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Photochemical syn–anti isomerization reactions in N^4-methoxycytosines A matrix isolation study

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Abstract

Photochemical syn–anti isomerizations were studied for N^4-methoxycytosine and 1-methyl-N^4-methoxycytosine isolated in argon or nitrogen low-temperature matrices. Upon UV ($\lambda > 295$ nm) irradiation photoconversion of the syn isomers into the corresponding anti forms was observed. This demonstrates that, although the syn–anti photoisomerization concerns rotation of a large methoxyl group, steric interactions with the matrix cage do not preclude it. The final stage of the reaction was a photostationary state. Subsequent UV ($\lambda > 335$ nm) irradiation led to photoisomerization in the opposite direction, resulting in partial recovery of the syn isomers of the investigated N^4-methoxycytosines.
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Keywords: Methoxycytosine; Syn; Anti; Imino; Photoisomerization; Photochemistry; Matrix isolation; Infrared spectra; Density functional theory

1. Introduction

N^4-methoxycytosine (mo^{4}C) is a product of the cytosine reaction with a known mutagen methoxylamine [1–3]. In the gas phase, in solutions and in the crystalline state this compound adopts practically exclusively the oxo–imino tautomeric form [4–7] with the methoxyl fragment in the syn orientation relative to the ring nitrogen N(3). For a complex of free bases: 1-methyl-N^4-methoxycytosine (1Me–mo^{4}C) and 9-methyladenine an inverted Watson–Crick, planar structure has been identified using ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy [8,9]. 1-Methyl-N^4-methoxycytosine (1Me–mo^{4}C) adopts in this complex the imino–oxo tautomeric form with the syn orientation of the methoxyl group relative to the N(3) atom of the pyrimidine ring.

Studies of artificial oligonucleotide duplexes demonstrated that mo^{4}C can base-pair with adenine as well as with guanine, i.e. behaves as uracil or cytosine, respectively. ^{1}H NMR investigations [10–12] on the heptanucleotide d(CAG(mo^{4}C)GGC) pairing with d(GTCACCG) and on duplex formation of the self complementary octanucleotide d(CGAAT(mo^{4}C)CG) dissolved in D_2O revealed that mo^{4}C forms a Watson–Crick base-pair with adenine [13]. In this base-pair mo^{4}C adopts the imino tautomeric form with the methoxyl group in anti orientation (Scheme 1A). Similar studies [10–12] on d(CAG(mo^{4}C)GGC) pairing with d(GTCGCCG) and on duplex formation of d(CGGAT(mo^{4}C)CG) resulted in the conclusion [14] that two types of base-pairing between mo^{4}C and guanine occur. One of the mo^{4}C–G pairs adopts a wobble geometry (with mo^{4}C in the syn imino form, see Scheme 1B) and the other is of canonical Watson–Crick structure (with mo^{4}C in the amino tautomeric form, see Scheme 1C). Slow conversion of one type of the mo^{4}C–G pair into the other was observed in the ^{1}H NMR time-scale.

Base-pairing of mo^{4}C was also studied by X-ray crystallographic methods. Structures of crystalline oligonucleotide duplexes have been determined for: d(CGCAAATT(mo^{4}C)-GCG) dodecamer [15], d(CGCGAATT(mo^{4}C)GCG) dodecamer [16,17] and d(CGCG(mo^{4}C)G) hexamer [18]. These studies revealed that a normal Watson–Crick pairing occurs when the base opposing to mo^{4}C is adenine. Such duplex crystallizes in a regular B shape helix and mo^{4}C appears in it as the oxo–imino tautomer with the anti orientation of the methoxyl group. In duplexes, where the base opposing to mo^{4}C is guanine, two types of base-pairing are possible. Guanine and mo^{4}C can form a normal Watson–Crick

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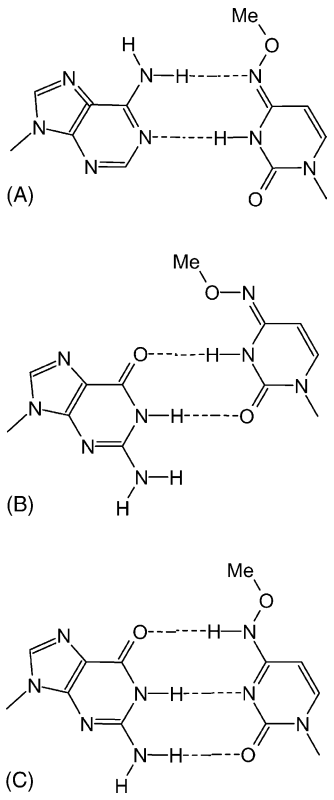


Scheme 1. Syn–anti photoisomerization in mo^{4}C and 1Me–mo^{4}C.

base-pair, which is possible only for mo^{4}C in the amino–oxo tautomer with anti orientation of the methoxyl group. Another, experimentally observed mo^{4}C–G base-pair was formed in a wobble geometry with the mo^{4}C residue in the syn conformation of the imino tautomer.

The studies quoted above demonstrated that mo^{4}C exhibits a dual face base-pairing behavior and that mo^{4}C pairing with adenine or guanine is related with the particular tautomeric form adopted by the modified base as well as with the syn or anti orientation of its methoxyl group.

Recently, tautomerism, infrared spectra and H-bonding properties of mo^{4}C were studied using the matrix isolation technique combined with DFT and MP2 theoretical calculations [5]. On the other hand, syn–anti photochemical reactions in 1-methyl-N^4-hydroxycytosine [19] and N^4-hydroxycytosine [20] were observed and investigated for matrix isolated monomers of the compounds. In this regard, it was interesting if syn–anti photoisomerization could occur also for N^4-methoxy derivatives of cytosine, although it would involve rotation of a much larger methoxyl group. A priori it was impossible to predict if such rotation would occur, especially in a rigid matrix environment. This question could be only answered on the basis of experimental work and that prompted us to carry out the present study on photochemical syn–anti interconversions in mo^{4}C and 1Me–mo^{4}C.

2. Experimental

N^4-methoxycytosine and 1-methyl-N^4-methoxycytosine used in the present study were synthesized following the procedures described by Brown et al. [21], Janion [4] and Janion et al. [22], respectively. Prior to the matrix experiments the compounds were purified by liquid chromatography and crystallization.

In order to deposit a matrix, a solid sample of a studied compound was heated in a microoven placed in the vacuum chamber of a continuous flow helium cryostat. The vapors of the compound were deposited, together with a large excess of the matrix gas on the CsI window cooled to 10 K. The matrix gases argon and nitrogen (both of spectral purity) were supplied by Linde AG and Technische Gase (Berlin), respectively. The IR spectra were recorded using Perkin-Elmer 580B or Thermo Nicolet Nexus 670 spectrometers. Integral intensities of the IR absorption bands were measured by numerical integration. Matrices were irradiated with the light from a high pressure mercury lamp HBO 200 fitted with a water filter and cut-off filters transmitting the light with $\lambda > 295$ nm or $\lambda > 335$ nm.

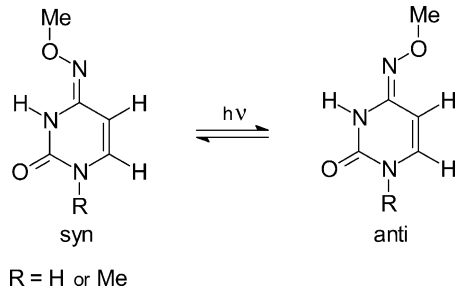
3. Computational

The equilibrium geometries of the mo^{4}C and 1Me–mo^{4}C isomers were fully optimized at the DFT(B3LYP)/6-31++G(d, p) level of theory [23,24]. Subsequently, the harmonic wavenumbers were calculated at the optimized geometries using the same theoretical method. All calculations were carried out using the GAUSSIAN 98 Program [25]. In order to correct for vibrational anharmonicity, basis set truncation and the neglected part of electron correlation, the calculated DFT wavenumbers were scaled down by an uniform factor of 0.98.

4. Results and discussion

4.1. Monomeric N^4-methoxycytosine and 1-methyl-N^4-methoxycytosine

The oxo–imino tautomeric form of mo^{4}C, with the syn orientation of the methoxyl group (Scheme 2), is the most stable isomer of the compound. This form is stabilized (with respect to the anti isomer) by an attractive interaction between the lone electron pairs of the methoxyl oxygen atom with the proton attached to the N(3) atom of the ring. The energy of the syn isomer was theoretically calculated [5] to be lower by $12/14\,\mathrm{kJ\,mol^{-1}}$ than the energy of the anti form (see Scheme 2). According to the theoretical calculations, all other isomers of mo^{4}C should be significantly less stable (by more than $32\,\mathrm{kJ\,mol^{-1}}$). The syn isomer of the oxo–imino form of mo^{4}C was found in the previous experiments [5] to strongly dominate in low-temperature



Scheme 2. Syn–anti photoisomerization in mo^{4}C and 1Me–mo^{4}C.

matrices. Methylation at the N(1) atom is not likely to have an important influence on the relative energies of the syn and anti isomers. Hence, for 1Me–mo^{4}C also the syn isomer of the oxo–imino tautomer is expected to be the strongly dominating species in low-temperature matrices.

The high frequency region of the IR spectra of mo^{4}C and 1Me–mo^{4}C isolated in Ar matrices is presented in Fig. 1. The bands due to the stretching vibrations of the NH groups are present in this spectral range. The assignment of the bands observed at 3488 and 3443 cm^{-1} in the spectrum of mo^{4}C as well as of the band observed at 3444 cm^{-1}, for matrix-isolated 1Me–mo^{4}C, is quite obvious. The band at 3488 cm^{-1} is due to the stretching vibration of the N(1)–H bond and the bands at 3443 and 3444 cm^{-1} should correspond to the stretching vibrations of N(3)–H bonds. This assignment is further supported by the results of the theoretical calculation graphically presented in Fig. 1.

The whole mid-infrared spectrum of mo^{4}C isolated in Ar matrix is virtually the same as that reported in the previous paper [5]. This spectrum is well reproduced by the spectrum theoretically calculated at the DFT(B3LYP)/6-31++G(d, p) level for the oxo–imino syn isomer of the compound. Good agreement between the experimental and theoretical spectra supports the correctness of the conclusion that the syn isomer of oxo–imino tautomers is the form adopted by mo^{4}C in low-temperature matrices. The same is true for 1Me–mo^{4}C.

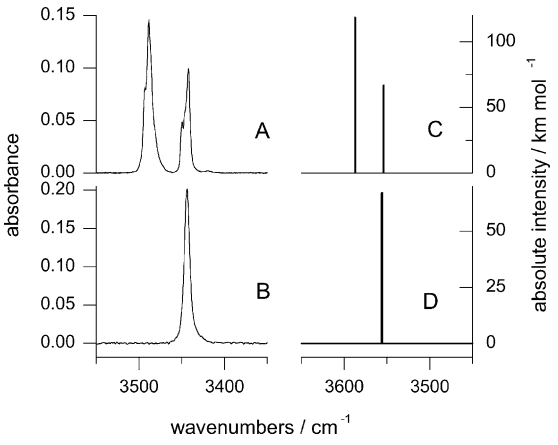


Fig. 1. High frequency range of: (A) the experimental spectrum of N^4-methoxycytosine (mo^{4}C) isolated in Ar matrix; (B) the experimental spectrum of 1-methyl-N^4-methoxycytosine (1Me–mo^{4}C) isolated in Ar matrix; (C) the theoretical spectrum of mo^{4}C; and (D) theoretical spectrum of 1Me–mo^{4}C. Theoretical spectra calculated at DFT(B3LYP)/6-31++G(d, p) level. Theoretical frequencies were scaled by an uniform factor of 0.98.

4.2. Effects of UV (λ > 295 nm) irradiation

Irradiation of matrix-isolated mo^{4}C and 1Me–mo^{4}C monomers with UV (λ > 295 nm) light led to a decrease of the IR bands in the initial spectra of the compounds and to the appearance of new bands due to photoproducts. Observation of the effects of UV irradiation was complicated by numerous cases of overlap between the bands in the spectra of the substrates and the corresponding photoproducts. Fortunately, there are spectral regions where the bands due to substrates and photoproducts do not overlap (or overlap only partially) allowing observation of the progress of the studied photoreactions (see e.g. the fragments presented in Figs. 2 and 3). The observed photoreactions do not lead to total consumption of the initial syn forms of the studied compounds. Even after prolonged UV (λ > 295 nm) irradiation, the spectra of the initial isomers, though reduced in intensity, were still observed. The progress of the reaction during UV irradiation of 1Me–mo^{4}C is presented in Fig. 4. Evidently, the final stage of the phototransformation

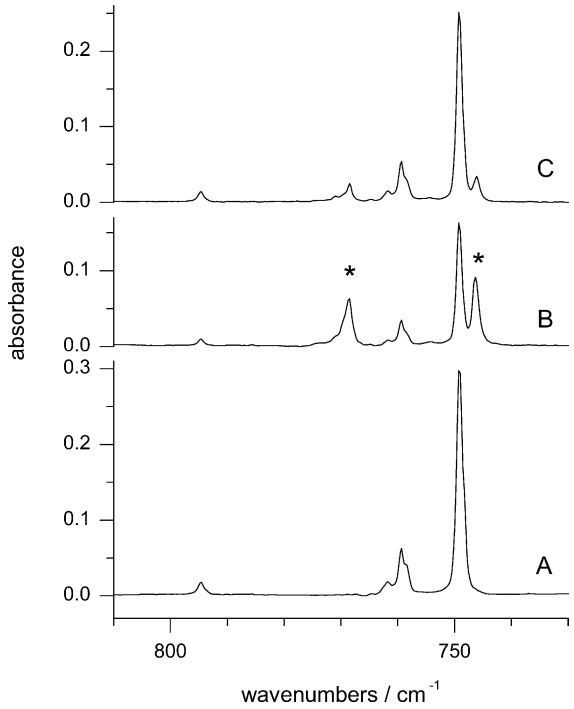


Fig. 2. Portion of the infrared spectrum of mo^{4}C isolated in Ar matrix: (A) after deposition of the matrix; (B) after 2 h of UV (λ > 295 nm) irradiation; and (C) after 2 h of UV (λ > 335 nm) irradiation. Asterisks indicate IR bands of the photoproduct (anti isomer).

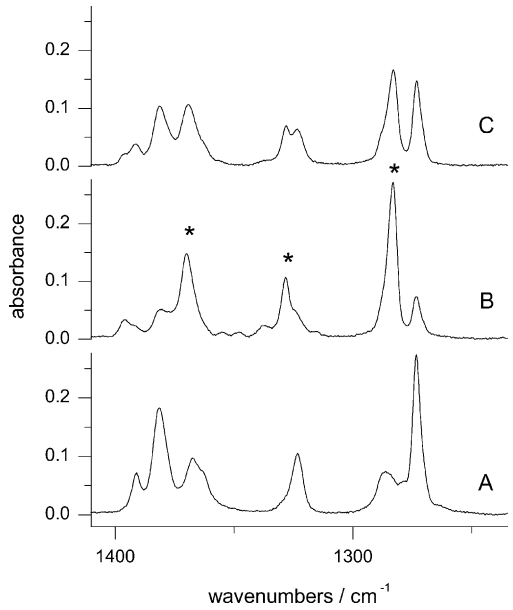


Fig. 3. Portion of the infrared spectrum of 1Me–mo^{4}C isolated in Ar matrix: (A) after deposition of the matrix; (B) after 2 h of UV ($\lambda > 295$ nm) irradiation; and (C) after 2 h of UV ($\lambda > 335$ nm) irradiation. Asterisks indicate most intense IR bands of the photoproduct (anti isomer).

is a photostationary state (for both mo^{4}C and 1Me–mo^{4}C). The position of the photostationary state corresponds to consumption of 55% of the syn isomer of mo^{4}C and to consumption of 71% of the syn isomer of 1Me–mo^{4}C isolated in argon matrices and irradiated with UV ($\lambda > 295$ nm) light.

The anti isomers of the oxo–imino tautomers of mo^{4}C and 1Me–mo^{4}C can be expected as the photoproduced species. This assumption is confirmed by comparison of the experimental spectra of the photoproducts with the spectra theoretically calculated for the anti forms. In general, identification

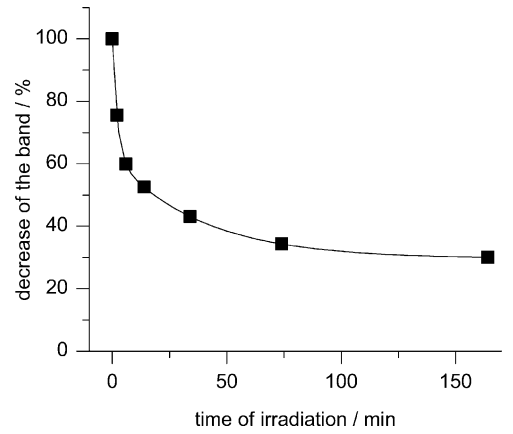


Fig. 4. Progress of the syn–anti photoreaction of 1Me–mo^{4}C (isolated in Ar matrix) as a function of the time of UV ($\lambda > 295$ nm) irradiation. The progress was monitored as a decrease of the intensity of the band at 1273 cm^{-1} (or of the band at 989 cm^{-1}) with respect to the intensity measured before irradiation.

of the syn and anti isomers of N^4-methoxycytosines on the basis of their IR spectra is not a straightforward task. There are no characteristic bands present in the spectrum of one of the forms which are absent in the spectrum of the other. Because the syn–anti isomerization concerns only reorientation of a small fragment in a comparatively large (14 or 17 atomic) molecule, the IR spectra of syn and anti isomers should be quite similar. No chemical bonds change their character by the isomerization. Hence, infrared bands due to stretching vibrations are placed at nearly the same frequencies as their counterparts in the spectrum of the other isomer. Such bands are not particularly useful for identification purposes. However, reliable identification of the syn and anti isomers becomes possible, when the lower-frequency region of the IR spectra is compared with the corresponding region of the theoretically simulated spectra. The patterns of low-frequency IR bands, due to in-plane and out-of-plane bending vibrations, are clearly different in the spectra of the two isomers. These patterns are well reproduced by the results of the theoretical calculations (as it is shown in Figs. 5 and 6). The very good agreement between the IR spectra recorded before UV irradiation and the theoretical

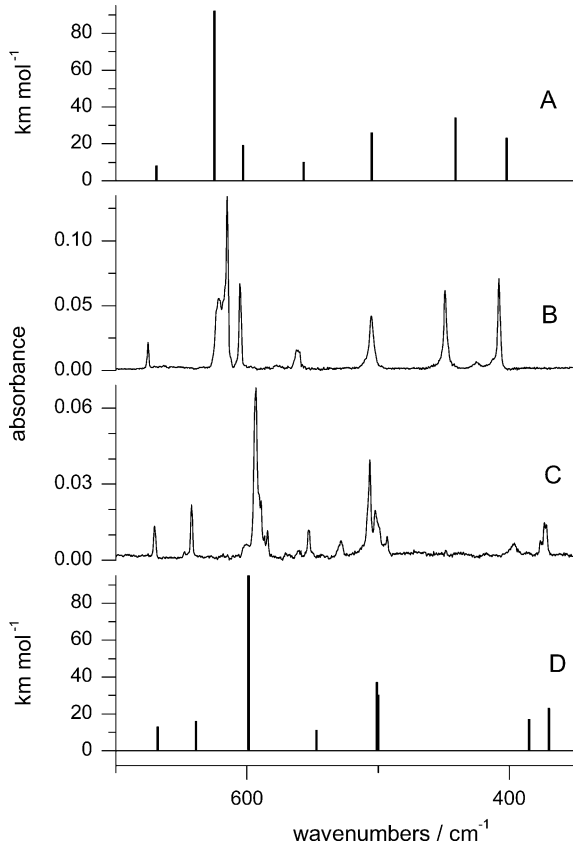


Fig. 5. Comparison of the experimental spectra of: (B) mo^{4}C isolated in Ar matrix; (C) the photoproduct generated upon UV ($\lambda > 295$ nm) irradiation; with the spectra calculated at the DFT(B3LYP)/6-31++G(d, p) level for syn (A) and anti (D) isomers of the oxo–imino tautomer of the compound. Theoretical frequencies were scaled by an uniform factor of 0.98.

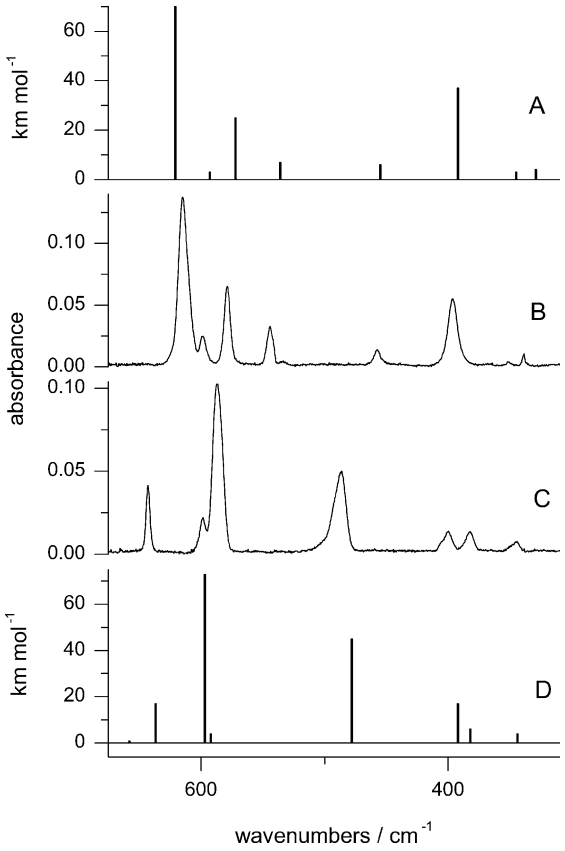


Fig. 6. Comparison of the experimental spectra of: (B) 1Me–mo^{4}C isolated in Ar matrix; (C) the photoproduct generated upon UV ($\lambda > 295$ nm) irradiation; with the spectra calculated at the DFT(B3LYP)/6-31++G(d, p) level for syn (A) and anti (D) isomers of the oxo–imino tautomer of the compound. Theoretical frequencies were scaled by an uniform factor of 0.98.

spectra of the syn forms as well as equally good agreement between the experimental spectra of the photoproduced species and the spectra theoretically simulated for the anti isomers leaves practically no doubt about the correctness of interpretation of the observed photoreactions in terms of syn–anti photoisomerization.

4.3. Effects of UV ($\lambda > 335$ nm) irradiation

Only photoreversible reactions can have a photostationary state as their final stage. Hence, the observation of photostationary states being established for the studied N^4-methoxycytosines demonstrates that both syn → anti and anti → syn photoreactions occur simultaneously upon UV ($\lambda > 295$ nm) irradiation. One of the factors which can influence the ratio of the rates of the reactions in the two directions is the change of the wavelength of the UV light used for irradiation. The UV absorption coefficients of the syn and anti isomers (at a given wavelength) should be similar, but there is no reason why they should be the same. The difference between the absorption coefficients can vary with varying wavelength [19]. Therefore application of different wavelength UV radiation can result in a shift of the position of a photostationary state.

In the experiments carried out for mo^{4}C and 1Me–mo^{4}C the low-temperature argon matrices, previously irradiated with UV ($\lambda > 295$ nm) light, were subsequently exposed to UV ($\lambda > 335$ nm) radiation. The effects of this additional irradiation are presented in Figs. 2 and 3. Significant repopulation of the initial syn isomer was observed for both investigated compounds. This observation provides a direct proof of the photoreversibility of the syn–anti photoisomerizations in mo^{4}C and 1Me–mo^{4}C.

4.4. Syn–anti photoisomerizations in N^4-methoxycytosine and 1-methyl-N^4-methoxycytosine isolated in nitrogen matrices

Photoisomerization reactions involving rotation around a double C=N bond are usually rationalized in terms of the shapes of the ground state and excited state potential energy surfaces (PES) [19,20]. In compounds with an imino group, the ground state minima corresponding to syn and anti isomers are separated by a high (150/200 kJ mol^{-1}) energy barrier [19,20]. However, in the first excited singlet state there is only one minimum on the PES and the molecule in this minimum has a geometry similar to that corresponding to the transition point in the ground state. In both cases, the methoxyl group is no longer coplanar with the heterocyclic ring, but located in the plane perpendicular to it. Small shifts of the position of the excited state minimum with respect to the top of the ground state barrier can significantly influence the relative rates of the syn → anti and anti → syn phototransformations. The factors which can modify the shape of the ground and excited state PES may be of intramolecular or intermolecular nature. The first class is represented in the present work by methylation at N(1), which is an example of a structural change in a fragment not involved in the photoizomerization. The influence of interactions with the environment on the position of the photostationary state was studied by comparison of the photochemical behavior of the compounds in question isolated in argon and in nitrogen matrices.

Fragments of the IR spectra of mo^{4}C and 1Me–mo^{4}C isolated in nitrogen matrices are presented in Figs. 7 and 8. Comparison of the spectra recorded before and after UV ($\lambda > 295$ nm) irradiation demonstrates that in these conditions the phototransformation of the syn isomer to the anti form is nearly complete (90% for mo^{4}C and 95% for 1Me–mo^{4}C). This means that the position of the photostationary state is significantly shifted, with respect to the results of the experiments carried out for the compounds isolated in argon matrices. On the basis of these observations, one can conclude that even slight changes in the shapes of the potential energy surfaces of the ground and excited electronic states, introduced by weak interactions with the matrix environment, can have significant consequences as

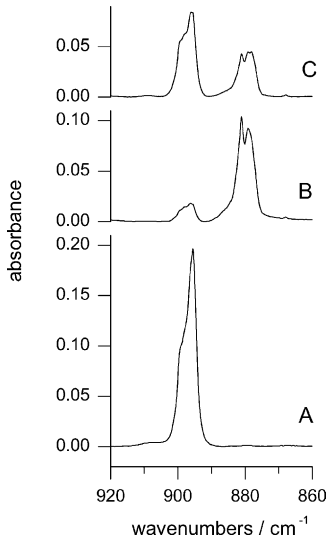


Fig. 7. Portion of the infrared spectrum of mo^{4}C isolated in N_2 matrix: (A) after deposition of the matrix; (B) after 2 h of UV ($\lambda > 295$ nm) irradiation; and (C) after 2 h of UV ($\lambda > 335$ nm) irradiation.

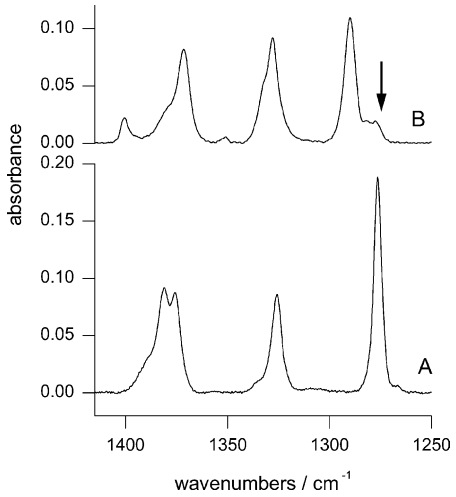


Fig. 8. Portion of the infrared spectrum of 1Me–mo^{4}C isolated in N_2 matrix: (A) after deposition of the matrix; and (B) after 2 h of UV ($\lambda > 295$ nm) irradiation. The arrow indicates the position of the band due to the initial syn isomer reduced in intensity upon UV irradiation.

far as the final, photostationary ratio of the photoproducts is concerned.

5. Conclusions

Syn–anti photoisomerization reactions were investigated for N^4-methoxycytosine (mo^{4}C) and 1-methyl-N^4-methoxycytosine (1Me–mo^{4}C) isolated in solid argon or solid nitrogen matrices. Because of the considerable size of the methoxyl fragment, its rotation in a rigid matrix environment (at 10 K) was an unexpected effect. Nevertheless, it was experimentally proven that the rotation of the methoxyl group around the C=N bond occurs when a mo^{4}C (or 1Me–mo^{4}C) molecule is excited by UV light. Steric hindrance to the methoxyl group rotation, introduced by interactions with the low-temperature matrix cavity, does not preclude this syn–anti photoisomerization.

For both mo^{4}C and 1Me–mo^{4}C, the final stage of the UV-induced syn–anti photoisomerization corresponds to a photostationary state. Replacement of the argon matrix environment by solid nitrogen results in a systematic shift (observed for both compounds) of the position of the photostationary state in favor of a higher population of an anti photoproduct. The reversibility of the syn–anti photoisomerization is proven by direct observation of a back anti → syn photoconversion induced by subsequent, longer wavelength UV irradiation of the matrix isolated monomers of the investigated compounds.

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