm}^{-3}$, $\mu = 0.11 \text{ mm}^{-1}$. 17965 Reflections were measured up to a resolution of $(\sin \theta/\lambda)_{\text{max}} = 0.65 \text{ \AA}^{-1}$. Friedel pairs were merged. 1024 Reflections were unique ($R_{\text{int}} = 0.019$), of which 1010 were observed [$I > 2\sigma(I)$].

The absolute structure was confirmed by a Hooft analysis^[32] prior to the merging of Friedel pairs. 109 parameters were refined with no restraints. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0263/ 0.0711. $R1/wR2$ [all refl.]: 0.0265/ 0.0714. $S = 1.095$. Residual electron density between -0.13 and 0.26 e \AA^{-3} .

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Conflict of interest

The authors declare no conflict of interest.

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