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Azo dicarboxylates are not conjugated: X-ray crystal structure and theoretical calculations on di-*t*-butylazodicarboxylate

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ABSTRACT

The X-ray crystal structure of *trans*-di-*t*-butyl azodicarboxylate (DTBAD, **2**) was determined and this revealed that the torsion angle between the N═N and C═O double bonds is 84.0(2)°, and that between the *anti*-disposed C═O vectors is 180°. This is the first report of the solid state structure of an azodicarboxylate ester. The molecule was subjected to Density Functional Theory geometry optimization at the B3LYP/6-31G(d) level in cyclohexane medium, and the global minimum structure agreed in principle with that determined in the solid state by crystallography. The N–C(O) torsion angle in the optimized structure is 107.7°, and the C═O vectors lie in an *anti* relationship. Similar calculations on the unknown *cis*-N═N isomer revealed an optimum geometry whose energy is predicted to lie only 11.9 kJ/mol higher than that of the *trans* isomer. M062X/6-311+G(d) model chemistry was used to determine relative electronic energies and to conduct Natural Bond Orbital (NBO) calculations. Exploration of the energetics of rotations about the N–C(O) bonds revealed a clear preference for near-orthogonality in azodicarboxylates, and suggests almost complete absence of classical conjugation between the neighbouring π bonds. Electronic transitions were simulated using the time-dependent DFT (TD-DFT) approach at the B3LYP/6-311+G(d) level, and the weak band in the near-UV for **2** in cyclohexane was reproduced in the calculations. The electronic isolation of the N═N bond may be important in the numerous applications of azodicarboxylates in organic synthesis, and the small energy difference between the *trans* and *cis* isomers implies the likely involvement of the latter in the successful photochemical *diaza*-Diels–Alder reaction of diethyl azodicarboxylate with 1,3-cyclohexadiene.

1. Introduction

Dialkyl azodicarboxylates ($RO_2C–N═N–CO_2R$, Scheme 1) are very useful starting materials and reagents for organic synthesis [1]. The diethyl ester **1**, known by its acronym DEAD, is frequently used in the Mitsunobu reaction for ester synthesis [2,3]. Large-scale use of this reagent is sometimes avoided due to concerns about its possible detonation when heated undiluted [1,2]. This has led to supply of the reagent as a 40% solution in toluene, or to the use of more robust esters, including diisopropyl (DIAD, an oil), dibenzyl (melting point 43–47 °C), di(4-chlorobenzyl) (m.p. 108–112 °C) and di-*t*-butyl (DTBAD, m.p. 89–92 °C, **2** [4]). Another significant use of azodicarboxylates is as Michael-type acceptors in aminations or other nucleophilic additions [1,4]. Azodicarboxylates have also been used as azadienophiles in *diaza*-Diels–Alder (DADA) reactions [5], and often the carbamate esters in the products are selectively removed by basic hydrolysis (Et, *i*-Pr), hydrogenolysis (Bz), or acidic hydrolysis (*t*-Bu), followed by spontaneous decarboxylation of the carbamic acids. Recently, we have used the DADA reaction in attempts to prepare novel azoporphyrins [6]. The primary targets of this work were not achieved, but our investigations of the DADA reaction using both **1** and **2** led us to look more closely at the structures and reactivities of these azadienophiles.

Both **1** and **2** react cleanly with acyclic dienes, such as 2,3-dimethyl-1,3-butadiene, but the reactions with cyclic aliphatic dienes, especially 1,3-cyclohexadiene (CHD), are problematic (Scheme 2). We reviewed the literature on this topic in our recent paper [6]. The aza–Alder-ene reaction, which involves an allylic H-transfer with double bond rearrangement, occurs in competition with the DADA reaction, leading to variable proportions of the isomeric products **3** and **4** [7–14]. This reaction is useful for C–N

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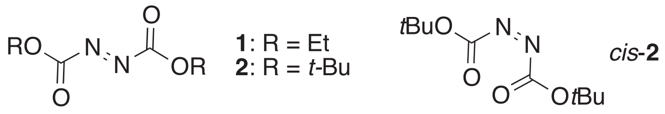


Scheme 1. Structures of diakylazodicarboxylates.

bond formation reactions involving azodicarboxylates and monoalkenes [1]. Early reports of high yields of the DADA products from 1,3-CHDs appear to have been erroneous, but in many other cases it is a very useful aza-dienophile [5,15–17]. The proportions of the two products vary depending on the experimental conditions, but in all cases, the aza-ene reaction dominates. The definitive paper on the DADA reaction of **1** with 1,3-CHD was published by Askani in 1965, who reported high yields of **3** (R = Et) when a dilute solution of the reactants was irradiated with a mercury lamp [18]. Askani ascribed the dominance of the DADA reaction under these conditions to the presence of a more reactive *cis* isomer in a photostationary mixture with the normal *trans* isomer. We found this method is clean and repeatable, although in our hands and using a high-pressure Hg lamp, the aza-ene product **4** is always present to the extent of about 20% [6]. In the case of the reaction of azodicarboxylates with anthracene (Scheme 2), for which the aza-ene reaction is impossible, the thermal DADA reaction of **1** to form the bicyclic product **5** is slow, requiring 30 h boiling in toluene to give a 52% yield [6]. However, we could not induce the corresponding reaction of anthracene with **2** at all, even at elevated temperatures for long periods. The much slower reactions of **2** compared to **1** were mentioned also in a recent study of microwave acceleration of DADA reactions [16,17].

During our work on the DADA reaction, we obtained high-quality single crystals of **2**. As there are no published crystal structures of dialkyl azodicarboxylates, we decided to examine its structure both experimentally (by X-ray crystallography) and theoretically (by Density Functional Theory, DFT). Our results reveal that this molecule is actually not “conjugated” in the usual sense of a carbon dienophile such as diethyl fumarate, and this fact may be relevant to the DADA chemistry of azodicarboxylates, and indeed to its other significant roles in organic synthesis.

2. X-ray analysis

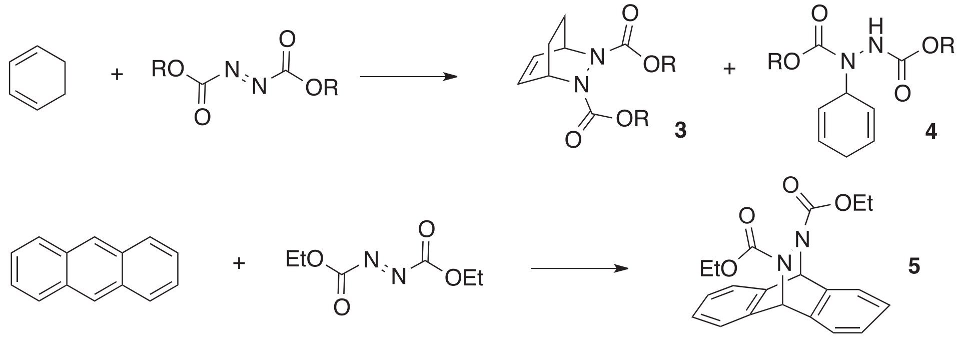
Single crystals of **2** suitable for X-ray structure determination were grown from a commercially available sample by simple evaporation of a solution of the compound in a 1:1 mixture of ethyl acetate and hexane in air. Single crystal X-ray diffraction data were collected for **2** at 173(2) K under the software control of CrysAlis CCD [19] on an Oxford Diffraction Gemini Ultra diffractometer using Mo–Kα radiation generated from a sealed tube. Data reduction was performed using CrysAlis RED [19]. Multiscan empirical absorption corrections were applied using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm, within CrysAlis RED [19] and subsequent computations were carried out using the WinGX-32 graphical user interface [20]. The structure was solved by direct methods using SIR97 [21] and refined with SHELXL-2014 [22]. Full occupancy non-hydrogen atoms were refined with anisotropic thermal parameters. C–H hydrogen atoms were included in idealized positions and a riding model was used for their refinement.

Crystal data and refinement details for **2**; $C_{10}H_{18}N_2O_4$, $M = 230.26$, monoclinic, $P2_1/c$, $a = 5.7905(8)$ Å, $b = 10.3980(7)$ Å, $c = 12.695(2)$ Å, $\beta = 122.11(2)°$, $V = 647.4(2)$ Å^3, $D_c = 1.181$ g cm^{-3}, $Z = 2$, crystal size 0.30 × 0.17 × 0.10 mm, pale yellow, temperature 173(2) K, λ(Mo-Kα) = 0.71073, T(Empirical)$_{\mathrm{min,max}}$ = 0.982, 1, $2\theta_{\max} = 54.72$, *hkl* range −7 to 7, −13 to 13, −15 to 17, $N = 4207$, $N_{\mathrm{ind}} = 1511$ ($R_{\mathrm{merge}} = 0.025$), $N_{\mathrm{obs}} = 1200$ ($I > 2\sigma(I)$), $N_{\mathrm{var}} = 73$, residuals $R1(F, 2\sigma) = 0.046$, $wR2(F^2, \mathrm{all}) = 0.129$, GoF(all) = 1.075, $\Delta\rho_{\mathrm{min,max}} = -0.198, 0.259$ e Å^{-3}. The refinement residuals are defined as $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$ and $wR2_{(\mathrm{all})} = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_c^2)^2]\}^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (0.06P)^2 + 0.12P]$, $P = (F_o^2 + 2F_c^2)/3$.

3. Computational methods

The Gaussian 09 [23] computational chemistry package was used for all theoretical calculations. Molecular geometries in cyclohexane were modelled using B3LYP functionals at the 6-31G(d) [24–27] level. To account for solvent effects, the integral equation formalism variant of the polarizable continuum model (IEFPCM) [28] was used with the default settings for cyclohexane in Gaussian. Vibrational frequencies calculations were used to confirm that structures had no imaginary frequencies in the case of local minima, or just one imaginary frequency for transition states. The calculated IR vibrational spectrum agreed well with the experimental one (Figure S1, Supplementary Material). M062X/6-311 + G(d) model chemistry was used to determine relative electronic energies and to conduct Natural Bond Orbital (NBO) calculations [29]. Electronic transitions were simulated using the time-dependent DFT (TD-DFT) approach [30] at the B3LYP/6-311 + G(d) level.

The atomic coordinates from the crystal structure of **2** and the related molecule *trans*-azodicarbonamide **6** [31–33] (Scheme 3) were convenient starting points for geometry calculations using DFT. As expected, convergence was rapidly achieved to structures which closely resembled their crystal structures, having either near-planar C_i symmetry (**6**) or approximate C_i symmetry (**2**) in the *trans* azo configuration. The latter structure is designated henceforth as “*trans*-**2**”. To locate a possible *cis*-**2** structure (Scheme 1)



Scheme 2. Diaza-Diels–Alder and aza-ene reactions of azodicarboxylates.