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Tetramerization of 3-Methyl-cyclopropene-3-carbonitrile: A Novel CN-Alder-ene Reaction

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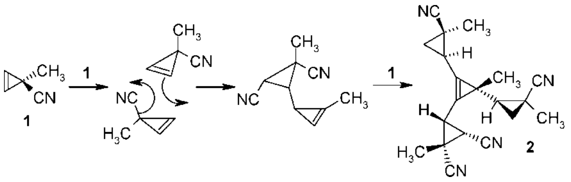
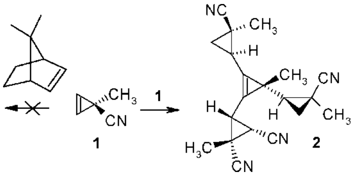


At elevated temperatures 3-methyl-cyclopropene-3-carbonitrile **1** was found to tetramerize giving compound **2** (3-methyl-2,3-bis(2-t-methyl-2-c-cyanocyclopropyl)-1-(2-t-methyl-2-c,3-c-dicyanocyclopropyl)-cyclopropene) in good yields. This is the first example of Alder-ene type oligomerization of a 3,3-disubstituted cyclopropene. On the basis of the product geometry and stereoselective character of the reaction, a mechanism of formation of **2** involving CN-Alder-ene reaction was proposed. DFT modeling of the mechanism has shown that the CN-Alder-ene reaction is possible as a stepwise process involving a biradical intermediate.

The 3-methyl-cyclopropene-3-carbonitrile (MCCN, **1**), while being a more thermally stable compound than other cyclopropenes, has a high reactivity due to its electron-acceptor character and presence of strained olephinic bond.[1] Earlier, we have demonstrated its reactivity toward cyclic and acyclic conjugated dienes, methylencyclohexane, allocymene, β-pinene, etc. in Diels−Alder and Alder-ene reactions.[2–4] These reactions were found to be highly stereoselective (always yielding products with syn-configuration with respect to the CN group of the MCCN acting as the eno-phile). However, when these reactions were conducted under elevated temperatures (120−140 °C), a new compound **2** was obtained along with the expected adducts as a minor product. When we attempted to conduct Alder-ene reaction of MCCN with more sterically strained polycyclic substrates like norbornene, nornobornadiene, and camphene under same conditions, the compound **2** was obtained as the main product. By heating a MCCN hydrocarbon solution in a sealed ampule to about 120 °C for several hours, one might convert **1** to **2** in up to 80% yields. According to the chromato-mass-spectroscopy measurements, the product **2** was an individual compound with molecular mass of 316. This, along with its ^{1}H NMR spectrum which consists of signals of four inequivalent methyl groups and eight signals of inequivalent cyclopropane hydrogens, as well as with IR spectrum having an intense band at 2243 cm^{-1} which corresponds to nitrile moiety, allowed us assuming that **2** is a MCCN tetramer.

SCHEME 1. MCCN Tetramerization



Molecular structure of **2** was determined by X-ray crystallography (it is presented on Figure S1 in the Supporting Information). The molecule consists of a tetra-substituted cyclopropene ring with methyl group and a methyl-cyclopropane-carbonitrile unit at the third carbon atom, with another methyl-cyclopropane-carbonitrile unit at second and a methyl-cyclopropane-dicarbonitrile unit at the first carbon atom, correspondingly. We note *Z*-orientation of both CN-groups of the latter dicyano-cyclopropane with respect to the central cyclopropene unit (Scheme 1).

Ability of the unsubstituted cyclopropenes to dimerization via Alder-ene reaction is long known.[5] Mechanisms of the dimerization of the unsubstituted cyclopropene, as well as its Alde-ene reactions with ethylene and propene have been modeled with both DFT and ab initio methods.[6,7] The cyclopropene system is a complicated object indeed. Depending on the organic substrate and the method employed, the Alder-ene reaction has been found to be either synchronous or stepwise

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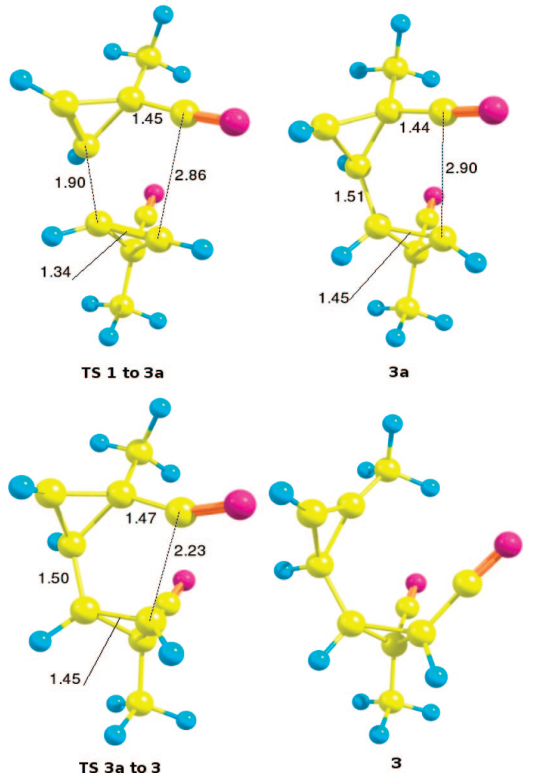
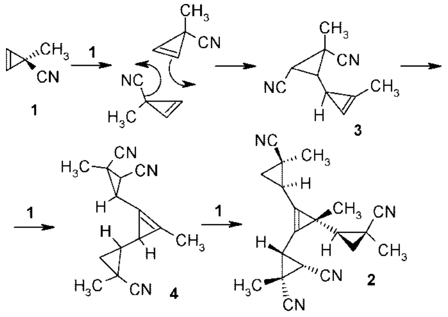


TS 1 to 3a 3a

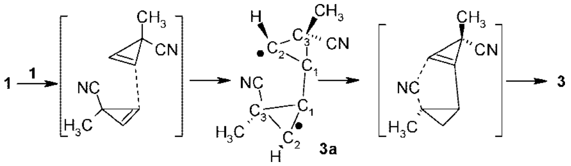
TS 3a to 3 3

FIGURE 1. Geometries of intermediate **3a**, dimer **3**, and transition states leading to them and as calculated by PBE0 method.

SCHEME 2. Proposed Mechanism for the MCCN Tetramerization



SCHEME 3. Mechanism for the CN-Alder-ene Dimerization Stage of MCCN Tetramerization, According to DFT Calculations[a]



[a] Square brackets denote transition states.

process involving formation of a singlet biradical quickly undergoing hydrogen shift. For the case of cyclopropene dimerization, both works report the stepwise path. [6,7]

Recently, cyclopropene oligomerization processes have attracted attention as a possible route of synthesis of compounds containing several cyclopropane rings.[8] Recent experimental works also demonstrated di-, tri-, and tetramerization of substituted cyclopropenes.[9–12] To our knowledge, in all cases reported, there was hydrogen at third cyclopropene carbon, thus allowing for Alder-ene reaction pathway. In the case of **1**, there is no such possibility. Obviously, formation of **2** has to involve a migration of a CN group from one cyclopropene unit to another, which is a rather rare process (although cases of intramolecular 1,4-CN-migration in a radical mechanism were documented (ref 13 and refs therein). The fact that the reaction is stereoselective, leading predominantly to single diastereomer of **2**, allows for assumption of an associative and of, to a certain degree, synchronous mechanism. That is, it excludes the possibility of dissociative mechanisms like abstraction of the carbonitrile anion prior to C$-$C bond formation between cyclopropene fragments, because such mechanism would lead to some random configuration of CN groups instead of the one shown at Figure 1. The absence of MCCN dimer and trimer in the products suggest that the first stage involving migration of the nitrile must be the rate-limiting step. The subsequent additions of third and fourth MCCN molecules take place quicker. Based on that, here we propose general scheme of the associative mechanism as shown on the Scheme 2.

We assume that the olygomerization process starts with some sort of "CN-Alder-ene reaction" involving migration of nitrile group instead of the hydrogen, yielding as a result dimer **3**. The dimer does have hydrogen attached to the C3 of its cyclopropene ring, thus allowing for subsequent addition of third (yielding trimer **4**) and then fourth MCCN molecules via regular Alder-ene mechanism. Because the final tetramer **2** does not have any hydrogens on its heavily substituted central cyclopropene ring, the reaction stops here.

To our knowledge such "CN-Alder-ene" reactions have not yet been studied. Thus to assess thermodynamic and kinetic possibility as well as selectivity of this reaction (that is, would it lead to any preference for the *syn*- orientation of CN groups?) in the present work we apply density functional theory, employing PBE and PBE0 density functionals.

Let us consider the first, "CN-Alder-ene" step. In our calculations we could not find a path corresponding to dissociative mechanisms − in which, for example, CN abstraction would take place prior to the addition of another MCCN. At the same time, we did not find a one-stage, synchronous path for the reaction. According to both DFT functionals, there is a reaction pathway for the "CN-Alder-ene" step which occurs as a stepwise process leading to the dimer **3** via a singlet biradical intermediate **3a**. The structure of the intermediate and transition states (TS) connected to it is presented in Figure 1. After its formation, **3a** undergoes intramolecular migration of the CN moiety, which closes back the cyclopropene ring and saturates the cyclopropane one, leading to the dimer **3** as shown in Scheme 3.

In the calculated intermediate structure, two C2 carbons (assuming that MCCNs are joined by C1 ones, see Scheme 3 for numeration) became, to some extent, pyramidal. Fuzzy atoms spin distribution in the intermediate[14] shows that the spin polarization is localized mostly on these C2 atoms, thus supporting its identification as a biradical. At PBE level of

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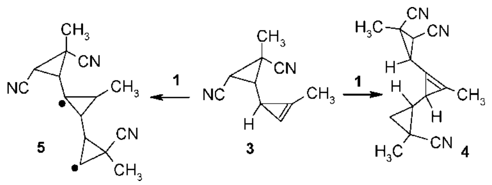
TABLE 1. Calculated Enthalpies and Gibbs Free Energies of Reactions (r) and Corresponding Activation Energies (a) for the Mechanism of MCCN Tetramerization, with Respect to Isolated Monomers of MCCN, kcal/mol

process	method	$\Delta H_{298}{}^{a}$	$\Delta G_{298}{}^{a}$	$\Delta H_{298}{}^{r}$	$\Delta G_{298}{}^{r}$
1 + **1** → **3a**	PBE	17.2	29.4	13.2	25.3
	PBE0	21.6	33.6	7.2	19.0
3a → **3**	PBE	−0.6	1.5	−58.3	−57.3
	PBE0	2.7	5.5	−55.2	−53.8
3 + **1** → **4**	PBE	9.8	23.0	−49.9	−36.2
	PBE0	13.6	26.2	−53.9	−40.8
3 + **1** → **5**	PBE	29.2	40.3	24.5	35.8
4 + **1** → **2**	PBE	13.5	27.0	−44.9	−30.9
1 + **1**+ **1** + **1** → **2**	PBE			−140.6	−100.5

SCHEME 4. Alternative Pathways for the Trimerization Step, Normal Alder-ene to 4 and Alternative Biradical 5 Formation, Then Possibly to CN-Alder-ene Yielding a Linear Polymer



SCHEME 5. Isomeric Approaches of MCCN Acting As Enophile for Alder-ene (R = H) and CN-Alder-ene (R = CN) Transition States

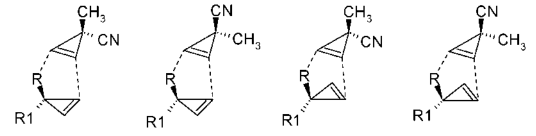


TABLE 2. Selectivity of CN-Alder-ene Dimerization and Alder-ene Trimerization Steps[a]

process	method	*exo*, *syn*	*exo*, *anti*	*endo*, *syn*	*endo*, *anti*
1 + **1**, first stage of the CN-Alder-ene reaction	PBE	0.0	2.1	3.1	5.9
	PBE0	0.0	2.1	3.2	5.5
3 + **1**, Alder-ene reaction	PBE	0.0	4.1	2.6	5.8

[a] Energy differences between isomeric transition states with respect to the most stable *exo*-, *syn*-TS configuration, kcal/mol.

theory, transition state (TS) leading to **3a** is not yet spin-polarized, whereas for the PBE0 functional it is already broken spin. Both methods yield spin-polarized solutions for **3a** and TS from it to **3**.

Enthalpies and free energies of calculated processes are shown in Table 1. The limiting step for the stepwise CN-Alder-ene dimerization is its first stage, namely, formation of the biradical **3a**. The second stage, nitrile moiety migration, has very small activation barrier with respect to the intermediate. Overall the CN-Alder-ene dimerization is strongly exoergic, thermodynamically favorable process. The stages of addition of the third and fourth MCCN molecule that proceed via normal Alder-ene way have lower activation barriers than the initial CN-Alder-ene dimerization. We have found a concerted mechanism for the former steps with both DFT functionals we use. Overall activation barriers as predicted by our calculations are small enough to make the process feasible under conditions of synthesis.

From Table 1 one can see that both pure GGA PBE and hybrid PBE0 yield quantitatively and qualitatively similar results. The former systematically predicts lower activation barriers for all reactions, which is a known deficiency of pure GGA. Otherwise results are very close. Thus, for calculation of the addition of fourth MCCN and for selectivity studies for the trimerization, we limit ourselves with PBE functional only. The Alder-ene addition of fourth MCCN monomer has about the same barrier and energy as the trimerization.

To have a complete characterization of the mechanism, we consider also an alternative CN-Alder-ene trimerization path where **3** acts as enophile and incoming MCCN as ene, forming biradical **5** (Scheme 4). PBE calculation shows that this way is very unfavorable as compared to path leading to **4** (Table 1).

For the ene reactions of MCCN acting as eno-phile, there are four possibilities for its orientation in TS with respect to the substrate, as shown on the Scheme 5: the TS can be either *endo*- or *exo*-, with CN group oriented *syn*- or *anti*- to the substrate. Earlier we have shown that for Alder-ene reactions of MCCN with regular enes, the *exo*-, *syn*- TS is the most stable[4] In this work, to assess the stereoselectivity of the tetramerization, we calculated all these four transition states for the biradical formation of the CN-Alder-ene dimerization and also for the subsequent Alder-ene trimerization. Results are in Table 2. For the trimerization, PBE predicted exactly same trend as reported by us in.[4] There is no reason to think that the next tetramerization step might be any different. As to the CN-Alder-ene dimerization, both PBE and PBE0 calculations yield the same preference for *exo*-, *syn*- configuration of the TS leading to the biradical that happens to be **3a**; the *exo*-, *anti*- pathway toward isomer of **3a** with *E*-configuration of cyclopropane's nitrile groups is less favorable. We note that, at least in our hands, only *exo*-biradicals would lead to subsequent nitrile migration leading to **3**:(*exo*-, *syn*-) or its isomer with *E*-configuration of CN groups (*exo*-, *anti*-). Geometry searches from *endo*-biradicals ended up in different ways of biradical closure (a tricyclohexane ring formation, for example).

Because the *exo*-, *syn*- path to the biradical is the most favorable, and makes the limiting step of the whole process, the resulting configuration of **2** is determined by it. The main tetrameric product **2** (Figure 1) has *Z*-configuration of nitrile groups attached to the diciano-cyclopropane ring; the configuration of **2** is in agreement with *exo*-, *syn*- preferences we got from DFT modeling. Thus, the proposed stepwise CN-Alder-ene reaction of MCCN, having *syn*- preferences, can explain experimentally observed structure of **2**.

We note that DFT is a single reference method having its well-known limitations. The broken-spin DFT approach we used in the present work has been applied for Alder-ene reactions with success.[6] For the proper description of fine details (that is, concerted vs stepwise mechanism), a more accurate multireference correlated methods might have to be used. But, be it synchronous or stepwise, selectivity of MCCN ene reactions should not change for it is determined by properties of this enophile.

In summary, we have found a new reaction − tetramerization of 3,3-disubstituted cyclopropene **1**. The reaction involves migration of nitrile group of one of one of MCCN's in Alder-ene like process. DFT calculations shown that there is a reaction channel corresponding to the proposed mechanism, and that the mechanism explains the observed reaction selectivity. Based on them, we conclude that the likely mechanism of initial stage of MCCN tetramerization might be a stepwise CN-Alder-ene reaction, which step is then followed by two steps of Alder-ene addition of MCCN.

Experimental Section

3-Methyl-cyclopropene-3-carbonitrile 1. 1 has been obtained using a standard procedure from ref 15.

3-Methyl-cyclopropene-3-carbonitrile tetramer 2. 2 has been obtained by heating of mixture of 0.158 g (2 mmol) of **1** and 1 g of decaline in a sealed ampule at 120−130 °C for 5 h. After removal of the hydrocarbon under reduced pressure the reaction mixture would crystallize. By recrystallization from acetone, colorless pine-like crystals of the compound **2** were obtained. (0.111 g, 70% yield, mp 145−146 °C). IR spectrum of **2** in liquid paraffin has an intense band at 2243 cm^{-1}. ^{1}H NMR spectrum of **2** (600 MHz, $CDCl_3$, 30 °C, chemical shifts (δ) are expressed in ppm downfield with respect to tetramethylsilane, coupling constants are in Hz): δ 2.89 (d, $J =$ 8.6, 1H); 2.44 (t, $J = 7.56$, 1H); 2.14 (d, $J = 8.6$, 1H); 1.76 (dd, $J = 7.32$, 8.10, 1H); 1.61 (s, 3H); 1.56 (d, $J = 7.32$, 1H); 1.54 (s, 3H); 1.52 (s, 3H); 1.45 (d, $J = 7.32$, 1H); 1.43 (s, 3H); 0.91 (dd, $J = 6.0$, 8.10, 1H); 0.77 (d, $J = 6.0$, 1H).

X-Ray Data for Compound 2. $C_{20}H_{20}N_4$, $M = 316.40$, orthorhombic, $a = 6.6748(5)$, $b = 16.397(4)$, $c = 16.741(6)$ Å, $V =$ 1832.3(8) Å,^{3} $T= 293(2)$ K, $Z = 4$, space group $P2_12_12_1$ (no. 19). Absolute configuration cannot be defined. Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre CCDC). These data can be obtained free of charge via the Internet at www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 622084.

Computational Methods. Density functional theory (DFT) calculations of reaction mechanism were performed using Priroda[16−18] program version 6. Generalized gradient approximation (GGA) exchange-correlation density functional by Perdew, Burke, and Ernzerhoff (PBE)[19] was used for most parts of the study. To assess quality of GGA results, a hybrid variant of this functional PBE0[20] containing 25% of exact Hartree−Fock exchange was used for for di- and trimerization stages of the mechanism as well. Gaussian basis set L11[21] ((6s, 2p)/[2s,1p] contracted for H, and (10s, 7p, 3d)/[4s,3p,1d] contracted for C and N atoms) along with corresponding optimized coulomb fitting basis was used in both PBE and PBE0 calculations. Unrestricted, spin-polarized SCF approach was used throughout this work.

Full, unconstrained geometry optimizations were performed in all the cases; on stationary points obtained with PBE, analytical Hessians were calculated. For the PBE0, Hessian calculations were performed numerically. All reactant and product geometries had zero, and all transition states had one negative Hessian eigenvalues. Calculated harmonic force constants were also used for thermochemistry calculations. To test the correspondence of all the found transition states (TS) to their reactants and products, intrinsic reaction coordinate calculations were performed. Fine numerical integration grids ($1*10^{-7}$) and optimization convergence criteria ($5*10^{-5}$) were used throughout the calculations.

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Supporting Information Available: A copy of ^{1}H NMR spectrum of the MCCN tetramer **2**; crystallographic information file for **2**, along with the corresponding X-ray figures and a table with detailed geometry data for **2**; the calculation data: exponents and contraction coefficients of the L11 orbital basis set; geometries and total energies of reactants, products, and transition states corresponding to the studied mechanism of MCCN tetramerization as calculated by DFT methods; calculated fuzzy atom charges and spin densities for dimerization transition states and the biradical intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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