UDC 544.15+544.176+547.738.1

D.S. Milokhov [a], A.V. Yatsymyrskyi [a], A.O. Poliudov [b], A.A. Fokin [b], A.V. Dobrydnev [a, c]

DMSO-ASSISTED ENOLIZATION OF β-KETO γ-SULTONES: A COMBINED NMR AND DFT STUDY

[a] Taras Shevchenko National University of Kyiv, Kyiv, Ukraine
[b] National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Kyiv, Ukraine
[c] Enamine Ltd., Kyiv, Ukraine

A cost-effective method for the synthesis of 5,5-disubstituted 1,2-oxathiolan-4-one 2,2-dioxides (β-keto γ-sultones) on a several-hundred-gram scale without the use of halogenated organic solvents has been developed. β-Keto γ-sultones exhibit selective anticancer activity and are considered bioisosteres of tetronic acid, promising pharmacological templates that possess active reactive centers allowing further structural modification and modulation of bioactivity. Because keto-enol tautomerism can strongly impact bioactivity by influencing binding interactions with biological targets and altering physicochemical properties, the keto-enol tautomerization of β-keto γ-sultones in DMSO was studied using EXSY NMR (exchange spectroscopy) in combination with DFT (density functional theory) calculations. The obtained experimental and computational data confirm the key role of DMSO in keto-enol tautomerization and proton exchange in β-keto γ-sultones. The developed mechanistic model can be applied to other carbonyl compounds and solvents, as well as to compounds that facilitate their enolization.

Keywords: cyclization, sulfonates, β-keto γ-sultones, EXSY, DFT calculations, tautomerization, reaction mechanism.

DOI: 10.32434/0321-4095-2026-165-2-41-50

Introduction

Bioisosteric substitution is indeed one of the cornerstones of contemporary drug design. It is based on the replacement of atoms or functional groups within a bioactive molecule by chemically or sterically similar moieties, aiming to retain the desired biological activity while improving physicochemical and pharmacokinetic properties. Moreover, rational bioisosteric modifications can enhance the binding affinity, selectivity, metabolic stability, and overall drug identity of candidate molecules. Sulfonamides and sulfonylated derivatives acting as bioisosteres of carbonyl compounds allowed the creation of many potent anticancer agents [1,2]. In this context, 1,2-oxathiolan-4-one 2,2-dioxides (β-keto γ-sultones) are considered as the bioisosters of naturally occurring tetronic acid (Fig. 1), whose framework is a key constituent of many vital biologically active compounds (ascorbic acid, penicillinic acid) and agricultural chemicals (insecticides spirodiclofen and spiromesifen). *In vitro* cytotoxicity assay showed that β-keto γ-sultones exhibited selective cytotoxicity against triple-negative breast cancer cell line MDA-MB-231, and did not affect non-malignant cells [3].

Previously, we developed procedures for a gram-scale synthesis of β-keto γ-sultones [3], explored their reactivity [4], and discovered their strong tendency towards tautomerization. Because this may influence

biological activity through effects on binding interactions, structural and physicochemical properties [5–7], a better understanding and control of tautomerism is necessary to achieve the design and optimization of biological activity of this class of molecules.

Considering β-keto γ-sultones as prospective templates with selective anticancer activity, possessing a set of synthetically valuable handles allowing further structural modification and activity modulation, we developed an improved procedure for their multi-hundred-gram scale synthesis. Accordingly, α-hydroxy acid esters **1a,b** were sulfonylated with methanesulfonyl chloride, and the resulting mesylates **2a,b** were further treated with potassium *tert*-butoxide in THF medium. *Sulfa*-Dieckmann condensation gave corresponding potassium enolates, which were quenched with glacial acetic acid to give the desired β-keto γ-sultones **3a,b** (Scheme 1).

The modified method is more general, cost-effective, and nonpolluting since the environmentally friendly solvents were used and their consumption was substantially reduced. Specifically, in comparison with our originally developed procedure [3], we eliminated the use of dichloromethane in the first step and trifluoroacetic acid in the second step. Moreover, all these changes had a positive impact on the overall yield of the final products.

Experimental

All the reagents and solvents were obtained from Enamine Ltd. (www.enamine.net) and UORSY (www.uorsy.com). Melting points were measured on MPA100 OptiMelt automated melting point system. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C nuclei). Chemical shifts are reported in ppm using residual solvent peak as a secondary reference standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument using chemical ionization (CI). Two-dimensional exchange spectra (2D EXSY) were recorded on a Bruker Avance III HD 600 MHz spectrometer (600 MHz for ^{1}H and 151 MHz for ^{13}C nuclei). 2D EXSY spectra with mixing times of 10, 50, and 100 ms were acquired using the phase-sensitive NOESY pulse sequence (noesygpph, Bruker). All spectra were recorded with 1024 data points in the F_2 dimension and 256 increments in the F_1 dimension. Each

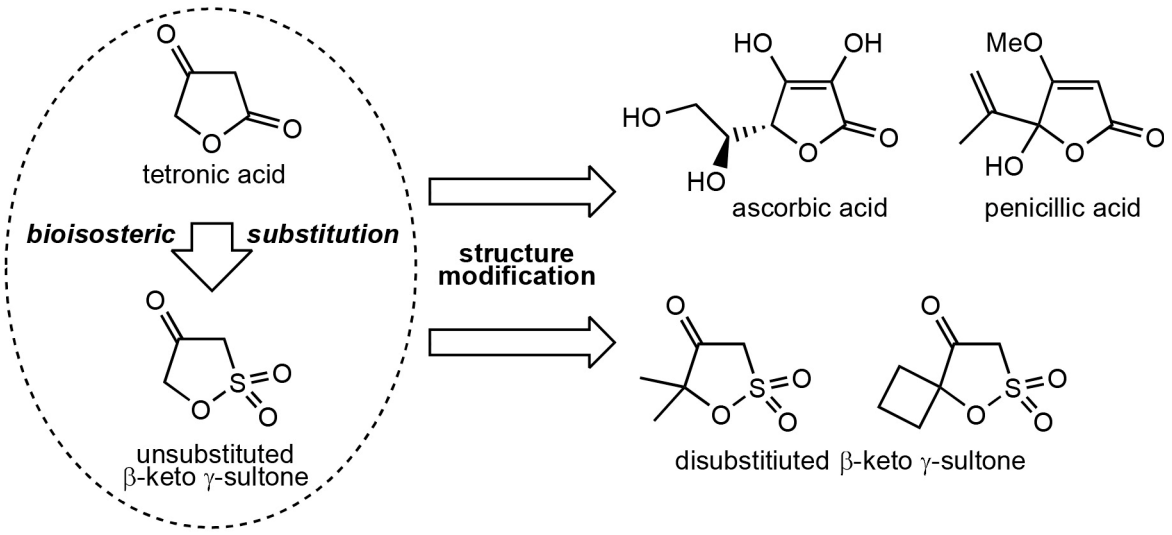
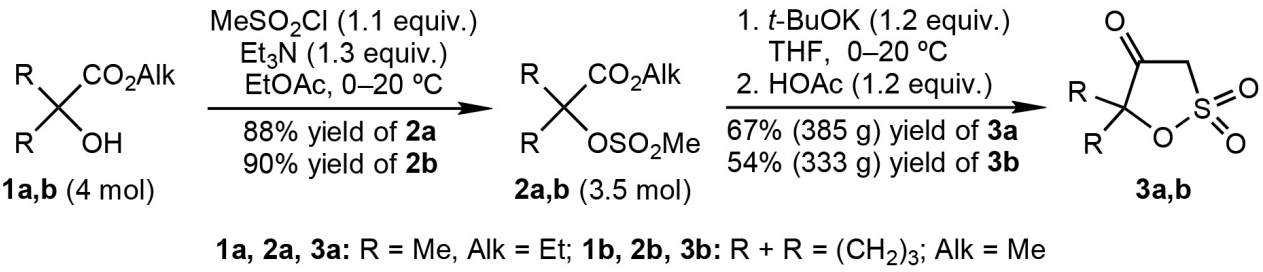


Fig. 1. Tetronic acid, their biologically active derivatives and bioisosters



Scheme 1. Synthesis of β-keto γ-sultones **3a,b** in a multi-hundred-gram scale

increment was obtained with 24 scans, a spectral width of 9862 Hz, and a relaxation delay of 2 s. After zero-filling to 1024 points in both dimensions, resulting in equal digital resolution, the time-domain data were multiplied in both dimensions by a π/2 sine-squared window function.

General procedure for the synthesis of alkyl 2-((methylsulfonyl)oxy)carboxylates 2a,b

α-Hydroxy ester **1a,b** (4 mol, 1 equiv.) was dissolved in ethyl acetate (7 L) loaded in a 20-L reactor equipped with an overhead stirrer and a calcium chloride tube. Then triethylamine (526 g, 721 mL, 5.2 mol, 1.3 equiv.) was added in one portion, and the resulting mixture was cooled with ice–water. When the internal temperature had dropped to 0°C, methanesulfonyl chloride (504 g, 341 mL, 4.4 mol, 1.1 equiv.) was added at a fast dropwise rate, maintaining the internal temperature below 5°C. After the addition had been finished, the reaction mixture was allowed to reach ambient temperature and stirred for 24 h. Then 1 M aqueous sodium hydrosulfate (3 L) was added in one portion and the resulting biphasic mixture was stirred for 10 min, the upper organic layer was separated, dried over anhydrous sodium sulfate (300 g), and evaporated at reduced pressure. The obtained residue was additionally dried *in vacuo* (0.1 Torr) at 50°C for 5 h to remove the residual quantities of ethyl acetate. Thus obtained *O*-mesylated α-hydroxy esters **2a,b** were used in the subsequent step without additional purification.

*Ethyl 2-methyl-2-((methylsulfonyl)oxy)propanoate (**2a**)* was obtained from ethyl 2-hydroxy-2-methylpropanoate (**1a**, 530 g). Yield 740 g (3.52 mol, 88%). White solid, mp=28–29°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (t, *J*=7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.71 (s, 6H, 2×CH_3), 3.12 (s, 3H, SO_2CH_3), 4.26 (q, *J*=7.1 Hz, 2H, $O\mathit{CH_2}CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ=14.1 ($OCH_2\mathit{CH_3}$), 26.3 (2×CH_3), 40.7 (SO_2CH_3), 62.2 ($O\mathit{CH_2}CH_3$), 86.5 (quaternary C), 171.7 (C=O) ppm. MS (CI): *m/z*=211 $[M+H]^+$. The physicochemical properties and spectra date are identical to that described elsewhere [3].

*Methyl 1-((methylsulfonyl)oxy)cyclobutane-1-carboxylate (**2b**)* was obtained from ethyl methyl 1-hydroxycyclobutane-1-carboxylate (**1b**, 520 g). Yield 750 g (3.6 mol, 90%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.89–2.03 (m, 2H, CH_2 cyclobutyl), 2.59 (qd, *J*=13.1, 9.2 Hz, 4H, 2×CH_2 cyclobutyl), 3.09 (s, 3H, SO_2CH_3), 3.78 (s, 3H, OCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ=14.3 (CH_2 cyclobutyl), 33.3 (2×CH_2 cyclobutyl), 40.2 (SO_2CH_3), 52.8 (OCH_3), 83.9 (quaternary C), 171.2 (C=O) ppm. MS (CI): *m/z*=209 $[M+H]^+$. The physicochemical properties and spectra date are identical to that described elsewhere [3].

General procedure for the synthesis of 1,2-oxathiolan-4-one 2,2-dioxides 3a,b

Potassium *tert*-butylate (471 g, 4.2 mol, 1.2 equiv.) was dispersed in THF (7 L) loaded in a 20-L reactor equipped with an overhead stirrer and a calcium chloride tube. The resulting mixture was cooled with ice water bath, and when the internal temperature had dropped to 0°C, the solution of *O*-mesylated α-hydroxy ester **2a,b** (3.5 mol, 1 equiv.) in THF (3 L) was added at a fast dropwise rate, maintaining the internal temperature below 5°C. After the addition had been finished, the reaction mixture was allowed to reach ambient temperature and stirred for 24 h. Then glacial acetic acid (252 g, 240 mL, 4.2 mol, 1.2 equiv.) was added at a fast dropwise rate, the resulting mixture was stirred for 10 min, and evaporated at reduced pressure to dryness. Water (180 mL) was added to dissolve the formed potassium acetate and the resulting slurry was diluted with ethyl acetate (4 L). The organic layer was separated, dried over anhydrous sodium sulfate (400 g), and evaporated at reduced pressure. Thus obtained residue was washed with hexane–ethyl acetate (3:1 (v/v), 2×50 mL) to give pure β-keto γ-sultones **3a,b**. If necessary, the product can be recrystallized from a minimal amount of propan-2-ol.

*5,5-Dimethyl-1,2-oxathiolan-4-one 2,2-dioxide (**3a**)* was obtained from *O*-mesylated α-hydroxy ester **2a** (736 g). Yield 385 g (2.35 mol, 67%). White solid, mp=61–62°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.53 (s, 6H, 2×CH_3), 4.82 (s, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ=24.7 (2×CH_3), 52.3 (CH_2), 95.1 (quaternary C), 202.1 (C=O) ppm. MS (CI): *m/z*=163 $[M-H]^-$. The physicochemical properties and spectra date are identical to that described elsewhere [3].

Spectra data for *4-Hydroxy-5,5-dimethyl-5H-1,2-oxathiole 2,2-dioxide (**4a**, an enol form of **3a**)*. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.53 (s, 6H, 2×CH_3), 6.01 (s, 1H, CH), 12.68 (s, 1H, OH) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ=23.6 (2×CH_3), 87.8 (CH), 92.2 (quaternary C), 169.2 (C–OH) ppm.

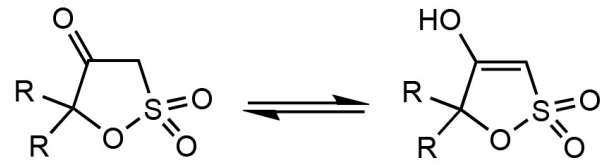
*5-Oxa-6-thiaspiro[3.4]octan-8-one 6,6-dioxide (**3b**)* was obtained from *O*-mesylated α-hydroxy ester **2b** (729 g). Yield 333 g (1.89 mol, 54%). White solid, mp=97–98°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.79 (q, *J*=8.8 Hz, 1H, CH_2 cyclobutyl), 1.85–2.00 (1H, m, CH_2 cyclobutyl), 2.54 (t, *J*=8.8 Hz, 4H, 2×CH_2 cyclobutyl), 4.65 (s, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ=13.5 (CH_2 cyclobutyl), 33.1 (2×CH_2 cyclobutyl), 52.5 (CH_2), 92.9 (quaternary C), 200.0 (C=O) ppm. MS (CI): *m/z*=175 $[M-H]^-$. The physicochemical properties and spectra date are identical to that described

elsewhere [3].

Spectra data for *8-hydroxy-5-oxa-6-thiaspiro[3.4]oct-7-ene 6,6-dioxide (**4b**, an enol form of **3b**)*. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.70–2.01 (m, 2H, CH_2 cyclobutyl), 2.54 (t, *J*=8.3 Hz, 4H, 2×CH_2 cyclobutyl), 6.03 (s, 1H, CH), 12.86 (s, 1H, OH) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ=12.7 (CH_2 cyclobutyl), 32.6 (2×CH_2 cyclobutyl), 86.7 (CH), 91.9 (quaternary C), 167.0 (C–OH) ppm.

Results and discussion

Having developed a multi-hundred-gram scale synthesis of β-keto γ-sultones **3a,b**, we focused on a study of their tautomerization (Scheme 2).



3a,b (ketone form) **4a,b** (enol form)

3a, 4a: R = Me; **3b, 4b:** R + R = $(CH_2)_3$

ΔG value for the keto-enol tautomerization:

$\Delta G = \Delta G$(enol form) – ΔG(ketone form)

Scheme 2. The keto-enol tautomerism of β-keto γ-sultones

In general, the enolization of carbonyl compounds, specifically ketones, belongs to a well-studied reaction [8], parameters of which can be readily determined utilizing density functional theory [9]. This background allows the creation of accurate theoretical models for the enolization of certain substances in a definite medium. However, the vast majority of the suggested models take into account the acid, base, or polarity of the solvent (medium), and only a few recent models take into account explicit solvation. To our knowledge, an appropriate theoretical model for the DMSO-assisted keto-enol tautomerization of carbonyl compounds has not been reported to date. Besides, this model is important for biochemistry since the aqueous DMSO is a standard medium for *in vitro* experiments.

When observing the tautomerization of sultones **3a,b** in DMSO medium, we found that the addition of water did not affect the ratio of tautomers. The computed Gibbs free energy change for the keto-enol tautomerism of water-solvated keto sultones also showed that hydrated ketone tautomers **3a,b** • H_2O remained more energetically favorable than the corresponding enol hydrates **4a,b** • H_2O [3]. This allowed us to conclude that the specific solvation with the DMSO molecule played a crucial role in the enolization process. Our assumption was supported by the results of previous studies, which proved that the oxygen atom of the DMSO molecule acts as a hard Lewis base, forming stronger H-bonds than those with water [10].

Building the theoretical model for the DMSO-assisted enolization of β-keto γ-sultones, we hypothesized that both tautomeric forms existed as solvates in DMSO medium (*i.e.*, keto form **3** • DMSO and enol form **4** • DMSO), which might greatly facilitate the enolization reaction. Thus, keto tautomers formed the corresponding solvates **3** • DMSO through a weak H-bonding of the CH_2 group with the oxygen atom of the DMSO molecule. In turn, enol tautomers **4** • DMSO formed a significantly stronger H-bond of the OH group with the oxygen atom of the DMSO molecule [3]. This statement was confirmed by the variable temperature ^{1}H NMR spectra of β-keto γ-sultone **3b** in DMSO d_6. Specifically, the peaks corresponding to the enol form and water broadened and moved toward coalescence upon heating, indicating rapid proton exchange. At the same time, the signals of cyclobutyl CH_2 protons of both keto and enol tautomers shifted away from the coalescence point, which was particularly evident for two signals at 1.8–1.9 ppm (Fig. 2).

Variable temperature ^{1}H NMR measurements revealed coupled chemical exchange processes occurring at different rates, prompting further investigation using the two-dimensional exchange spectroscopy (2D EXSY). These experiments belong to an NMR technique that has a great opportunity for elucidating molecular dynamics, such as chemical or conformational changes [11,12]. 2D EXSY studies focus on slow molecular motions to provide valuable insight into the kinetics of exchange processes, allowing the determination of rate constants and activation barriers [13,14].

EXSY uses the same pulse sequence as the NOESY (nuclear Overhauser effect spectroscopy) experiment, observing the magnetization transfer between different spin systems through exchange. NOESY experiment operates with magnetization transfer by cross-relaxation using mixing times in a range of T1 time scale. Since exchange processes typically occur faster than nOe accumulation, EXSY experiments generally use shorter mixing times, which should be selected to overlap with the expected time frame of the exchange process. As a result, the EXSY cross-peaks have the opposite sign phase to the NOESY cross-peaks and the same phase as the diagonal peaks. This feature allows us to distinguish them within the same 2D spectra obtained for small molecules.

The kinetic parameters of exchange processes

can be derived from 2D EXSY data using the matrix method developed by Charles Perrin [13]. For a first-order multispin system involving chemical exchange, the peak intensity in 2D EXSY spectra is related to the exchange rate constant, the relaxation rate, and the mixing time (τ_m) by the expression given by the matrices [13,14]:

$$A=M_0 \cdot \exp(-R \cdot \tau_m)$$

Intensity matrix A consists of the peak volumes extracted from the 2D EXSY spectrum with a given mixing time (τ_m). Reference matrix M_0 is a diagonal matrix of equilibrium magnetization values obtained from a 2D EXSY spectrum with a reference «zero» mixing time ($\tau_m \approx 0$) or simply measured from a one-dimensional spectrum. Relaxation matrix R contains the kinetic parameters to be determined, namely chemical exchange and longitudinal relaxation rates.

A series of 2D EXSY spectra was recorded for sultones **3a,b** at different mixing times (10, 50, and 100 ms) in DMSO-d_6 at 25^{0}C (Fig. 3). EXSY spectra have reviled magnetization exchange between four exchanging sites **A**–**D** related to proton signals of keto-enol form of the studied sultones and $H_2O \cdot$ DMSO-d_6 solvate. Species **A** and **B** were assigned to the signals of the OH and CH groups of enol form **4**. The species **C** was assigned to the signal of the CH_2 group of ketone form **3**, while species **D** corresponds to the $H_2O \cdot$ DMSO-d_6 solvate.

EXSY spectra revealed 16 main peaks (4 diagonal auto-peaks and 12 cross-peaks), which were used to build up the intensity matrix **A** by measuring their volume. The reference matrix M_0 of the initial magnetization population was generated from a ^{1}H NMR spectrum. Then, the relaxation matrix R was calculated using EXSYCalc software, yielding the corresponding rate constants. In this way, quantitative information on the exchange dynamics between the involved species depicted in Scheme 3 was obtained.

It should be noted that even at the lowest mixing time τ_m=10 ms, measurable magnetization exchange rate constants were obtained, indicating a fast exchange process. The magnetization exchange rates determined at a mixing time of 10 ms had a substantial values for k_{AC}, k_{CA}, k_{CB}, k_{BC}, k_{AD}, k_{DA}, and a negligible ones for k_{AB}, k_{BA}, k_{BD}, k_{DB}, k_{CD}, k_{DC} (about ≤ 1 s^{-1}). Interestingly, increasing the mixing time to 50 or 100 ms promoted a further distribution of magnetization among the exchange sites **A**–**D**, leading

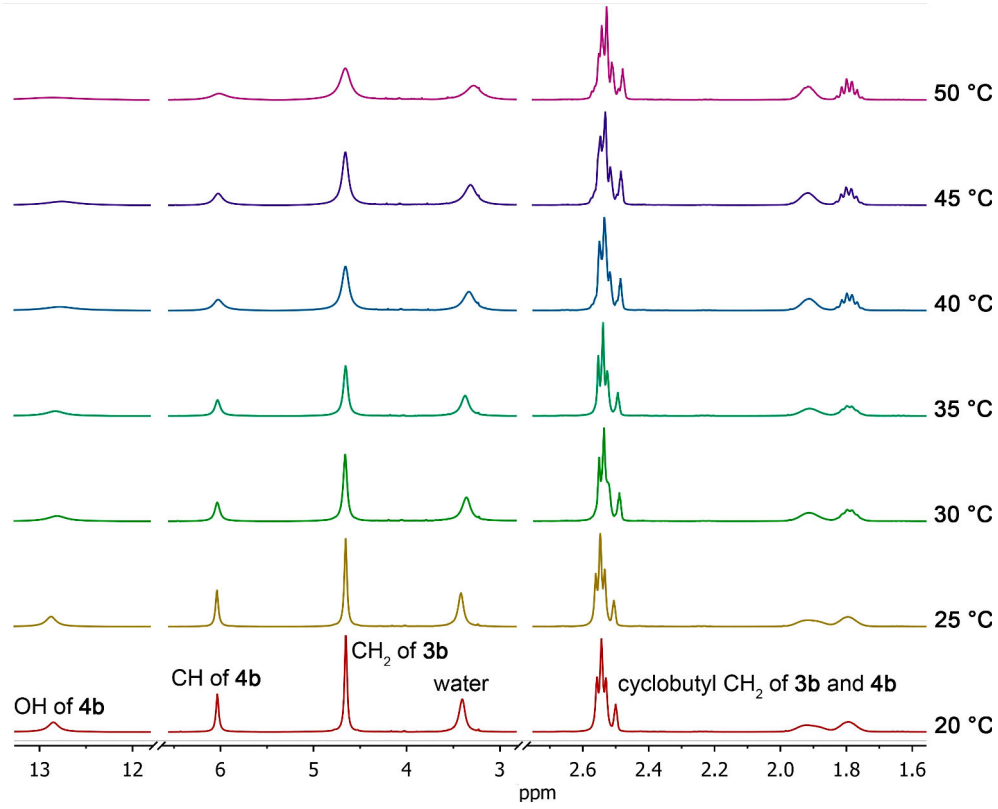


Fig. 2. Variable temperature ^{1}H NMR spectra of β-keto γ-sultone **4b** in DMSO d_6 from 20 to 50^{0}C. The height of the signals of the cyclobutyl fragment was understated

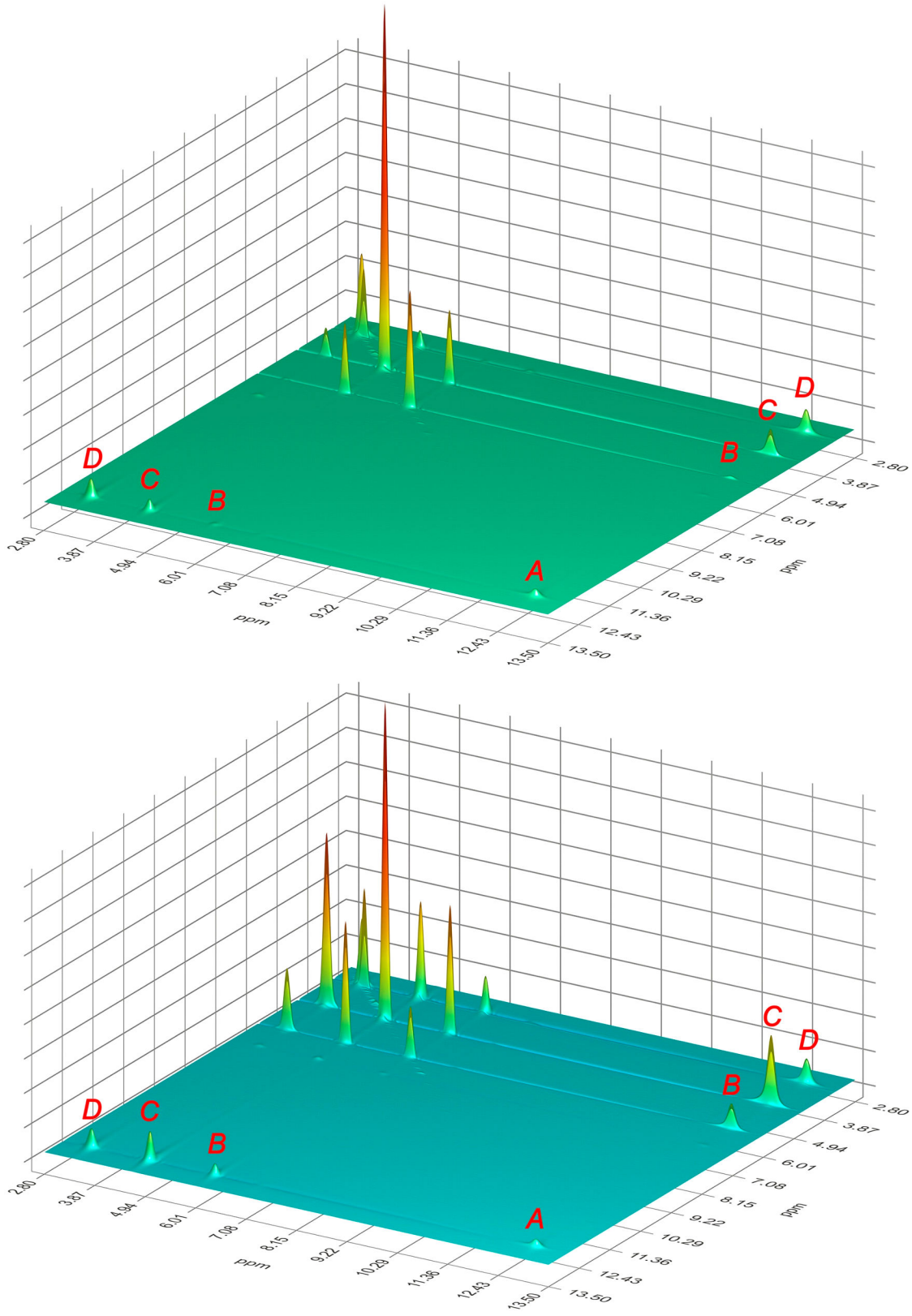


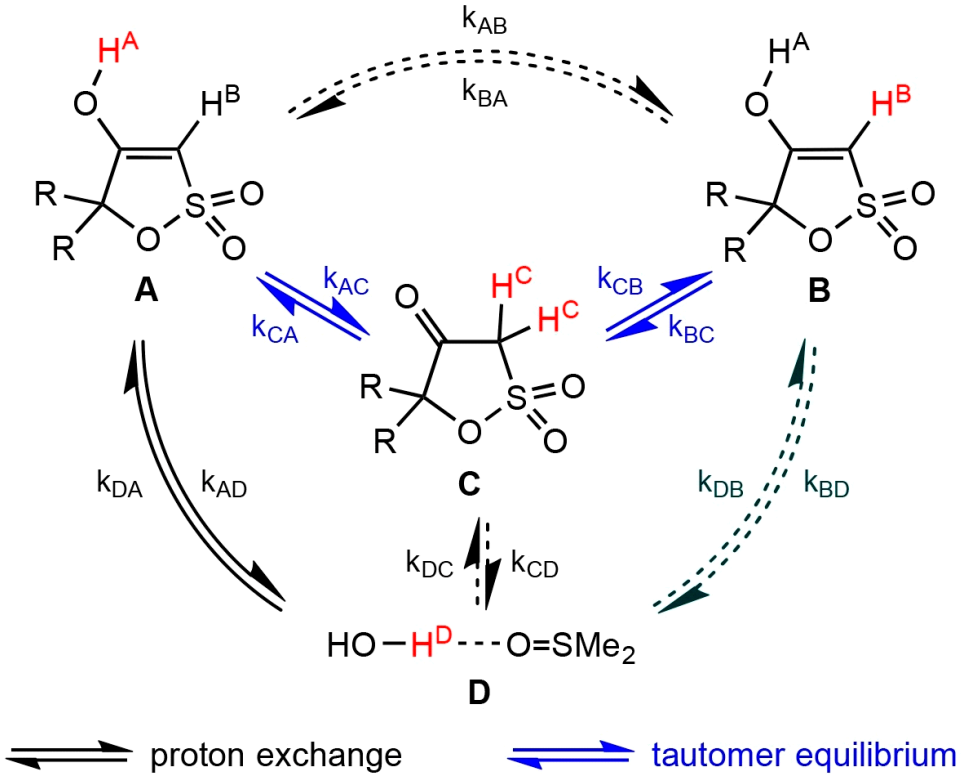
Fig. 3. 3D view of 2D EXSY spectra of sultone **3b** in DMSO-d_6 at 25^{0}C with a mixing time of 10 ms (on the top) and 100 ms (in the bottom)

to the appearance of noticeably higher rate constants for k_{AB}, k_{BA}, k_{BD}, k_{DB}, k_{CD}, k_{DC}. At the same time, k_{CA}, k_{CB}, k_{AD}, k_{DA} decreased while k_{CA} and k_{CB} still remained essentially unchanged.

These experimental results demonstrated how two coupled processes, *i.e.*, keto-enol tautomerism and proton exchange were reflected in the EXSY data. At short mixing times, magnetization exchange occurred only between directly exchanging sites, corresponding to the chemical exchange rate constants shown in Scheme 4. The increase in mixing time allowed magnetization to equilibrate among all sites due to exchange processes and longitudinal relaxation. Therefore, we observed «pseudo» proton-exchange rate constants, such as between the keto species **C** and water, which were actually mediated through the enol species **A**. Similarly, the exchange reaction between H^A and H^B protons of the enol species **A** and **B** occurred indirectly through the keto species **C**. These «pseudo» proton-exchange reactions were marked with dotted arrows (Scheme 3). Therefore, kinetic parameters of coupled chemical equilibrium should be determined from EXSY data acquired at short mixing times, when spin diffusion contributions are negligible (τ_m=10−50 ms).

Having the established cyclic network of magnetization exchange processes, we took into account the Onsager reciprocal relation, which states that the product of the forward and reverse rate constants in a closed cycle is equal. Consequently, the observed chemical exchange constants represent a composite contribution from the individual magnetization exchange rates involved in the cycle. Further analysis of the kinetics parameter clearly verified a coupled chemical exchange process: keto-enol equilibrium and proton exchange between enol form and the $H_2O \cdot$ DMSO-d_6 solvate **D** (Scheme 4). Moreover, the absence of proton exchange between the keto form and water served as important evidence for the mechanism of keto-enol tautomerization involving DMSO. The kinetic parameters obtained and the activation energies calculated using the Eyring equation for chemical exchange processes are summarized in Table.

Taking into account the above experimental data we suggested a plausible mechanism for the DMSO-assisted enolization of β-keto γ-sultones, which involves the proton shift inside the **3a,b** • DMSO solvate. This process occurred through the transition structure for proton transfer (**TS**) from C−H bond of



Scheme 3. Magnetization exchange rates according to the EXSY NMR spectra. Depicted in red hydrogen atoms $H^{A,B,C,D}$ and their chemical shifts correspond to those ones involved in magnetization exchange, forming peaks in the 2D EXSY spectrum

sultone to DMSO molecule followed by formation solvated enol **4a,b** · DMSO through the ion pair intermediate (Scheme 5).

The above mechanism for the explicit DMSO-assisted interconversion of the tautomers **3** and **4** was modeled by DFT calculations at the PBE0/QZVP level of theory using SMD (DMSO) solvation model. DFT calculations were performed using ORCA 5.0.3 software package [15]. The nature of the stationary points of the potential energy surface was revealed based on the calculations of harmonic frequencies (NIMAG=0 and 1 for minima and transition structures, respectively). The barriers for the proton transfer from **3** · DMSO through the transition state TS are within 13–14 kcal/mol; we were able to detect the corresponding ion pair on the potential energy

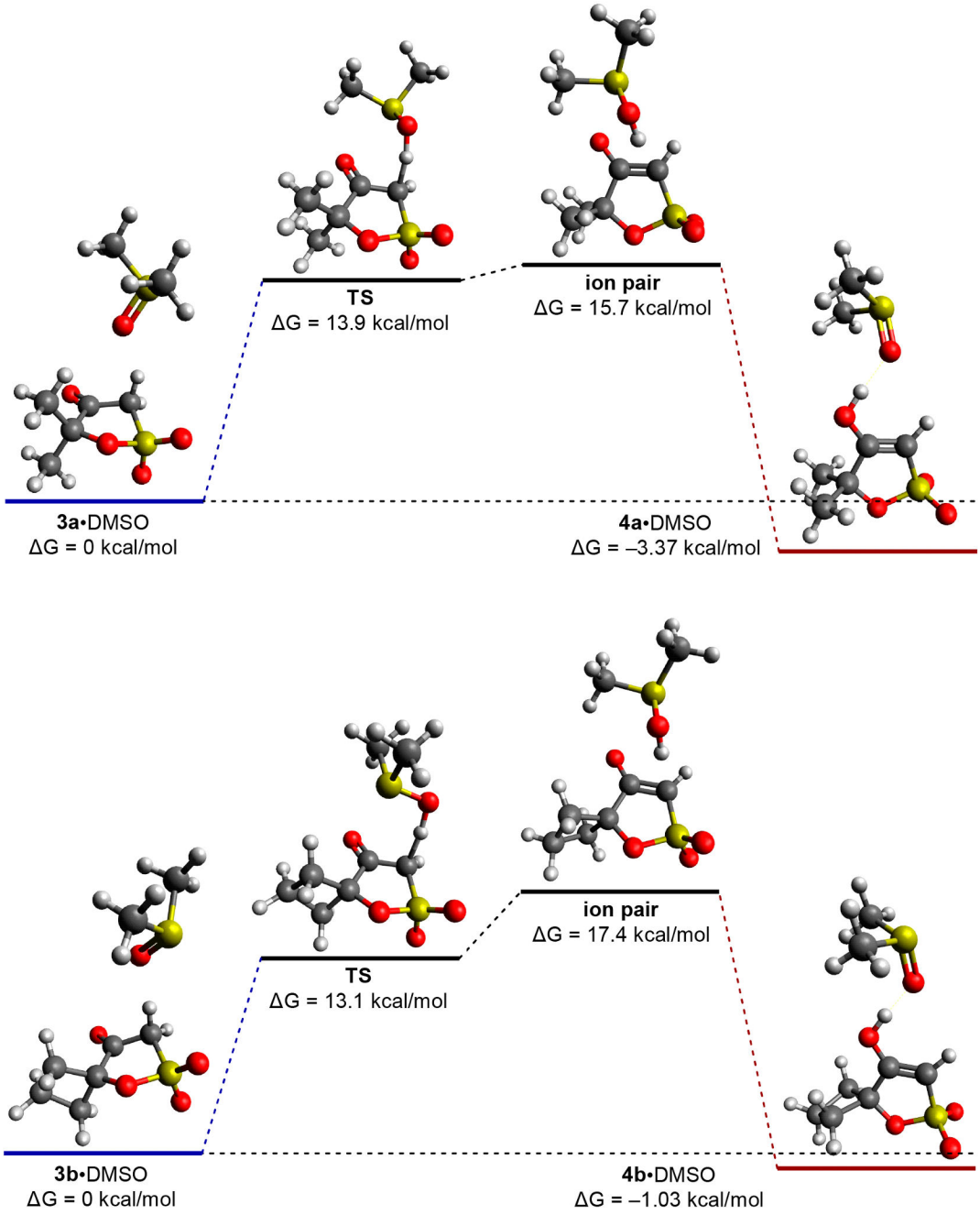
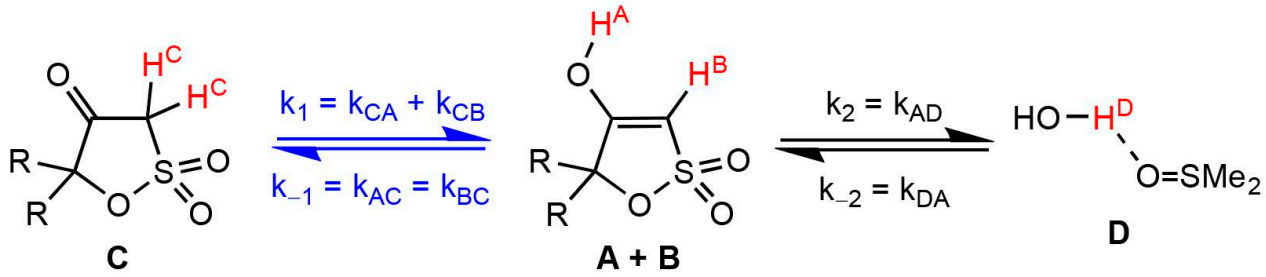


Fig. 4. Potential energy surface for the DMSO-assisted enolization of β-keto g-sultones **3a** (top) and **3b** (bottom) calculated at the PBE0/QZVP level of theory using SMD (DMSO) solvation model

surface, which lie only slightly above the corresponding transition structures. The proton transfer in the ion pair resulted in exergonic formation of enol solvates **4**·DMSO that are 1–3 kcal/mol more stable than the starting keto solvate **3**·DMSO (Fig. 4). These results explained and rationalized the experimental data, since the calculated reaction barriers were in complete agreement with those obtained in the EXSY NMR experiment.

Conclusions

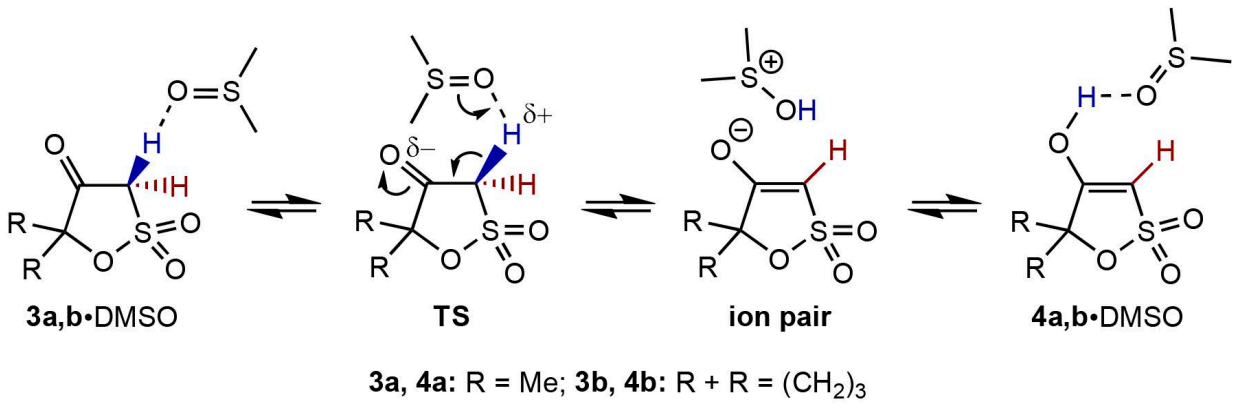
As a result, we developed a cost-effective method for the multi-hundred-gram scale synthesis of 5,5-disubstituted β-keto γ-sultones. Given the pharmacological potential of this class of molecules, we studied their DMSO-mediated tautomerization in detail using NMR experiments combined with DFT computations. In particular, 2D EXSY spectra allowed us to obtain rate constants and experimental activation barriers that agree well with the theoretical model only when explicit solvation with DMSO is considered. Since DMSO is a standard *in vitro* testing medium, we hope that our model will be useful for drug development based on enolizable molecules.



Scheme 4. Chemical exchange rates outlined the tautomer equilibrium and proton exchange

Rate constant and activation free energies for the proton exchange reactions of β-keto γ-sultones in DMSO-d_6 medium (T=298 K, τ_m=10 ms)

Entry	Proton transfer reaction	Rate constant		Activation energy ΔG, kcal/mol
		equation	k, s^{-1}	
1	**3a→4a**	$k_1=k_{CA}+k_{CB}$	56.5	15.1
2	**4a→3a**	$k_{-1}=k_{AC}=k_{BC}$	38.3	15.3
3	**4a→H_2O**	$k_2=k_{AD}$	180	14.4
4	H_2O→**4a**	$k_{-2}=k_{DA}$	168	14.4
5	**3b→4b**	$k_1=k_{CA}+k_{CB}$	49.7	15.1
6	**4b→3b**	$k_{-1}=k_{AC}=k_{BC}$	51.6	15.1
7	**4b→H_2O**	$k_2=k_{AD}$	168	14.4
8	H_2O→**4b**	$k_{-2}=k_{DA}$	101	14.7



Scheme 5. A plausible mechanism for the DMSO-assisted enolization of β-keto γ-sultones **3a,b**

Acknowledgements

We thank Dr. Heike Hausmann and Prof. Dr. Peter R. Schreiner (Institute of Organic Chemistry, University of Giessen, Germany) for their assistance in obtaining the EXSY NMR experimental data presented in this paper.

REFERENCES

1. *Sulfonamides* and sulfonylated derivatives as anticancer agents / Casini A., Scozzafava A., Mastrolorenzo A., Supuran C.T. // Curr. Cancer Drug Targets. – 2002. – Vol.2. – No. 1. – P.55-75.

2. *Anticancer* drug design using scaffolds of β-lactams, sulfonamides, quinoline, quinoxaline and natural products. Drugs advances in clinical trials / Balderas-Renteria I., Gonzalez-Barranco P., Garcia A., Banik B.K., Rivera G. // Curr. Med. Chem. – 2012. – Vol.19. – No. 26. – P.4377-4398.

3. *Synthesis*, tautomerism, and anticancer activity of 5,5-disubstituted 1,2-oxathiolan-4-one 2,2-dioxides / Poliudov A.O., Havryshko D.Y., Sorokin M.D., Yatsymyrskyi A.V., Virych P.A., Shishkina S.V., Fokin A.A., Omelian T.V., Kysil A.I., Milokhov D.S., Dobrydnev A.V. // J. Mol. Struct. – 2025. – Vol.1325. – Art. No. 140952.

4. *Exploring* the reactivity of 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide and their spirocyclopropyl counterpart / Poliudov A.O., Havryshko D.Y., Krasilov D.I., Sorokin M.D., Milokhov D.S., Virych P.A., Virych P.A., Omelian T.V., Kysil A.I., Dobrydnev A.V. // Tetrahedron. – 2025. – Vol.181. – Art. No. 134684.

5. *Jena N.R.* Role of different tautomers in the base-pairing abilities of some of the vital antiviral drugs used against COVID-19 // Phys. Chem. Chem. Phys. – 2020. – Vol.22. – No. 48. – P.28115-28122.

6. *Importance* of tautomerism in drugs / Bharatam P.V., Valanju O.R., Wani A.A., Dhaked D.K. // Drug Discov. Today. – 2023. – Vol.28. – No. 4. – Art. No. 103494.

7. *Quantum* simulation of preferred tautomeric state prediction / Shee Y., Yeh T.-L., Hsiao J.-Y., Yang A., Lin Y.-C., Hsieh M.-H. // Npj Quant. Inf. – 2023. – Vol.9. – No. 1. – Art. No. 102.

8. *Toullec J.* Enolisation of simple carbonyl compounds and related reactions // Adv. Phys. Org. Chem. – 1982. – Vol.18. – P.1-77.

9. *Calculating* thermodynamic stabilities of keto–enol tautomers of aldehydes, ketones, esters, and amides / Wachter N.M., Kreth E.H., D'Amelia R.P. // J. Chem. Educ. – 2024. – Vol.101. – No. 7. – P.2920-2924.

10. *Brown I.D.* Structural chemistry and solvent properties of dimethylsulfoxide // J. Solut. Chem. – 1987. – Vol.16. – No. 3. – P.205-224.

11. *Strained* cyclophane macrocycles: impact of progressive ring size reduction on synthesis and structure / Bogdan A.R., Jerome S.V., Houk K.N., James K. // J. Am. Chem. Soc. – 2012. – Vol.134. – No. 4. – P.2127-2138.

12. *Nikitin K., O'Gara R.* Mechanisms and beyond: elucidation of fluxional dynamics by exchange NMR spectroscopy // Chem. Eur. J. – 2019. – Vol.25. – No. 18. – P.4551-4589.

13. *Perrin C.L., Dwyer T.J.* Application of two-dimensional NMR to kinetics of chemical exchange // Chem. Rev. – 1990. – Vol.90. – No. 6. – P.935-967.

14. *Bain A.D.* Chemical exchange in NMR // Prog. Nucl. Magn. Reson. Spectrosc. – 2003. – Vol.43. – No. 3-4. – P.63-103.

15. *Neese F.* Software update: the ORCA program system – Version 5.0 // WIREs Comput. Mol. Sci. – 2022. – Vol.12. – No. 5. – Art. No. e1606.

Received 06.11.2025
Revised 01.12.2025
Accepted 16.03.2026
Published 28.04.2026

ДМСО-ОПОСЕРЕДКОВАНА ЕНОЛІЗАЦІЯ β-КЕТО γ-СУЛЬТОНІВ: КОМБІНОВАНЕ ДОСЛІДЖЕННЯ МЕТОДАМИ ЯМР ТА ТФГ

Д.С. Мілохов, А.В. Яцимирський, А.О. Полюдов, А.А. Фокін, О.В. Добриднєв

Розроблено економічно ефективний метод синтезу 5,5-дизаміщених 1,2-оксатіолан-4-он 2,2-діоксидів (β-кето γ-сультонів) у масштабі кількох сотень грамів без використання галогенованих органічних розчинників. β-Кето γ-сультони проявляють селективну протиракову активність і розглядаються як біоізостери тетронової кислоти і вважаються біоізостерами тетронової кислоти – перспективними фармакологічними шаблонами, що мають активні реакційні центри, що дозволяють подальшу структурну модифікацію та модуляцію біоактивності. Оскільки кето-енольна таутомерія може мати сильний вплив на біоактивність, впливаючи на зв'язування з біологічними мішенями та змінюючи фізико-хімічні властивості, кето-енольну таутомеризацію β-кето γ-сультонів в середовищі ДМСО було досліджено за допомогою EXSY (обмінної спектроскопії) ЯМР (ядерного магнітного резонансу) у поєднанні з розрахунками ТФГ (теорії функціоналу густини). Отримані експериментальні та розрахункові дані підтверджують ключову роль ДМСО в кето-енольній таутомеризації та протонному обміні в β-кето γ-сультонах. Розроблену механістичну модель можна застосовувати до інших карбонільних сполук та розчинників, а також до сполук, що сприяють їх енолізації.

Ключові слова: циклізація; сульфонати; β-кето γ-сультони; EXSY (обмінна спектроскопія); DFT-розрахунки; таутомеризація; механізм реакції

DMSO-ASSISTED ENOLIZATION OF β-KETO γ-SULTONES: A COMBINED NMR AND DFT STUDY

D.S. Milokhov [a], A.V. Yatsymyrskyi [a], A.O. Poliudov [b], A.A. Fokin [b], A.V. Dobrydnev [a, c, *]

[a] Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

[b] National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Kyiv, Ukraine

[c] Enamine Ltd., Kyiv, Ukraine

[*] e-mail: alexey.pierrot@gmail.com

A cost-effective method for the synthesis of 5,5-disubstituted 1,2-oxathiolan-4-one 2,2-dioxides (β-keto γ-sultones) on a several-hundred-gram scale without the use of halogenated organic solvents has been developed. β-Keto γ-sultones exhibit selective anticancer activity and are considered bioisosteres of tetronic acid, promising pharmacological templates that possess active reactive centers allowing further structural modification and modulation of bioactivity. Because keto-enol tautomerism can strongly impact bioactivity by influencing binding interactions with biological targets and altering physicochemical properties, the keto-enol tautomerization of β-keto γ-sultones in DMSO was studied using EXSY NMR (exchange spectroscopy) in combination with DFT (density functional theory) calculations. The obtained experimental and computational data confirm the key role of DMSO in keto-enol tautomerization and proton exchange in β-keto γ-sultones. The developed mechanistic model can be applied to other carbonyl compounds and solvents, as well as to compounds that facilitate their enolization.

Keywords: cyclization; sulfonates; β-keto γ-sultones; EXSY; DFT calculations; tautomerization; reaction mechanism.

REFERENCES

1. Casini A, Scozzafava A, Mastrolorenzo A, Supuran LT. Sulfonamides and sulfonylated derivatives as anticancer agents. *Curr Cancer Drug Targets*. 2002; 2(1): 55-75. doi: 10.2174/1568009023334060.

2. Balderas-Renteria I, Gonzalez-Barranco P, Garcia A, Banik BK, Rivera G. Anticancer drug design using scaffolds of β-lactams, sulfonamides, quinoline, quinoxaline and natural products. Drugs advances in clinical trials. *Curr Med Chem*. 2012; 19(26): 4377-4398. doi: 10.2174/092986712803251593.

3. Poliudov AO, Havryshko DY, Sorokin MD, Yatsymyrskyi AV, Virych PA, Shishkina SV, et al. Synthesis, tautomerism, and anticancer activity of 5,5-disubstituted 1,2-oxathiolan-4-one 2,2-dioxides. *J Mol Struct*. 2025; 1325: 140952. doi: 10.1016/j.molstruc.2024.140952.

4. Poliudov AO, Havryshko DY, Krasilov DI, Sorokin MD, Milokhov DS, Virych PA, et al. Exploring the reactivity of 5,5-dimethyl-1,2-oxathiolan-4-one 2,2-dioxide and their spirocyclopropyl counterpart. *Tetrahedron*. 2025; 181: 134684. doi: 10.1016/j.tet.2025.134684.

5. Jena NR. Role of different tautomers in the base-pairing abilities of some of the vital antiviral drugs used against COVID-19. *Phys Chem Chem Phys*. 2020; 22: 28115-28122. doi: 10.1039/D0CP05297C.

6. Bharatam PV, Valanju OR, Wani AA, Dhaked DK. Importance of tautomerism in drugs. *Drug Discov Today*. 2023; 28(4): 103494. doi: 10.1016/j.drudis.2023.103494.

7. Shee Y, Yeh TL, Hsiao JY, Yang A, Lin YC, Hsieh MH. Quantum simulation of preferred tautomeric state prediction. *Npj Quant Inf*. 2023; 9: 102. doi: 10.1038/s41534-023-00767-9.

8. Toullec J. Enolisation of simple carbonyl compounds and related reactions. *Adv Phys Org Chem*. 1982; 18: 1-77. doi: 10.1016/S0065-3160(08)60138-0.

9. Wachter NM, Kreth EH, D'Amelia RP. Calculating thermodynamic stabilities of keto−enol tautomers of aldehydes, ketones, esters, and amides. *J Chem Educ*. 2024; 101(7): 2920-2924. doi: 10.1021/acs.jchemed.4c00234.

10. Brown ID. Structural chemistry and solvent properties of dimethylsulfoxide. *J Solut Chem*. 1987; 16: 205-224. doi: 10.1007/BF00646987.

11. Bogdan AR, Jerome SV, Houk KN, James K. Strained cyclophane macrocycles: impact of progressive ring size reduction on synthesis and structure. *J Am Chem Soc*. 2012; 134(4): 2127-2138. doi: 10.1021/ja208503y.

12. Nikitin K, O'Gara R. Mechanisms and beyond: elucidation of fluxional dynamics by exchange NMR spectroscopy. *Chem Eur J*. 2019; 25(18): 4551-4589. doi: 10.1002/chem.201804123.

13. Perrin CL., Dwyer TJ. Application of two-dimensional NMR to kinetics of chemical exchange. *Chem Rev*. 1990; 90(6): 935-967. doi: 10.1021/cr00104a002.

14. Bain AD. Chemical exchange in NMR. *Prog Nucl Magn Reson Spectrosc*. 2003; 43: 63-103. doi: 10.1016/j.pnmrs.2003.08.001.

15. Neese F. Software update: the ORCA program system − Version 5.0. *WIREs Comput Mol Sci*. 2022; 12(5): e1606. doi: 10.1002/wcms.1606.