Concerted *vs.* Non-Concerted 1,3-Dipolar Cycloadditions of Azomethine Ylides to Electron-Deficient Dialkyl 2,3-Dicyanobut-2-enedioates

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Dedicated to Professor *Jacek Gawroński*, University of Poznań, on the occasion of his 70th birthday

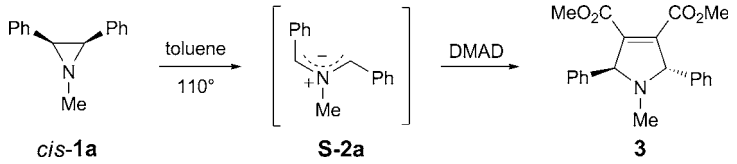
The quantum-chemical calculations of the thermal ring opening of 1-methyl-2,3-diphenyl- and 1,2,3-triphenylaziridine with formation of the corresponding azomethine ylides of S-, U-, and W-type as well as their cycloaddition to dimethyl acetylenedicarboxylate (DMAD) and dimethyl 2,3-dicyanobut-2-enedioate, were performed at the DFT B3LYP/6-31G(d) level of theory with the PCM solvation model. The calculations are in complete accordance with experimental results and explain the switch from the concerted to the non-concerted pathway depending on substituents in the dipolarophile and the ylide. It was found that strong electron-withdrawing substituents in dipolarophiles, such as in dialkyl dicyanobutenedioates, significantly reduce the barrier for the formation of zwitterionic intermediates in the reaction of azomethine ylides with such dipoles. This can render the stepwise cycloaddition competitive with the concerted one. However, the concertedness of the cycloaddition even to dipolarophiles with several electron-withdrawing substituents is governed by a fine balance of electronic and steric effects in both ylide and dipolarophile counterparts. The hypothesis that introduction of substituents in the azomethine ylide that destabilize the positive charge in a corresponding zwitterion will favor the concerted cycloaddition even with dialkyl dicyanobutenedioates was tested theoretically and experimentally.

Introduction. – The concertedness of 1,3-dipolar cycloaddition reactions is a feature of these processes with great importance for synthetic applications and for the theory of organic reactions [1]. The alternative stepwise mechanisms *via* a diradical or a zwitterionic intermediate were also postulated [2][3]. In the case of electron-rich 1,3-dipoles such as thiocarbonyl *S*-methanides, reactions with electron-deficient dipolarophiles bearing CF_3, CN, and CO_2R groups, respectively, were shown to proceed *via* zwitterionic intermediates [4a][4b]. The appearance of the latter was evidenced either by the formation of a mixture of stereoisomeric cycloadducts or by isolation of seven-membered cyclic ketene imines as the products of a competitive 1,7-dipolar electrocyclization. The concertedness of the formation of 1,2-oxazolidines from the reactions of electron-deficient alkenes with nitrones has been studied extensively using both experimental and computational tools [4c][4d]. Steric hindrance at a terminal position,

and a large energy gap between frontier orbitals of the dipolarophile and the 1,3-dipole are decisive for the switch from a concerted to a stepwise zwitterionic pathway [3][4].

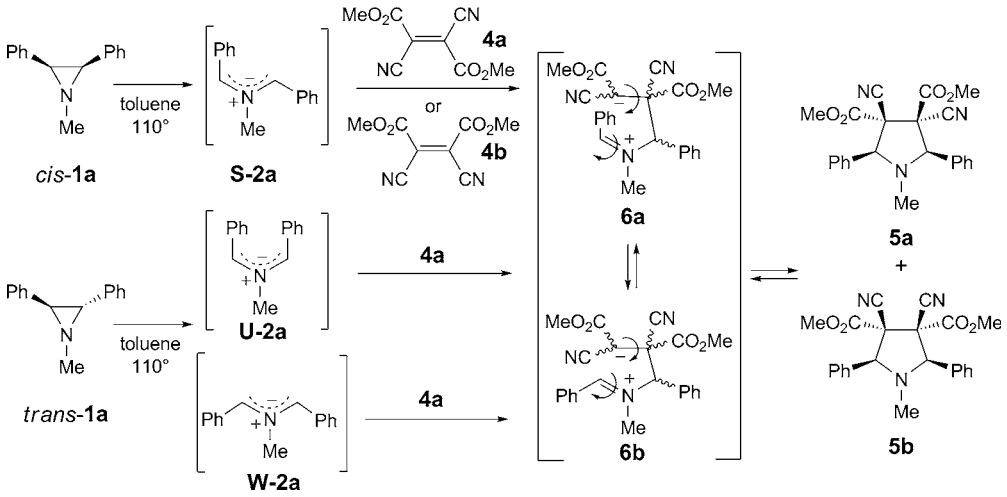
Azomethine ylides belong to the classical *N*-centered 1,3-dipoles, and the thermal conrotatory ring opening of 1-substituted aziridines is a superior method for their *in situ* generation [5]. Isomeric *cis*- and *trans*-1-benzyl-2,3-diphenylaziridines were reported to react with dimethyl fumarate (=dimethyl (*E*)-but-2-enedioate) and dimethyl maleate (=dimethyl (*Z*)-but-2-enedioate) stereoselectively to yield the corresponding diastereoisomeric products [6]. A similar observation was made for *cis*-1-methyl-2,3-diphenylaziridine (*cis*-**1a**) [7]. Analogous studies performed with C≡C, C=O, and C=S (thioketones) dipolarophiles showed that the formation of the corresponding five-membered cycloadducts occurs stereoselectively, *i.e.*, the intermediate azomethine ylides formed by conrotatory ring opening did not undergo isomerization in boiling toluene [8]. For example, the thermal reaction of *cis*-**1a** with dimethyl acetylenedicarboxylate (DMAD) in boiling toluene yielded dimethyl *trans*-2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (**3**) *via* a concerted [2+3]cycloaddition of the intermediate 'S-shaped' azomethine ylide **S-2a** in accordance with orbital symmetry-controlled reactions [9] (*Scheme 1*).

Scheme 1



On the other hand, the reactions of *cis*- and *trans*-**1a** with dimethyl 2,3-dicyanofumarate (**4a**), unexpectedly, led to a mixture of diastereoisomeric pyrrolidines **5a** (*trans-trans-cis*) and **5b** (*trans-cis-trans*), and the same result was obtained when dimethyl 2,3-dicyanomaleate (**4b**) was used as a dipolarophile [9] (*Scheme 2*). The

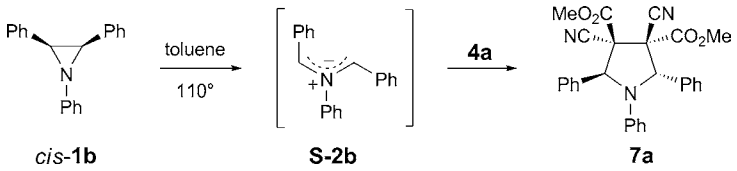
Scheme 2



formation of **5a** and **5b** was explained *via* a stepwise reaction mechanism, in which the intermediate zwitterions **6a** and **6b** are in equilibrium.

However, the reaction of *cis*-1,2,3-triphenylaziridine (*cis*-**1b**) with **4a** gave only one stereoisomeric pyrrolidine-3,4-dicarboxylate **7a**, with the configuration predicted on the basis of orbital-symmetry control, *i.e.*, *via* concerted-reaction steps [9] (*Scheme 3*).

Scheme 3



cis-**1b** **S-2b** **7a**

To verify the proposed reaction mechanism and to disclose the reasons for the difference in the reactivity of aziridines **1a** towards DMAD, and compounds **4a** and **4b**, respectively, as well as of *cis*-**1b** towards **4a**, the free energy profiles of the transformations of aziridines **1a** and *cis*-**1b** to the corresponding ylides, the isomerization of the ylides, the addition of the ylides to the dipolarophiles, and the formation and transformations of the corresponding zwitterions were computed at the DFT B3LYP/6-31G(d) level.

Results and Discussion. – According to these calculations, the barrier to conrotatory ring opening of aziridine *cis*-**1a** leading to the S-ylide **S-2a** is much higher than the barrier to conrotatory ring opening of aziridine *trans*-**1a** to W-ylide **W-2a** (*Fig. 1*). The transformation of *trans*-**1a** to the U-ylide **U-2a** requires the highest activation energy. The barrier to the interconversion of **S-2a** and **W-2a** is much higher than the barriers to ring opening of aziridines *cis*- and *trans*-**1a**, and, therefore, if there is a process, *e.g.*, cycloaddition, with a barrier lower than the barrier of the interconversion of the ylides, no isomerization of the ylides takes place. This also implies faster consumption of aziridine *trans*-**1a** compared to *cis*-**1a** in the reaction with dipolarophiles, in accordance with the result reported in [9].

Indeed, according to the calculations, the concerted cycloaddition of **S-2a** with DMAD proceeds *via* the barrier that is much lower than the barrier for the isomerization of **S-2a** to **W-2a** or **U-2a** (*Figs. 1* and *2*). Formation of the zwitterion **8a** is quite unfavorable compared with the concerted cycloaddition. All this should lead to the formation of pyrroline **3** as the sole product of the reaction of aziridine *cis*-**1a** with DMAD, in accordance with the reported experimental results [9].

Introduction of additional electron-withdrawing substituents, which would stabilize the negative charge of a zwitterion, renders the reaction path *via* zwitterion formation more favorable than the concerted cycloaddition. This might be the case with dicyanobutenedioates **4**. Indeed, according to the calculations, addition of S-ylide **S-2a** to **4a** leading to the zwitterion **6ba** proceeds *via* the transition state (TS) with a lower free energy than the TS energy of the isomerization of **S-2a** to **W-2a** (*Figs. 1* and *3*, and *Scheme 2*), and the TS energy of the concerted, albeit very non-synchronous,

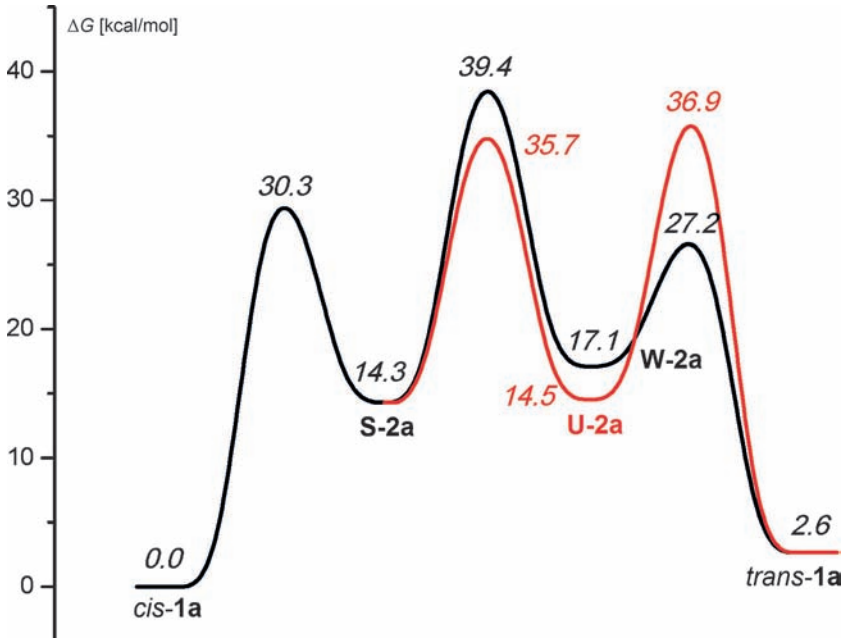


Fig. 1. *Energy profiles for transformations of 1-methyl-2,3-diphenylaziridines*, cis- *and* trans-**1a**, *and ylides* **S-2a**, **W-2a**, *and* **U-2a**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

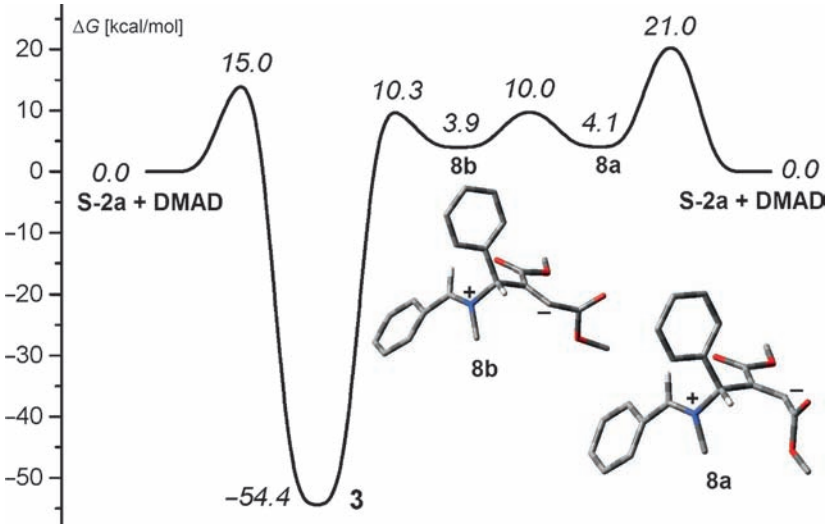


Fig. 2. *Energy profiles for the addition of S-ylide* **S-2a** *to DMAD.* Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level. H-Atoms on the Ph rings and the Me groups are omitted for clarity.

cycloaddition of **S-2a** to **4a** leading to pyrrolidine **5c**. Therefore, the concerted mode cannot compete with the zwitterionic pathway (*Fig. 3*).

The kinetically most favored route of transformation of zwitterion **6ba** leads to pyrrolidine **5d**, which is the least thermodynamically favorable product. The second kinetically favored transformation of **6ba** furnishes pyrrolidine **5a**, one of the isolated,

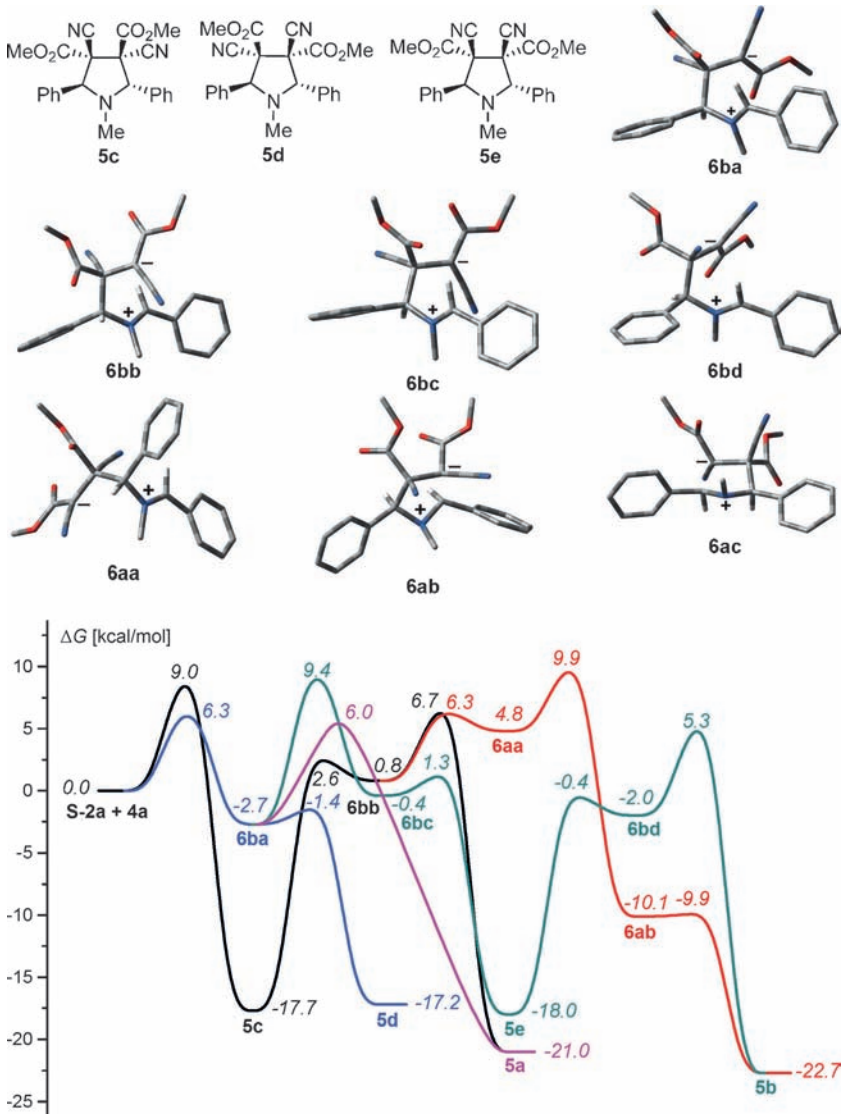


Fig. 3. *Energy profiles for the addition of S-ylide* **S-2a** *to dimethyl* (*E*)*-2,3-dicyanobut-2-enedioate* (**4a**)*, and for transformations of zwitterions* **6ba**–**6ab** *and pyrrolidines* **5a**–**5e**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level. H-Atoms on the Ph rings and the Me groups are omitted for clarity.

non-stereoselectively formed products of the reaction of aziridine *cis*-**1a** with **4a**. According to the calculations, the relative free energies of the pyrrolidines, which could be formed in the reaction, are 0.0 (**5d**), −0.5 (**5c**), −0.8 (**5e**), −3.8 (**5a**), and −5.5 kcal/mol (**5b**). This *Gibbs* energy distribution corresponds to the following product ratios at 298 K: **5b** (94.49%), **5a** (5.45%), **5e** (0.04%), **5c** (0.02%), and **5d** (0.01%), provided that the reaction proceeds under thermodynamic control. The correction for 383 K suggests a **5b**/**5a** ratio of 92:8. These data correspond to the finding that pyrrolidine **5a** isomerizes completely to **5b** under appropriate conditions [9]. The reaction of aziridine *cis*-**1a** with **4a** in boiling toluene gave pyrrolidines **5b** and **5a** in a ratio of 2:1 after 13 h [9]. This implies that the duration of the reaction was not long enough to reach the equilibrium distribution of the products, as the transformation of **5a** to **5b** by the least-energy route, *i.e.*, **5a** → **6ba** → **6bc** → **5e** → **6bd** → **5b**, has to proceed *via* TS(**6ba** → **6bc**), which is by 3.4 kcal/mol higher than the TS leading from **6ba** to **5a** (*Fig. 3*). An alternative route from **5a** to **5b**, **5a** → **6bb** → **6aa** → **6ab** → **5b**, proceeds *via* the TS(**6aa** → **6ab**), the energy of which is by 0.5 kcal/mol higher than that of TS(**6ba** → **6bc**).

According to the calculations, the addition of **W-2a**, generated thermally from aziridine *trans*-**1a**, to dicyanofumarate **4a** leads to the zwitterion **6ac** and further to pyrrolidine **5a**, and the barrier for this addition is lower than that for the addition of **S-2a** (*Fig. 4*). Again, pyrrolidine **5a** is the kinetic product, and it can be transformed to **5b** *via* a cascade of zwitterions, *i.e.*, **5a** → **6ba** → **6bc** → **5e** → **6bd** → **5b** or *via* **5a** → **6bb** → **6aa** → **6ab** → **5b**, as discussed above. The noteworthy difference is the shorter time of the reaction (4 instead of 13 h) due to a lower energy barrier. The decrease in the reaction time results in a **5b**/**5a** ratio of 1:1, because the system is farther from the equilibrium distribution of products.

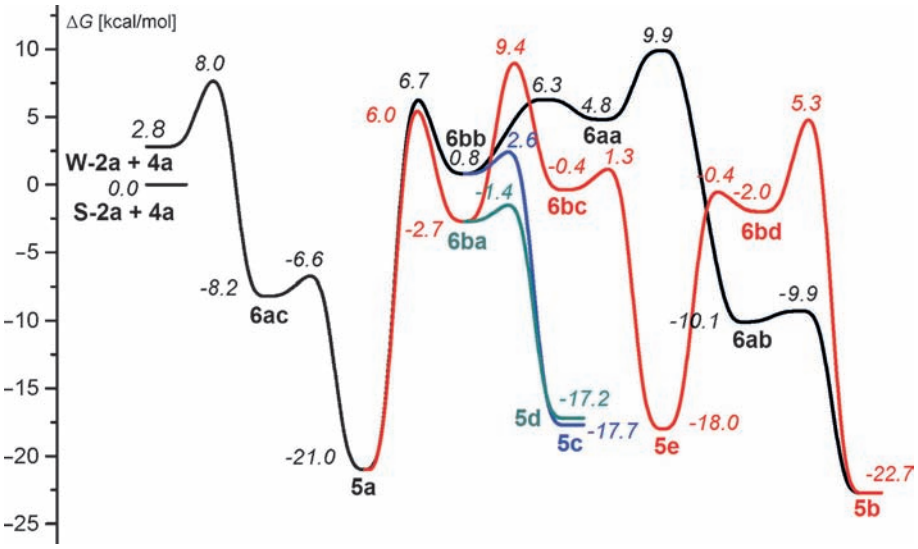


Fig. 4. *Energy profiles for the addition of W-ylide* **W-2a** *to dimethyl* (*E*)*-2,3-dicyanobut-2-enedioate* (**4a**)*, and for transformations of zwitterions* **6ba**–**6ab** *and pyrrolidines* **5a**–**5d**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

It was mentioned that the reaction of aziridine *cis*-**1a** with dimethyl 2,3-dicyanomaleate (**4b**) afforded the same products as the reaction with **4a** in comparable amounts [9]. According to the calculations, pyrrolidine **5e** should be the kinetic product, but in boiling toluene it could be transformed to the thermodynamically more stable pyrrolidines **5b** and **5a** (*Fig. 5*). However, the route **5e** → **6bd** → **5b** is kinetically much more favorable than the route **5e** → **6bc** → **6ba** → **5a**.

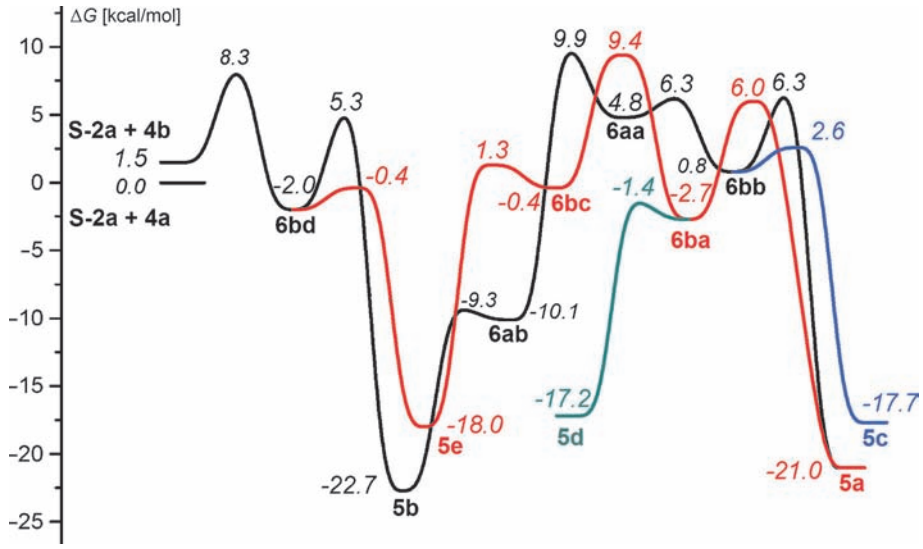


Fig. 5. *Energy profiles for the addition of S-ylide* **S-2a** *to dimethyl* (*Z*)*-2,3-dicyanobut-2-enedioate* (**4b**)*, and for the transformations of zwitterions* **6ba**–**6ab** *and pyrrolidines* **5a**–**5d**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

The replacement of the Me by the Ph group in aziridine *cis*-**1a**, unexpectedly resulted in the stereoselective formation of the cycloadduct **7** from aziridine *cis*-**1b** and dicyanofumarate **4a** [9]. According to the calculations, the replacement of the Me group in *cis*-**1a** and *trans*-**1a** by a Ph group lowers the barrier to ring opening of the aziridines, but raises the barriers for interconversion of the corresponding ylides (*Fig. 6*).

Therefore, the isomerization of S-ylide **S-2b**, derived from aziridine *cis*-**1b**, to the corresponding U- and W-ylides occurs too slow in boiling toluene. The replacement of the Me by the Ph group can influence the stability and formation of probable intermediate zwitterions. In fact, this change destabilizes corresponding zwitterions, because the Ph group cannot delocalize a positive charge of the zwitterion and adopt a planar conformation, as the molecules under discussion are very crowded. In other words, the Ph group in this case exhibits a $-I$ rather than a $+M$ effect. The calculations reveal that **S-2b** can react with **4a** concertedly *via* two non-synchronous TS (depending on *exo*/*endo* orientation of the dipole and the dipolarophile), leading to two possible pyrrolidines **7a** and **7b** (*Fig. 7*). The almost equal energy barriers for the concerted cycloadditions are quite low. The zwitterionic routes to the pyrrolidines are

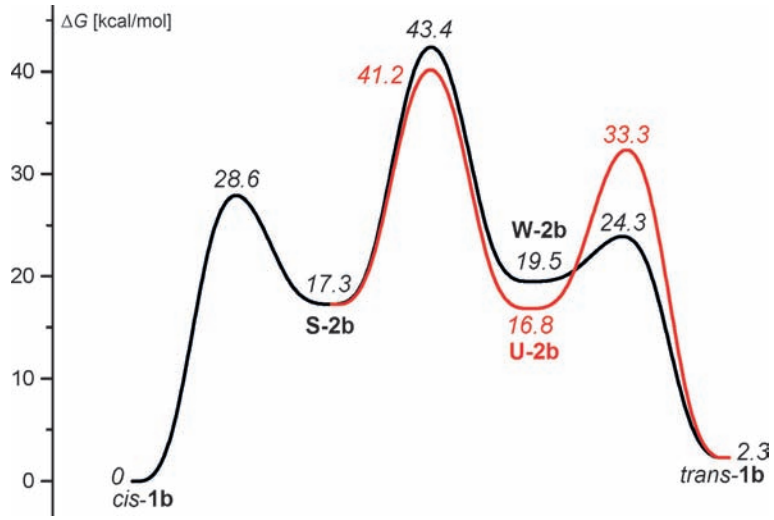


Fig. 6. *Energy profiles for transformations of 1,2,3-triphenylaziridines,* cis- *and* trans-**1b**, *and S-ylide* **S-2b**, *W-ylide* **W-2b**, *and U-ylide* **U-2b**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

less favorable (*i.e.*, *via* **9a** and **9b**). In principle, pyrrolidines **7a** and **7b** can rearrange into the isomers **7c** and **7d** *via* zwitterions **9c** and **9d**. However, only the transformation of **7b** into **7c** can be considered, as the free energy of the highest TS leading from **7b** to **7c** is much lower than the free energy of the TS for the formation of **7b**. Compound **7a** was isolated in 62% yield from the reaction of *cis*-**1b** and **4a** [9]. The isomeric compounds **7b** and **7c** that should be present in the reaction mixture in considerably smaller amounts probably escaped detection.

Another way to direct the reaction of azomethine ylides with dipolarophiles through a concerted mechanism consists in the introduction of electron-withdrawing substituents in the starting aziridine. This would destabilize the corresponding zwitterions by placing these substituents at the positively charged part of the intermediates. It was found earlier that 1-arylaziridine-2,3-dicarboxylates are good sources of azomethine ylides [10][11]. To verify the above hypothesis, we performed theoretical (*Scheme 4*) and experimental (*Scheme 5*) investigations of the reactions of diethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylates (**1c**) with dicyanofumarates **4a** and **4b**.

According to the calculations (*Fig. 8*), the barriers for the formation of W-ylide **W-2c** and U-ylide **U-2c** from aziridine *trans*-**1c** are very close (the free-energy difference is only 0.7 kcal/mol); therefore, one can expect formation of both ylides, with a little higher probability for the first one. But the reactivity of these ylides should be quite different. The ylide **W-2c** can easily undergo a concerted cycloaddition to dipolarophile **4a** with formation of pyrrolidine **10a**, and this is the only process that can be realized for **W-2c**, as the barrier of its transformation to ylide **S-2c** is very high. A concerted cycloaddition of U-ylide **U-2c** to **4a** cannot compete with the cycloaddition of **W-2c**, because the corresponding energy barrier is too high. The only way of further

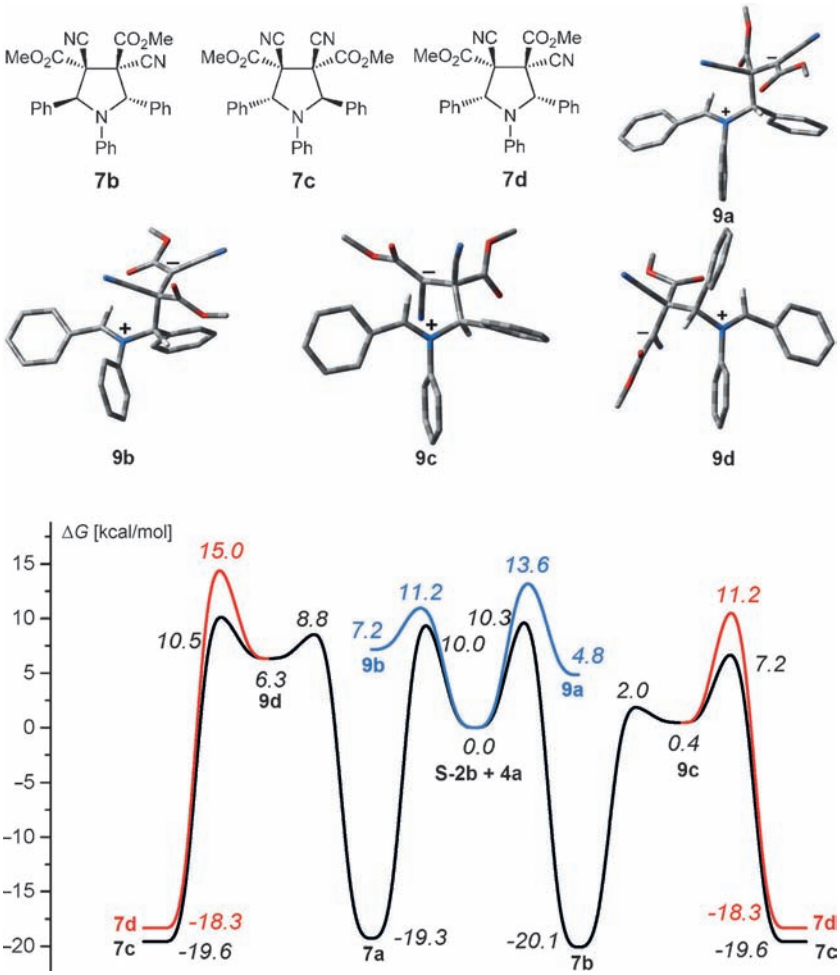
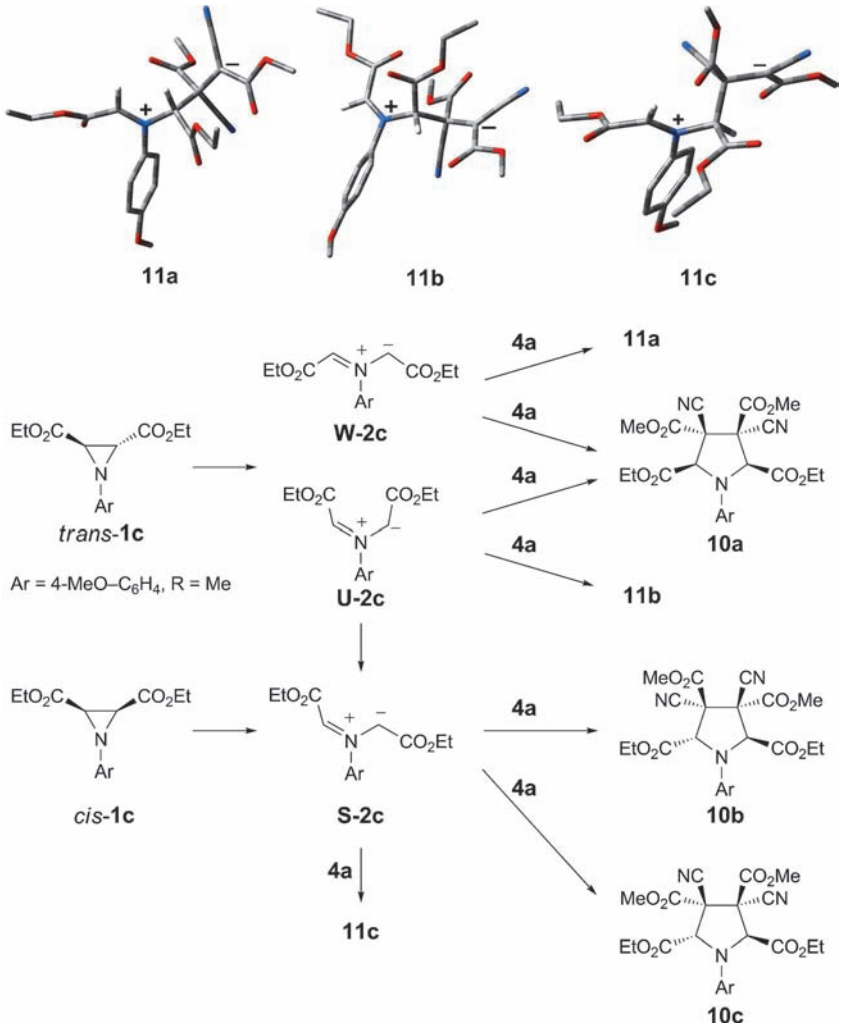


Fig. 7. *Energy profiles for the formation of pyrrolidines* **7a**–**7c** *from S-ylide* **S-2b** *and dimethyl* (*E*)*-2,3-dicyanobut-2-enedioate* (**4a**) *in the reaction of aziridine cis-***1b**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, toluene (pcm)) computed at the DFT B3LYP/6-31G(d) level. H-Atoms on the Ph rings and the Me groups are omitted for clarity.

transformation of **U-2c** is the isomerization to **S-2c**, but the free energy of the corresponding TS is higher than the free energy of the TS for the cyclization back to aziridine *trans*-**1c**. The ylide **S-2c** can undergo a concerted cycloaddition to dipolarophile **4a** to give pyrrolidines **10b** and **10c** (depending on the *exo*/*endo* orientation of the dipole and the dipolarophile), with predominant formation of pyrrolidine **10b**. One can also conclude from the results presented in *Fig. 8* that the formation of zwitterions **11a** and **11b** should not be observed. Thus, it follows from the calculations that pyrrolidine **10a** has to be the main product of the reaction of *trans*-**1c** with **4a**, pyrrolidine **10b** should be formed in much smaller quantity, and **10c** in even smaller amount.

Scheme 4



Furthermore, the calculations (*Fig. 9*) revealed that the conrotatory ring opening of aziridine *cis*-**1c** leads to S-ylide **S-2c**, which can easily undergo a concerted cycloaddition to **4a** with formation of pyrrolidine **10b**, while the concerted cycloaddition with another relative orientation of **S-2c** and **4a**, leading to the isomeric pyrrolidine **10c**, is less favorable (the difference in free energy of the corresponding TS is 1.6 kcal/mol). At the same time, the isomerization of **S-2c** to **U-2c** and especially to **W-2c** has to proceed *via* a TS of very high energy, and therefore, no formation of pyrrolidine **10a** should be observed (*Figs. 8* and *9*). One can conclude also from the results presented in *Fig. 9* that the formation of the zwitterion **11c** should be strongly disfavored. Thus, pyrrolidine **10b** has to be the main product of the reaction of *cis*-**1c** with **4a**, while pyrrolidine **10c** should be formed in smaller quantity.

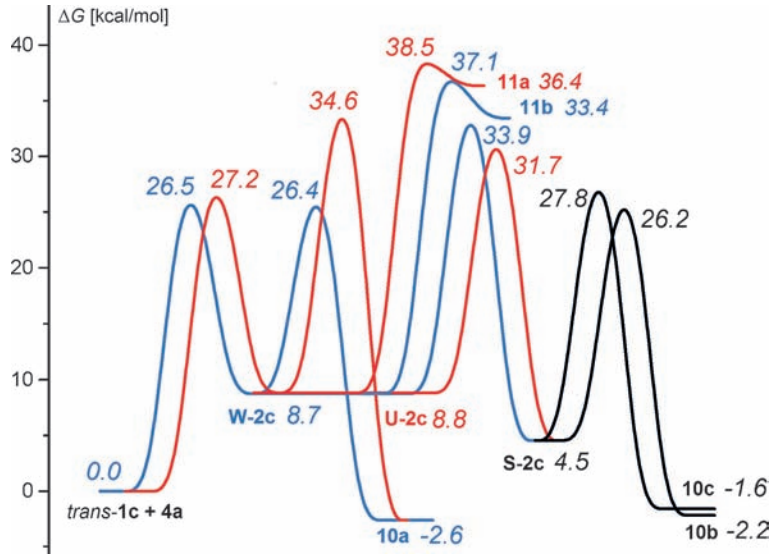


Fig. 8. *Energy profiles for the transformations of diethyl* trans*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate* (*trans*-**1c**)*, W-ylide* **W-2c**, *U-ylide* **U-2c**, *and S-ylide* **S-2c**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, chlorobenzene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

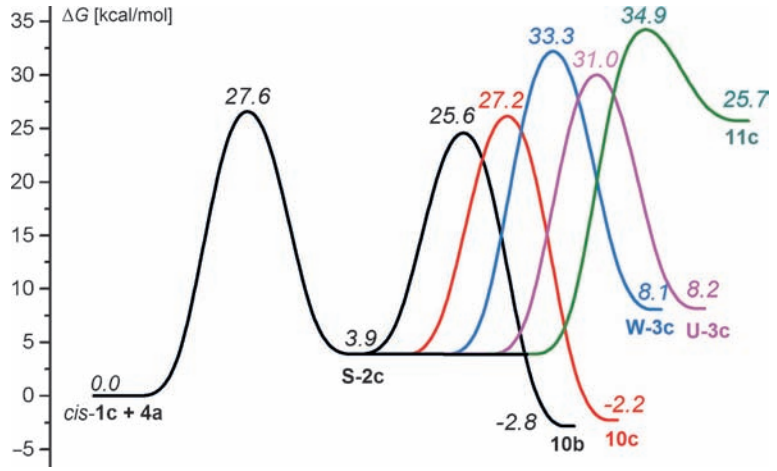
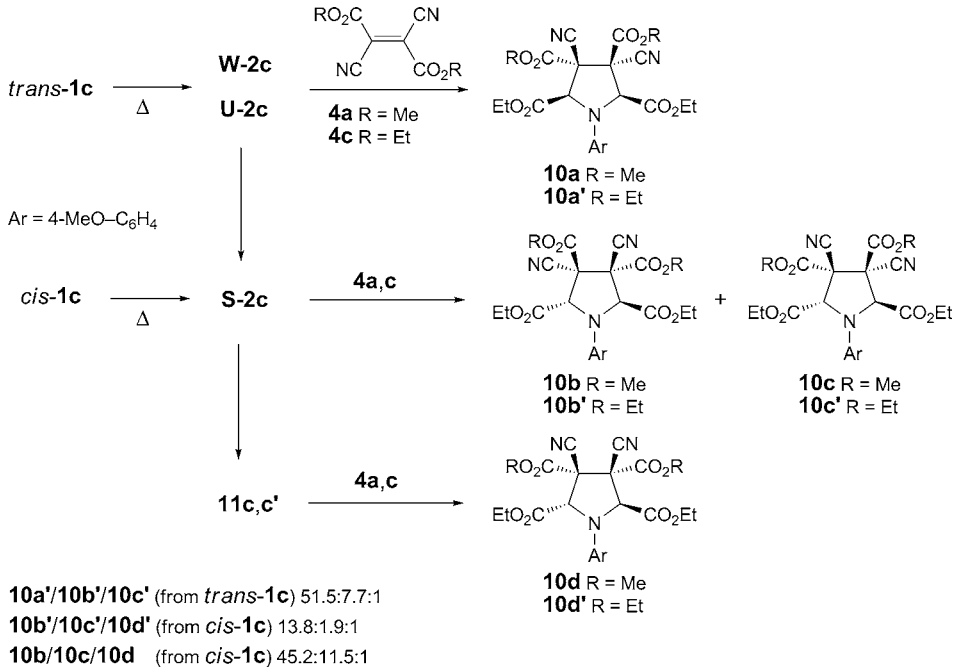


Fig. 9. *Energy profiles for the transformations of diethyl* cis*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate* (*cis*-**1c**)*, W-ylide* **W-2c**, *U-ylide* **U-2c**, *and S-ylide* **S-2c**. Relative free *Gibbs* energies (in kcal mol^{-1}, 298 K, chlorobenzene (pcm)) computed at the DFT B3LYP/6-31G(d) level.

For the experimental verification of the above conclusions, we synthesized aziridines **1c** and reacted them with dimethyl and diethyl 2,3-dicyanofumarates (**4a** and **4c**, resp.; *cf. Scheme 5*). Our first attempt to react *cis*-**1c** with **4a** resulted in the formation of three cycloadducts, according to the ^{1}H-NMR spectrum of the reaction

Scheme 5



mixture: two isomers of C_2 or C_s symmetry (signals of both pyrrolidine H-atoms appear as one *singlet* at 5.47 ppm for the major isomer and at 5.42 for the minor isomer) and trace amounts of an isomer of C_1 symmetry (two *singlet*s at 5.22 and 5.45 ppm). Unfortunately, the obtained mixture of isomers could not be separated by column chromatography as they underwent degradation on silica gel. Thus, the ^{1}H-NMR spectrum of one of the eluated fractions consisted mostly of signals, which were not detected in the spectrum of the reaction mixture. Fortunately, we succeeded to grow monocrystals of the major isomer, and analysis by X-ray crystallography showed that it is pyrrolidine **10b** (*Fig. 10*). Based on the symmetry of the compounds, the other two products can be considered as **10c** (C_2) and **10d** (C_1). Due to the mentioned difficulty of separation of the mixture of **10b**–**10d**, we turned our attention to the reactions of diethyl 2,3-dicyanofumarate (**4c**).

According to the ^{1}H-NMR spectrum of the reaction mixture, the reaction of aziridine *trans*-**1c** with **4c** yielded a mixture of cycloadducts **10a′** (*s* at 4.94 and 4.97 ppm), **10b′** (*s* at 5.46 ppm), and **10c′** (*s* at 5.39 ppm) in a ratio of 52:8:1 (*Scheme 5*). Adduct **10a′** results from the cycloaddition of ylide **U-2c** or **W-2c**, generated from *trans*-**1c**, with **4c**, while adducts **10b′** and **10c′** result from the cycloaddition of ylide **S-2c**, resulting from the isomerization of **U-2c** or **W-2c**, to **4c**. The configurations of adducts **10b′** and **10c′** were established by X-ray-analysis (*Fig. 10*). These data imply that, although isomerization of the initially formed U- and W-ylides occurs, there is no evidence for the presence of open-chain intermediates in this case.

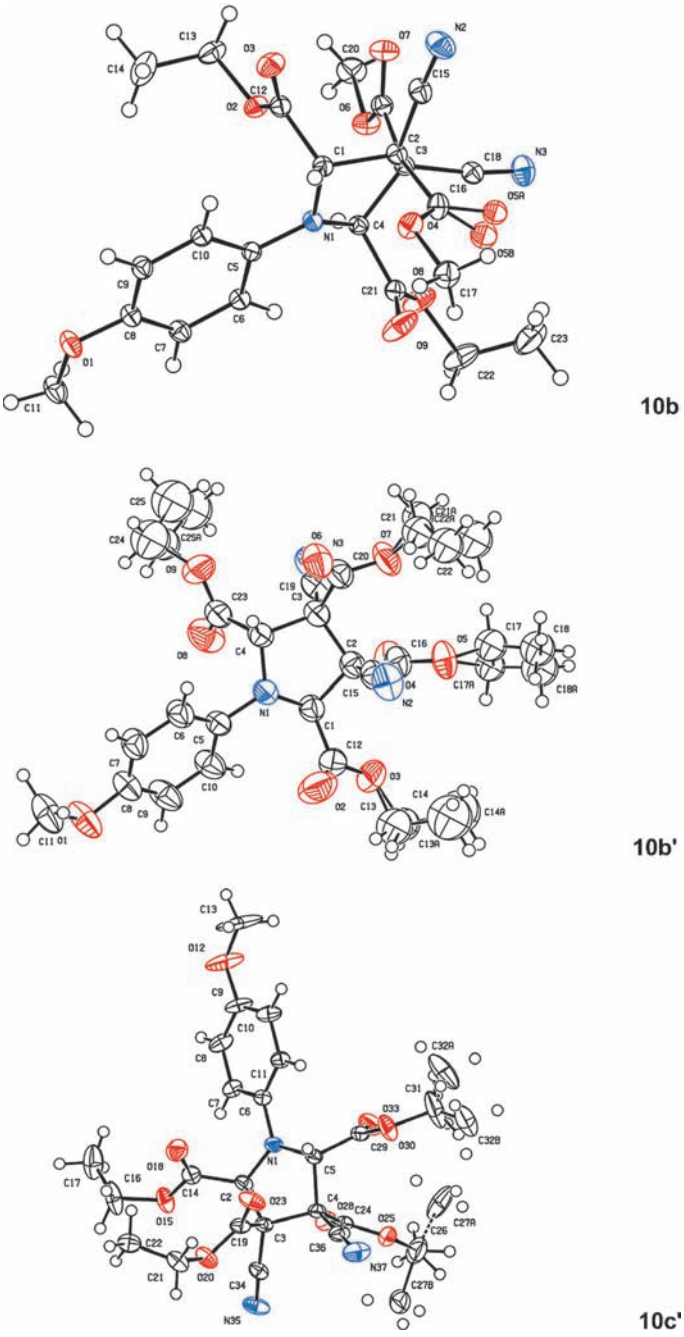


Fig. 10. *ORTEP Plots of the molecular structures of* **10b**, **10b′**, *and* **10c′** (arbitrary numbering of the atoms; 50% probability ellipsoids)

In full accordance with the calculations, no signal of compound **10a′** was observed in the ^{1}H-NMR spectrum of the mixture obtained from the reaction of aziridine *cis*-**1c** with **4c** under the same conditions. As expected, the reaction gave adducts **10b′** and **10c′**, with the configurations at C(3) and C(4) corresponding to a stereospecific reaction. Surprisingly, a small amount of cycloadduct **10d′** (*s* at 5.22 and 5.46 ppm) was also present in the reaction mixture, with a **10b′**/**10c′**/**10d′** ratio of 14 : 2 : 1. Compound **10d′** belongs to the symmetry group C_1, as it shows two *singlet*s for the pyrrolidine H-atoms. There are only two possible cycloadducts with this symmetry, *i.e.*, with 2,5-*cis*-3,4-*trans* or 2,5-*trans*-3,4-*cis* arrangement of the ester groups. All other configurations result either in C_2 or C_s symmetry. The configuration 2,5-*cis*-3,4-*trans* is realized in compound **10a′**. This inevitably means that **10d′** has the 2,5-*trans*-3,4-*cis* configuration, *i.e.*, this is the product of a non-stereospecific cycloaddition. Its formation implies that a route *via* the zwitterion **11c′** (*Scheme 5*) is marginally realized in this case.

It should also be noted that the ratio **10b′**/**10c′** is almost the same (*ca.* 7 : 1) from the reaction of both *cis*-**1c** and *trans*-**1c** with diethyl 2,3-dicyanofumarate (**4c**), revealing that it depends only on the rates of *exo*/*endo*-additions of S-ylide **S-2c** across the C=C bond of the dipolarophile. Expectedly, changing the EtO substituent in the dipolarophile to less bulky MeO group resulted in a decrease of diastereoselectivity in the reaction with *cis*-**1c**, yielding the corresponding cycloadducts **10b** (*s* at 5.46 ppm) and **10c** (*s* at 5.42 ppm) in a 4 : 1 ratio.

Conclusions. – The above quantum-chemical calculations at the DFT B3LYP/6-31G(d) level of theory confirm that strong electron-withdrawing substituents in dipolarophiles, like in dialkyl 2,3-dicyanobut-2-enedioates (dicyanofumarates and maleates), significantly reduce the barrier for the formation of zwitterionic intermediates in the reaction of azomethine ylides with the dipolarophile. This can make the non-concerted cycloaddition competitive with the concerted one. However, the ratio of concerted *vs.* unconcerted cycloaddition, even for dipolarophiles appropriate for non-concerted cycloaddition such as dialkyl dicyanobutenedioates, is governed by a fine balance of electronic and steric effects in both ylide and dipolarophile counterparts. Thus, introduction of substituents into the azomethine ylide that destabilize the positive charge in a corresponding zwitterion favor the concerted cycloaddition even with dialkyl dicyanobutenedioates.

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Experimental Part

1. *General*. Diethyl *trans*- and *cis*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylates **1c** were synthesized as described in [11c]. Dimethyl and diethyl 2,3-dicyanofumarate, **4a** and **4c**, were prepared from the corresponding alkyl cyanoacetates by treatment with HCl-free $SOCl_2$ as described in [12]. Commercial chlorobenzene was distilled prior to use. M.p.: Hot-stage microscope; uncorrected. IR spectra: *Bruker TENSOR 27* spectrometer, in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DPX 300* spectrometer;

at 300 and 75 MHz, resp., in $CDCl_3$ or (D_6)DMSO; δ in ppm rel. to Me_4Si as an internal standard, J in Hz. ESI-MS: *Bruker micrOTOF* mass spectrometer; in m/z.

2. *Calculations.* All calculations were carried out at the DFT B3LYP/6-31G(d) level [13] by using the Gaussian 09 suite of quantum-chemical programs [14] at 'Computer Center of Saint Petersburg State University'. Geometry optimizations of intermediates, transition states, reactants, and products in toluene or chlorobenzene were performed using polarizable continuum model (PCM). Intrinsic reaction coordinates were calculated to authenticate all transition states.

3. *NMR Determination of the Ratio of Cycloadducts in the Reactions of* cis- *or* trans-**1c** *with Diethyl 2,3-Dicyanofumarate* (**4c**). A mixture of aziridine **1c** (18 mg, 0.06 mmol) and dipolarophile **4c** (14 mg, 0.06 mmol) in PhCl (1 ml) was subjected to microwave irradiation (160 W, T_{max} 130°) for 45 min. The solvent was removed *in vacuo*, and the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H-NMR spectroscopy.

4. *Reaction of Aziridine* trans-**1c** *with* **4c**. A mixture of *trans*-**1c** (20 mg, 0.07 mmol) and **4c** (15 mg, 0.07 mmol) in PhCl (1 ml) was subjected to microwave irradiation (160 W, T_{max} 130°) for 45 min. Then, the solvent was removed *in vacuo*, and the residue was subjected to chromatographic separation (silica gel; AcOEt/petroleum ether (PE), from 1:6 to neat AcOEt), to give the cycloadduct **10a′** (26 mg, 74%) along with **10b′** (2.5 mg, 7%), and a mixture of cycloadducts, **10a′**/**10b′**/**10c′** (3 mg, 9%), which were not separated in this case.

*Tetraethyl (2*RS*,3*RS*,4*RS*,5*SR*)-3,4-Dicyano-1-(4-methoxyphenyl)pyrrolidine-2,3,4,5-tetracarboxylate* (**10a′**). Colorless crystals. M.p. 138–139° (acetone/H_2O). IR (KBr): 1766 (C=O), 1754 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.317 (*t*, *J* = 7.1, *Me*CH_2); 1.324 (*t*, *J* = 7.1, *Me*CH_2); 1.42 (*t*, *J* = 7.1, *Me*CH_2); 1.43 (*t*, *J* = 7.1, *Me*CH_2); 3.79 (*s*, MeO); 4.25–4.40 (*m*, 2 CH_2); 4.40–4.55 (*m*, 2 CH_2); 4.94 (*s*, 1 H, H–C(2/5)); 4.98 (*s*, 1 H, H–C(5/2)); 6.87 (pseudo *s*, 4 arom. H). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.16 (*t*, *J* = 7.0, *Me*CH_2); 1.18 (*t*, *J* = 6.4, *Me*CH_2); 1.22 (*t*, *J* = 6.8, *Me*CH_2); 1.29 (*t*, *J* = 7.1, *Me*CH_2); 3.70 (*s*, MeO); 4.15 (*q*, *J* = 7.1, 2 CH_2); 4.2–4.5 (*m*, 2 CH_2); 5.20 (*s*, 1 H, H–C(2/5)); 5.36 (*s*, 1 H, H–C(5/2)); 6.78 (*d*-like, *J* = 9.1, 2 arom. H); 6.84 (*d*-like, *J* = 9.1, 2 arom. H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 13.4, 13.5, 13.7, 13.9 (4 *Me*CH_2); 55.3 (MeO); 55.4, 56.6 (C(3,4)); 62.0, 62.1, 64.8, 65.1 (4 CH_2); 67.1, 68.1 (C(5,2)), 112.2, 114.1 (2 CN); 114.2, 115.5 (4 arom. CH); 139.7, 153.4 (2 arom. C); 161.8, 162.7, 166.4, 166.6 (4 C=O). HR-ESI-TOF-MS: 516.1982 ($[M+H]^+$, $C_{25}H_{30}N_3O_9^+$; calc. 516.1977).

5. *Reaction of* cis-**1c** *with* **4c**. A mixture of aziridine *cis*-**1c** (116 mg, 0.4 mmol) and **4b** (90 mg, 0.4 mmol) in PhCl (5 ml) was subjected to microwave irradiation (160 W, T_{max} 130°) for 45 min. The solvent was removed *in vacuo*, and the residue was subjected to chromatographic separation (silica gel, AcOEt/PE, from 1:6 to neat AcOEt) to furnish the cycloadduct **10b′** (147 mg, 72%), **10d′** (9 mg, 4%), and a mixture **10b′**/**10c′** (1:4.8; 18 mg, 9%).

*Tetraethyl (2*RS*,3*RS*,4*RS*,5*RS*)-3,4-Dicyano-1-(4-methoxyphenyl)pyrrolidine-2,3,4,5-tetracarboxylate* (**10b′**). Colorless crystals. M.p. 72–77° (hexane/AcOEt). IR (KBr): 1770 sh (C=O), 1757 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.1, 2 *Me*CH_2); 1.46 (*t*, *J* = 7.1, 2 *Me*CH_2); 3.77 (*s*, MeO); 4.10–4.30 (*m*, 2 CH_2); 4.40–4.60 (*m*, 2 CH_2); 5.46 (*s*, H–C(2,5)); 6.83 (pseudo-*s*, 4 arom. H). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.10 (*t*, *J* = 7.1, 2 *Me*CH_2); 1.33 (*t*, *J* = 7.1, 2 *Me*CH_2); 3.69 (*s*, MeO); 4.0–4.2 (*m*, 2 CH_2); 4.35–4.55 (*m*, 2 CH_2); 5.45 (*s*, H–C(2,5)); 6.83 (pseudo-*s*, 4 arom. H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 13.5, 13.6 (4 *Me*CH_2); 55.2 (MeO); 56.4 (C(3,4)); 62.1, 65.4 (4 CH_2); 67.2 (C(2,5)); 112.7 (2 CN); 114.1, 119.4 (4 arom. CH); 136.7, 154.4 (2 arom. C); 161.5, 166.3 (4 C=O). HR-ESI-TOF-MS: 516.1981 ($[M+H]^+$, $C_{25}H_{30}N_3O_9^+$; calc. 516.1977), 538.1799 ($[M+Na]^+$, $C_{25}H_{29}N_3NaO_9^+$; calc. 538.1796), 554.1548 ($[M+K]^+$, $C_{25}H_{29}KN_3O_9^+$; calc. 554.1535).

Crystals for X-ray crystallography were grown from hexane/AcOEt.

*Tetraethyl (2*RS*,3*SR*,4*SR*,5*RS*)-3,4-Dicyano-1-(4-methoxyphenyl)pyrrolidine-2,3,4,5-tetracarboxylate* (**10c′**). Colorless crystals. M.p. 86–92° (acetone/cyclohexane). IR (KBr): 1760 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.1, 2 *Me*CH_2); 1.42 (*t*, *J* = 7.1, 2 *Me*CH_2); 3.77 (*s*, MeO); 4.15 (*q*, *J* = 7.1, CH_2); 4.16 (*q*, *J* = 7.1, CH_2); 4.35–4.55 (*m*, 2 CH_2); 5.39 (*s*, H–C(2,5)); 6.75–6.85 (*m*, 4 arom. H). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.08 (*t*, *J* = 7.0, 2 *Me*CH_2); 1.30 (*t*, *J* = 7.3, 2 *Me*CH_2); 3.69 (*s*, MeO); 4.0–4.2 (*m*, 2 CH_2); 4.30–4.50 (*m*, 2 CH_2); 5.57 (*s*, H–C(2,5)); 6.80 (*d*-like, *J* = 9.1, 2 arom. H); 6.86 (*d*-like, *J* = 9.1, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.7, 13.8 (4 *Me*CH_2); 55.4 (MeO); 55.5 (C(3,4));

62.4, 65.1 (4 CH_2); 68.8 (C(2,5)); 113.8 (2 CN); 114.5, 119.6 (4 arom. CH); 136.4, 155.0 (2 arom. C); 162.0, 166.7 (4 C=O). HR-ESI-TOF-MS: 516.1972 ($[M+H]^+$, $C_{25}H_{30}N_3O_9^+$; calc. 516.1977).

Crystals for X-ray crystallography were grown from acetone/cyclohexane.

*Tetraethyl (2*RS*,3*SR*,4*RS*,5*RS*)-3,4-Dicyano-1-(4-methoxyphenyl)pyrrolidine-2,3,4,5-tetracarboxylate* (**10d′**). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.16 (*t*, *J* = 7.1, *Me*CH_2); 1.30 (*t*, *J* = 7.2, *Me*CH_2); 1.35 (*t*, *J* = 7.3, *Me*CH_2); 1.39 (*t*, *J* = 7.2, *Me*CH_2); 3.75 (*s*, MeO); 4.10–4.38 (*m*, 3 CH_2); 4.42 (*q*, *J* = 7.2, CH_2); 5.22 (*s*, 1 H, H–C(2/5)); 5.46 (*s*, 1 H, H–C(5/2)); 6.65–6.72 (*m*, 2 arom. H); 6.77–6.84 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.60, 13.64, 13.8, 14.0 (4 *Me*CH_2); 55.5 (MeO); 56.0, 56.4 (C(3,4)); 62.5, 62.6, 64.8, 65.0 (4 CH_2); 67.2, 68.1 (C(2,5)); 113.0, 113.3 (2 CN); 114.6, 118.6 (4 arom. CH); 136.5, 154.9 (2 arom. C); 161.8, 162.2, 166.3, 167.7 (4 C=O). HR-ESI-TOF-MS: 554.1529 ($[M+K]^+$, $C_{25}H_{29}KN_3O_9^+$; calc. 554.1535).

6. *Reaction of* cis-**1c** *with* **4a**. A mixture of *cis*-**1c** (61 mg, 0.21 mmol) and **4a** (42 mg, 0.22 mmol) in PhCl (5 ml) was subjected to microwave irradiation (160 W, T_{max} 130°) for 45 min. The solvent was removed *in vacuo*, and the residue was subjected to chromatographic separation (silica gel, AcOEt/PE 1:5) to afford a mixture **10b**/**10c** (86 mg, 85%) as a yellow oil, from which crystals of **10b** were grown (hexane/AcOEt).

*2,5-Diethyl 3,4-Dimethyl (2*RS*,3*RS*,4*RS*,5*RS*)-3,4-Dicyano-1-(4-methoxyphenyl)pyrrolidine-2,3,4,5-tetracarboxylate* (**10b**). Colorless crystals. M.p. 159–160° (hexane/AcOEt). IR (KBr): 1762 (C=O), 1755 (C=O), 1737 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21 (*t*, *J* = 7.1, 2 *Me*CH_2); 3.77 (*s*, MeO–Ar); 4.06 (*s*, 2 CO_2Me); 4.10–4.30 (*m*, 2 CH_2); 5.46 (*s*, H–C(2,5)); 6.83 (pseudo-*s*, 4 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.8 (2 *Me*CH_2); 55.1 (C(3), C(4)); 55.5 (2 CO_2*Me*); 56.8 (MeO–Ar); 62.6 (2 CH_2); 68.0 (C(2,5)); 112.6 (2 CN); 114.4, 120.2 (4 arom. CH); 136.4, 155.4 (2 arom. C); 162.3, 166.8 (4 C=O). HR-ESI-TOF-MS: 488.1660 ($[M+H]^+$, $C_{23}H_{26}N_3O_9^+$; calc. 488.1699), 510.1480 ($[M+Na]^+$, $C_{23}H_{25}N_3NaO_9^+$; calc. 510.1483), 526.1209 ($[M+K]^+$, $C_{23}H_{25}KN_3O_9^+$; calc. 526.1222).

Table. *Crystallographic Data and Parameters of Structure Refinement of Compounds* **10b**, **10b′**, *and* **10c′**

	10b	**10b′**	**10c′**
Empirical formula	$C_{23}H_{25}N_3O_9$	$C_{25}H_{29}N_3O_9$	$C_{25}H_{29}N_3O_9$
M_r	487.46	515.51	515.51
Temp. [K]	120	250	100
Crystal system	triclinic	monoclinic	orthorhombic
Space group	$P\bar{1}$	$C2/c$	$P2_12_12_1$
Unit cell parameters:			
a [Å]	8.5849(4)	26.2695(17)	9.4416(4)
b [Å]	11.8806(6)	10.4154(7)	9.8267(4)
c [Å]	13.2353(6)	21.4775(14)	28.4282(14)
α [°]	110.2740(10)	90	90
β [°]	107.4190(10)	112.707(2)	90
γ [°]	96.2660(10)	90	90
V [Å^3]	1173.54(10)	5420.9(6)	2637.5(2)
Z	2	8	4
ρ_{calc} [mg mm^{-3}]	1.379	1.263	1.298
μ(MoK_α) [mm^{-1}]	0.108	0.097	0.100
F(000)	512.0	2176.0	1088
Reflections collected	19476	29337	22277
Independent reflections/R_{int}	6231/0.0207	6235/0.0592	6021/0.0336
Data/restraints/parameters	6231/1/415	6235/56/370	6021/0/362
Goodness-of-fit on F^2	1.051	1.079	1.106
Final R_1/wR_2 indexes [$I > 2\sigma(I)$]	0.0443/0.1198	0.072/0.2120	0.0576/0.1163
Final R_1/wR_2 indexes [all data]	0.0522/0.1271	0.1218/0.2484	0.0679/0.1208
Largest diff. peak/hole [e Å^{-3}]	0.72; −0.43	0.68; −0.54	0.27; −0.26

7. *X-Ray Crystal-Structure Determination of* **10b**, **10b′**, *and* **10c′** (*Table* and *Fig. 10*)[1]). The X-ray single-crystal data were collected on a *Bruker SMART CCD 6000* (for **10b** and **10b′**) and *EOS XCalibur* (for **10c′**) diffractometers (graphite monochromator, MoK_α, λ 0.71073 Å) equipped with a *Cryostream* (*Oxford Cryosystems*) open-flow nitrogen cryostate at 250(2) (for **10b′**), 120(2) (for **10b**), and 100(2) K (for **10c′**). The crystals of **10b′** undergo a phase transition at 156–157 K. This phase transitions results in tripling of *b*-axis and, unfortunately, also in significant deterioration of the crystal quality. It was the reason for unusual choice of the temp. of data collection. All structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using Olex2 [15] and SHELXTL [16] software. All non-disordered non-H-atoms were refined anisotropically, the H-atoms of structures **10b** and **10b′** were refined isotropically, the H-atoms of disordered groups of **10b′** and **10c′** were placed in the calculated positions and refined in the riding mode. Disordered atoms in structure **10b′** were refined isotropically with fixed SOF of 0.5. Crystal data and parameters of refinement are compiled in the *Table*.

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[1]) CCDC 968848–968850 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, *via* www.ccdc.cam.ac.uk/data_request/cif.

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