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Note

Topological Resonance Energies of Thienopyrimidines

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Topological resonance energies of isomeric thienopyrimidines are reported. They show all thienopyrimidines to be aromatic compounds, but thieno[3,4-d]pyrimidine to be by 20% less aromatic than thieno[2,3-d]pyrimidine and thieno[3,2-d]pyrimidine. This result is also in agreement with a simple resonance-theoretic argument according to which thieno[2,3-d]pyrimidine and thieno[3,2-d]pyrimidine should be more aromatic than thieno[3,4-d]pyrimidine because they possess two resonance structures while the latter isomer only one. The HOMO-LUMO energy separation indicates that thieno[3,4-d]pyrimidine should be more reactive than either of the two remaining isomeric thienopyrimidines. It is conjectured that, despite a relatively high aromaticity, thieno[3,4-d]pyrimidine was never isolated because it is a rather reactive compound.

In the present report the topological resonance energy (TRE) model[1] is applied to thienopyrimidines. There are three isomeric thienopyrimidines: thieno[2,3-d]pyrimidine (**1**), thieno[3,2,-d]pyrimidine (**2**) and thieno[3,4-d]pyrimidine (**3**). Their hydrogen-suppressed diagrams and the numbering of atoms are given in Figure 1.

There is a considerable contemporary interest in thienopyrimidines since they possess interesting physical, chemical and especially biological properties.[2] For example, the 2- and 4-alkyl and aryl derivatives of **1** exhibited CNS depressant activity, analgesic, antiinflammatory, antipyretic, anticholesteremic and blood-sugar lowering effects. Similarly, the 4-amino de-

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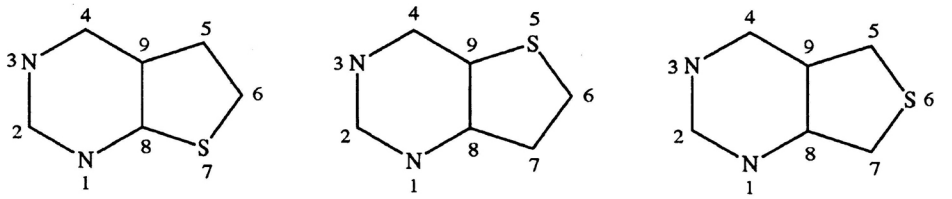

1 **2** **3**

Figure 1. Hydrogen-suppressed diagrams of thienopyrimidines.

rivatives of **2** are antimicrobial, hypoglycemic, antiviral, insecticidal and fungicidal agents and exhibit antiulcer activity, while the 4-amino derivatives of **3** possess analeptic activity.

We studied aromatic stabilities of thienopyrimidines using the TRE model, which has been shown to be quite a useful energetic criterion[3] for predicting aromaticity in various polycyclic conjugated systems[1,3,4] and especially in fullerenes.[5] The TRE values are computed using the following expression:

$$\mathrm{TRE} = \sum_{j=1}^{N} g_j \, (x_j - x_j^{ac}) \tag{1}$$

where the x_j's are solutions of the Hückel determinant corresponding to the molecular π-energy levels, x_j^{ac}'s are solutions of the matching polynomial corresponding to π-energy levels of the acyclic reference structure and g_j=0, 1 or 2, respectively, for empty, half-occupied or fully occupied π-molecular orbitals. The parameters for heteroatoms (nitrogen and sulphur) and heterobonds (carbon-nitrogen and carbon-sulphur bonds) have been taken from Hess and Schaad.[6]

In order to compare aromatic stabilities of conjugated systems of different sizes, the normalized form of the TRE, TRE per π-electron TRE/*e*, is used:[7]

$$\mathrm{TRE}/e = \mathrm{TRE}/N \tag{2}$$

where N is the total number of π-electrons in conjugated systems.

The TRE and TRE/*e* values, respectively, for three isomeric thienopyrimidines are: 0.261, 0.026 (**1**), 0.263, 0.026 (**2**) and 0.208, 0.021 (**3**). These values indicate that all three thienopyrimidines are aromatic compounds, but **3** is by 20% less aromatic than **1** or **2**. The structure of thieno[3,4-d]pyrimidine is similar to the structures of compounds collectively called orthoquinonoid compounds.[8] Perhaps, the best known among them are isobenzofuran, isoindole and isobenzothiophene. It has been found

that orthoquinonoid compounds always possess a smaller aromatic character than the corresponding fully conjugated positional isomers, but still possess substantial aromaticity.[1c,8,9]

The lower aromatic stability of **3** in comparison with the stabilities of **1** and **2** is also congruent with a simple resonance-theoretic argument: **3** possesses only one non-ionic resonance structure, while **1** and **2** possess two non-ionic resonance structures and, thus, **3** should possess a smaller resonance energy than **1** and **2**. The non-ionic resonance structures of thienopyrimidines are given in Figure 2.

If one considers benzene as the paradigmatic aromatic compound[10] (with TRE=0.276 and TRE/*e*=0.046 values), then thienopyrimidines possess only half of its aromaticity. The constituent cyclic substructures of thienopyrimidines are related to thiophene and pyrimidine. Their TRE and TRE/*e* values are similar: 0.198, 0.033 (thiophene) and 0.192, 0.032 (pyrimidine) and they are considered aromatic compounds possessing 70% of the benzene aromatic

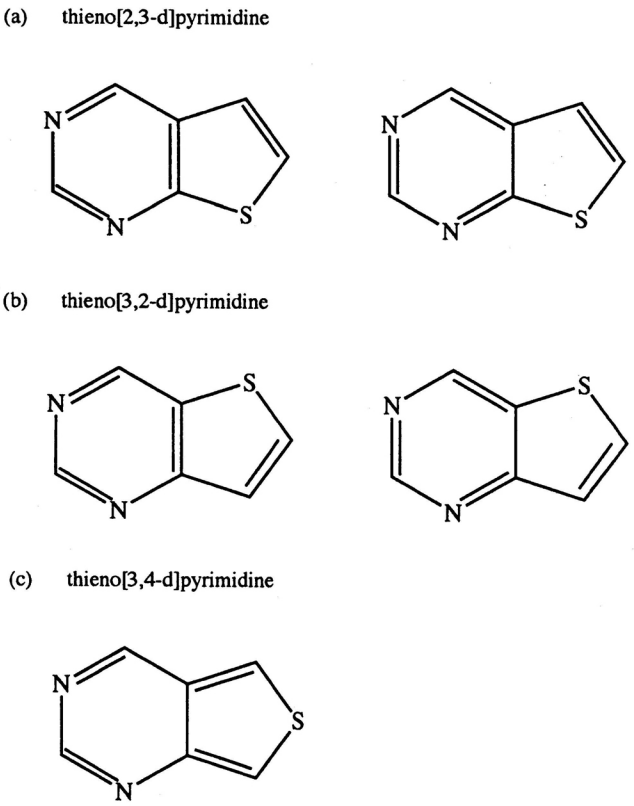

Figure 2. Non-ionic resonance structures of thienopyrimidines.

stability. The fusion of thiophene and pyrimidine results in three thienopyrimidines which are less aromatic than the constituting parts by more than 20% (**3** even by about 35%).

The difference in aromaticity between **1** and **2**, and **3** is reflected in their preparation. While isomers **1** and **2** have been known for almost thirty years, isomer **3** in the unsubstituted form has never been prepared.[2] Thieno[2,3-d]pyrimidine and its derivatives can be prepared by more than one procedure, starting either from pyrimidine derivatives or more coveniently from thiophene derivatives or from selected other compounds. Most preparative approaches to thieno[3,2-d]pyrimidine and its derivatives follow the thiophene route. Unsubstituted thieno[3,4-d]pyrimidine has never been prepared, but many of its derivatives are known. Preparation of thieno[3,4-d]pyrimidine derivatives also follows the thiophene route.

It is interesting to note that the HOMO-LUMO energy separation, which can be considered as an indication of kinetic stability of conjugated systems,[11] follows the aromatic (thermodynamic) stabilities of thienopyrimidines: 1.14 β (**1**), 1.09 β (**2**) and 0.74 β (**3**). **3** is predicted to be more reactive than either **1** or **2**. This may be the reason why the preparation of thieno[3,4-d]pyrimidine has never been successful – this particular thienopyrimidine isomer is just too reactive to be isolated.

The final point we wish to stress is as follows. The necessary prerequisites for conjugated compounds to be biologically active are a lower aromaticity than that of benzene and considerable reactivity, that is, they must be more or less reactive in order to be active in living organisms, but must be stable enough to survive for a certain period. Thienopyrimidines are such compounds: they are reasonably aromatic but also sufficiently reactive.

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SAŽETAK

Topologijske rezonancijske energije tienopirimidina

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Izračunane su topologijske rezonancijske energije tienopirimidina. One ukazuju da su sva tri izomerna tienopirimidina aromatični spojevi, ali da je tieno[3,4,-d]pirimidin za 20% manje aromatičan nego tieno[2,3-d]pirimidin i tieno[3,2-d]pirimidin. Taj je

rezultat u skladu s predviđanjem jednostavne rezonancijske teorije, jer tieno[2,3-d]pirimidin i tieno[3,2-d]pirimidin imaju dvije, a tieno[3,4-d]pirimidin samo jednu rezonancijsku strukturu. Energijska separacija HOMO-LUMO nagovješćuje da bi tieno[3,4-d]pirimidin trebao biti mnogo reaktivniji od ostala dva izomera što je u skladu i s eksperimentalnim činjenicama. Pretpostavljeno je da je razlog zašto se tieno[3,4-d]pirimidin ne može izolirati, premda je dosta aromatičan, njegova velika reaktivnost.