# On the Aromatic Stability of Positional Isomers Consisting of Bicyclic Systems Composed Entirely of Five-Membered Heterocycles*

*M. Milun** and N. Trinajstić*

*»Ruđer Bošković« Institute, P.O.B. 1016, 41000 Zagreb, Croatia, Yugoslavia*

Received June 2, 1976.

Isomeric bicyclic conjugated systems consisting entirely of five-membered heterocycles were studied using a novel aromaticity index named topological resonance energy (*TRE*). *TRE* has correctly predicted the aromatic behaviour of all the groups of isomers studied. (These isomers called positional isomers because they formally differ only by the position of σ-bivalent heteroatoms) may be classified into a particular group according their annelation mode, which closely parallels *TRE* predictions and experimental findings.

Positional isomers are structurally closely related heterocycles differing formally only by the position of the σ-bivalent heteroatoms (*e. g.*, Ö, ṄH, S̈, S̈e, *etc.*)[1]. Positional isomers have an interesting feature: their stabilities and properties are related to the position of the heteroatoms.

Hence, some of the positional isomers are expected to be stable and well defined molecules, while others, belonging to the same set of positional isomers, are not. The best known example of positional isomerism is the isomeric pair obtained by the annelation of benzene and five-membered heterocycles containing nitrogen, oxygen, or sulphur[1-3]: benzofuran-isobenzofuran, indole- -isoindole and thionaphthene-isothionaphthene.

In this paper we wish to report our studies on the positional isomers obtained by the annelation of two five-membered heterocycles each containing six π-electrons (*e. g.*, furan, pyrrole, thiophene, *etc.*). They are generated by annelation at the *a*- or *b*-sides of the five-membered ring systems. Thus, using intuitive topology reasoning[4] these molecules can be classified into three groups according the annelation mode. This is displayed in Figure 1.

In addition, the annelation may occur between the two five-membered rings, either of the same quality, (for example, between two thiophene ring systems leading to four isomeric thiophenes) or different quality (for example, between pyrrole and thiophene ring systems leading to five isomeric thieno-pyrroles; in this case there are five possible isomers, because there are two possibilities for the (1,5)-isomer depending on the placement of the N and the S

---

* Contribution No. 193 of the Laboratory of Physical Chemistry.

atoms, *i. e.* ($N_1S_5$) and ($N_5S_1$)). Hence, there are four (or five) possible isomers within each set of these bicyclic molecules: (1,6) and (1,4) belonging to a class (a,a), (1,5), /or (1,5) and (5,1)/ to a class (a,b), and finally, (2,5) belonging to a class (b,b).



ANNELATION MODE                                    POSITIONAL ISOMER

(a, a)

( 1,6 )                              ( 1, 4 )
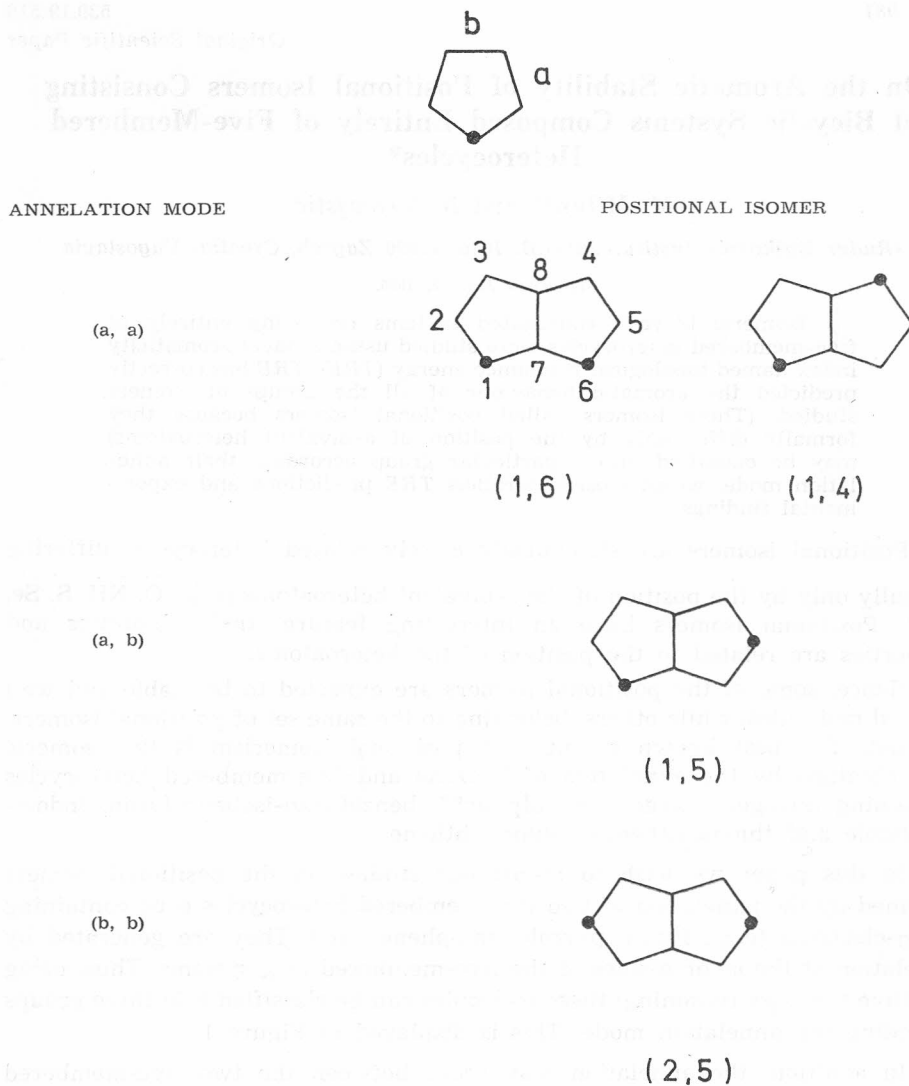
(a, b)

(1,5)

(b, b)

( 2,5 )

Figure 1. The classification scheme of bicyclic systems composed entirely of five-membered ring systems according to the annelation mode.

If we confine ourselves only to the furan, pyrrole, and thiophene ring systems there will be 27 possible combinations: 12 belonging to isomers containing the same σ-bivalent heteroatoms and 15 containing two different heteroatoms at the same time (see Figure 2.)
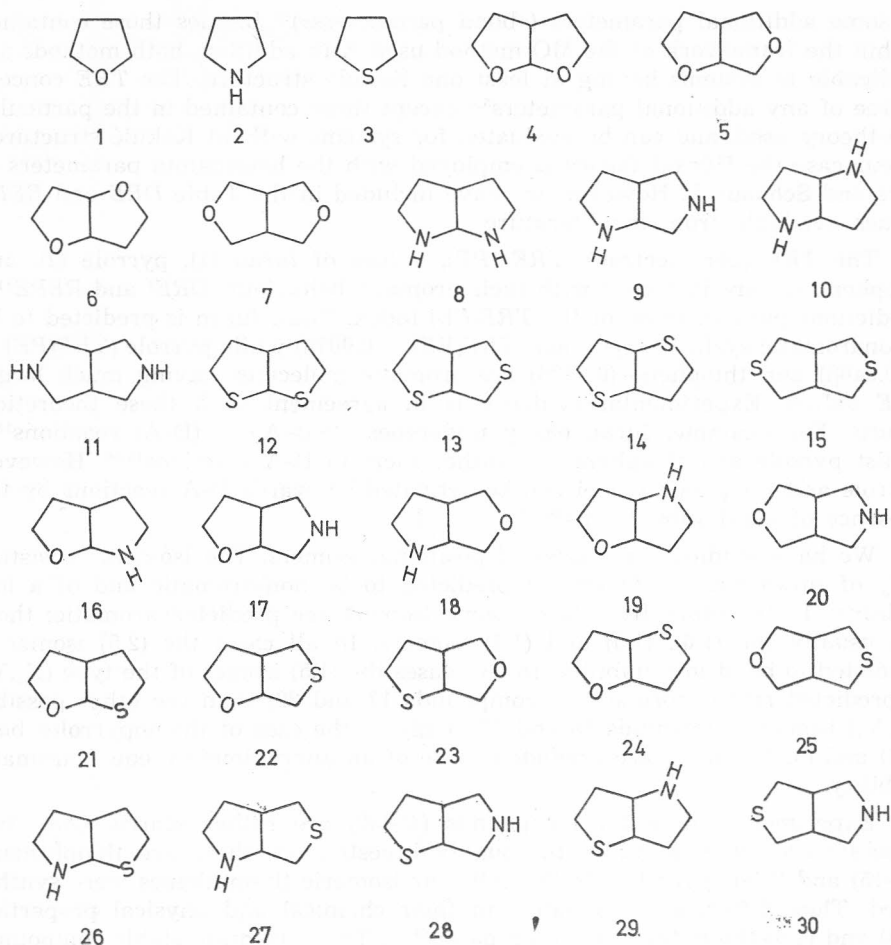
Figure. 2. List of molecules studied

We have calculated for all these molecules (including furan, pyrrole, and thiophene) the topological resonance energy[5,6], *TRE*.

*TRE* can be calculated using the following simple relation:

$$TRE = \sum_j g_j (x_j - x_j^{ac})$$

where $g_j$ is the occupancy number of the j-th molecular orbital, $x_j$'s are the roots of the characteristic polynomial, $P_{(x)}$, belonging to a cyclic molecule, and $x_j^{ac}$'s are the roots of the acyclic characteristic polynomial, $P_{(x)}^{ac}$, belonging to the same molecule. The structure of $P_{(x)}^{ac}$ is described elsewhere[5]. The *TRE* values of all the molecules studied are given in the Table.

We could, of course, employ for our purpose some other theoretical index, like the Dewar resonance energy[7], *DRE*[8], or the resonance energy per electron, *REPE*, the index of Hess and Schaad[9], but, to a certain extent they both depend

on some additional parameters (»bond parameters«)[10] besides those contained within the framework of the MO method used[7,9]. In addition, both methods are applicable to systems having at least one Kekulé structure. The *TRE* concept is free of any additional parameters[5,6] except those contained in the particular MO theory used, and can be evaluated for systems without Kekulé structures. In our case the Hückel theory is employed with the heteroatom parameters of Hess and Schaad[11,12]. However, we have included in the Table *DRE* and *REPE* values available from the literature.

The *TRE* (per electron), *TRE (PE)*, values of furan (1), pyrrole (2), and thiophene (3), are in accord with their aromatic behaviour. *DRE*[1] and *REPE*[11,12] predictions parallel those of the *TRE(PE)* index. Thus, furan is predicted to be a nonaromatic cyclic dienyl ether *(TRE(PE) = 0.007β)* while pyrrole *(TRE(PE) = = 0.040β)* and thiophene (0.033β) are aromatic molecules having much larger *TRE* values. Experimental evidence is in agreement with these theoretical results. For example, furan easily undergoes Diels-Alder (D-A) reactions[13,14] whilst pyrrole and thiophene are rather inert in D-A reactions[15,16]. However, pyrrole and thiophene nuclei can be activated[17] towards D-A reactions by the presence of alkyl substituents[18-20].

We have studied six classes of positional isomers. The isomers consisting only of furan rings (4-6) are all predicted to be non-aromatic and of a low stability. In the other five classes some isomers are predicted aromatic; these are usually the (1,6), (1,5) and (1,4) isomers. In all cases the (2,5) isomer is predicted to be of low stability. In two cases the (1,5) isomer of the type $(X_1, Y_5)$ is predicted much more stable (compounds 17 and 22) than the other possible $(X_5, Y_1)$ isomer (compounds 18 and 23). Only in the case of thienopyrroles both (1,5) and (5,1) isomers are predicted to be of an approximately equal aromatic stability.

Experimental data for compounds (4)-(30) are rather scarce. Only two classes were experimentally thoroughly investigated; these are thiophthenes (12-15) and thienopyrroles (26-30). All four isomeric thiophthenes were synthesized. They differ, as anticipated, in their chemical and physical properties. (1,4) and (1,6)-thiophthene were prepared[21-24]. They are quite stable compounds and undergo electrophilic substitution[25], (a property of classical aromatic molecules). (1,5)-thiophthene was also prepared, but it undergoes air oxidation relatively easily[26]. Note that our *TRE(PE)* index correctly differentiated between the more stable (1,4)-isomer (0.031β) and (1,6)-isomer (0.031β) and the less stable (1,5)-isomer (0.026β). However this result was also obtained by the *DRE* and *REPE* indices. The (2,5)-isomer, a non-classical thiophthene, was reported only as a transient, very reactive species[27,28]. Its *TRE(PE)* value is much lower (7-8 times) than that of three other classical thiophthenes.

Thienopyrroles (26-30) were all prepared, but the $(S_5N_1)$-isomer. The interest in the chemistry of thienopyrroles is conected with their potential physiological activity, since these compounds are isosteric with the derivatives of indole. (1,4)- and (1,6)-thienopyrroles were relatively easily synthetized[29,30], but they are air sensitive at room temperature. However, *N*-benzyl derivatives are much more stable and could be safely stored at room temperature for longer periods of time[31]. $(S_1N_5)$-thienopyrrole is less stable than the (1,4)- and (1,6)-isomers. Only the *N*-benzyl derivative was prepared[32,33], but it rapidly turned yellow standing in air, and it appears to be acid sensitive. It could be kept only at

TABLE

TRE *per Electron (in units of β) and, where available,* DRE *(in kcal/mole) and* REPE *(in units of β) Indices of the Studied Heterocycles*

| Molecule[a] | TRE per electron | DRE[b] | REPE[c] | Stability[d] | Reference to the preparative work |
|---|---|---|---|---|---|
| 1 | 0.007 | 4.3 | 0.007 | stable | e |
| 2 | 0.040 | 5.3 | 0.039 | stable | f |
| 3 | 0.033 | 6.5 | 0.032 | stable | g |
| 4 | 0.008 | | | — | — |
| 5 | 0.005 | | | — | — |
| 6 | 0.008 | | | — | — |
| 7 | 0.003 | | | — | — |
| 8 | 0.038 | | | — | — |
| 9 | 0.033 | | | — | — |
| 10 | 0.038 | | | — | — |
| 11 | 0.007 | | | — | — |
| 12 | 0.031 | 10.5 | 0.022 | stable | h, i |
| 13 | 0.026 | 9.5 | 0.015 | moderat. stable | j |
| 14 | 0.031 | 11.3 | 0.024 | stable | h, i |
| 15 | 0.004 | —33.9 | | unstable | k, l |
| 16 | 0.025 | | | — | — |
| 17 | 0.024 | | | — | — |
| 18 | 0.009 | | | — | — |
| 19 | 0.024 | | | — | — |
| 20 | 0.005 | | | — | — |
| 21 | 0.021 | | | — | — |
| 22 | 0.020 | | | — | — |
| 23 | 0.008 | | | — | — |
| 24 | 0.021 | | | — | — |
| 25 | 0.004 | | | unstable | l |
| 26 | 0.034 | 11.4 | | stable | m, n |
| 27 | 0.028 | | | — | — |
| 28 | 0.030 | 0.5 | | | o |
| 29 | 0.035 | 12.3 | | stable | r, s, t, u |
| 30 | 0.006 | —24.9 | | unstable | l |

[a] The numbers denote molecules in Figure 2.

[b] The DRE values are taken from: M. J. S. D e w a r and N. T r i n a j s t i ć, *J. Amer. Chem. Soc.* **92** (1970) 1453, *Theoret. Chim. Acta* **17** (1970) 235; L. K l a s i n c and N. T r i n a j s t i ć, *Tetrahedron* **27** (1971) 4045.

[c] The REPE values are taken from Refs. 11 and 12.

[d] The term *stability* is used in the everyday laboratory sense, *i. e. stable* denotes isolable compounds with well defined properties, *modestly stable* denotes compounds stable in solution or when isolated, they either easily undergo Diels-Alder reactions or air oxidation or have a limited life time, and *unstable* denotes reactive, transient and short lived species. The term *unknown* is used in order to indicate those compounds for which there are no records of preparation available.

[e] R. C. E l d e r f i e l d and T. D. D o d d, in: »*Heterocyclic Compounds*«, Edited by R. C. E l d e r f i e l d, Wiley, New-York 1950, Vol. 1. p. 277.

[f] A. H. C o r w i n, in: »*Heterocyclic Chemistry*«, Edited by R. C. Elderfield, Wiley, New-York 1950, p. 119.

[g] H. D. H a r t o u g h, »*Thiophene and Its Derivatives*«, Interscience, New-York 1952.

[h] Ref. 21. [i] Ref. 22. [j] Ref. 26. [k] Ref. 27. [l] Ref. 34 [m] Ref. 30.

[n] M. F o r m e r, S. S o t h and P. F u r n a r i, *C. R. Acad. Sci C* **277** (1973) 1149.

[o] Ref. 32. [p] Ref. 33.

[r] D. S. M a t t e s o n and H. R. S n y d e r, *J. Org. Chem.* **22** (1957) 1500.

[s] Ref. 29. [t] Ref. 31.

[u] S. G r o n o w i t z, and I. A n d e r, *Acta Chem. Scand.* B **29** (1957) 513.

253 K under nitrogen. (2,5)-thienopyrrole was observed only as a transient species[34]. The *TRE(PE)* and *DRE* index correctly order isomeric thienopyrroles, predicting 26 (0.034β) and 29 (0.035β) to be more stable than the non-classical isomer 30 (0.006β).

In addition, the non-classical thienofuran (25) has also been observed as an elusive species[34]; its *TRE(PE)* value (0.004β) also indicates that this molecule is considerably less stable than the other possible isomers of the thienofuran class.

Experimental data and the examination of *TRE(PE)* indices where available, indicate that, there is, in general, the following stability order among the isomers of the same class

$$(1,4) \approx (1,6) > (1,5) \gg (2,5)$$

This result parallels the annelation mode. Therefore, the annelation at the short bonds of five-membered rings in either the *trans* or *cis* position leads to stable isomers. The annelation of a short-to-long bond produces a less stable compound. Finally, the annelation at long bonds leads to non-classical structure. Hence, any set of isomers of this type should, generally, exhibit experimental behaviour in agreement with the above result. Therefore, we can safely predict that the compounds containing Se, Te, .... should also behave similarly. Classical isomeric selenophthenes are known and indeed behave in accordance with this result[35,36].

## REFERENCES

1. N. Trinajstić, *Record Chem. Progress* **32** (1971) 85.
2. R. Warrener, *J. Amer. Chem. Soc.* **93** (1971) 2346.
3. L. Klasinc, E. Pop, N. Trinajstić, and J. V. Knop, *Tetrahedron* **28** (1972) 3465.
4. B. H. Arnold, *Intuitive Concepts in Elementary Topology*, Prentice Hall, New York 1962.
5. I. Gutman, M. Milun, and N. Trinajstić, *Croat. Chem. Acta* **48** (1976) 78.
6. I. Gutman and N. Trinajstić, *Acta Chim. Hung.*, in press.
7. M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York 1969, Chapter V.
8. N. C. Baird, *J. Chem. Educ.* **48** (1971) 509.
9. B. A. Hess, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.* **93** (1971) 305.
10. M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.* **87** (1965) 692.
11. B. A. Hess, Jr., L. J. Schaad, and C. W. Holyoke, Jr., *Tetrahedron* **28** (1972) 3657; *ibid.* **28** (1972) 5299.
12. B. A. Hess, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.* **95** (1973) 3907.
13. R. B. Woodward and H. Baer, *J. Amer. Chem. Soc.* **70** (1948) 1161.
14. H. Kwart and I. Burchuk, *J. Amer. Chem. Soc.* **74** (1952) 3094.
15. P. J. Garratt, *Aromaticity*, McGraw-Hill, London 1971.
16. N. L. Allinger, M. P. Cava, D. C. De Jongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, *Organic Chem., Worth Publishers*, New York 1971.
17. M. C. Kloetzel and H. L. Herzog, *J. Amer. Chem. Soc.* **72** (1950) 1991.
18. L. Mandell and W. Blanchard, *J. Amer. Chem. Soc.* **79** (1957) 6198.
19. R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, (1962) 1148.
20. R. Helder and H. Wynberg, *Tetrahedron Lett.*, (1972) 605.
21. V. V. Ghaisas and B. D. Tilak, *Proc. Indian Acad. Sci.* **39** A (1954) 14.
22. S. Gronowitz, U. Rudè, and B. Gestblom, *Arkiv Kemi* **20** (1963) 297.
23. Ya. L. Gol'dfarb, S. Orolius, and V. P. Litvinov, *Khim. Geterotsikl. Soedin*, (1967) 935

24. V. P. L i t v i n o v, I. P. K o m y a e v a, and Ya. L. G o l' d f a r b, *Izv. Akad. Nauk. SSSR, Ser. Khim.* (1974) 1575.
25. F. C h a l l a n g e r and J. L. H o l m e s, *J. Chem. Soc.* (1953) 1837.
26. H. W y n b e r g and D. J. Z w a n e n b u r g, *Tetrahedron Lett.,* (1967) 761.
27. M. P. C a v a and N. M. P o l l a c k, *J. Amer. Chem. Soc.* **89** (1967) 3639.
28. M. P. C a v a, N. M. P o l l a c k, and D. A. R e p e l l a, *J. Amer. Chem. Soc.* **87** (1967) 3640.
29. H. R. S n y d e r, L. A. C a r p i n o, J. F. Z a c k, Jr., and J. F. M i l l s, *J. Amer. Chem. Soc.* **79** (1957) 2556.
30. R. K. O l s e n and H. R. S n y d e r, *J. Org. Chem.,* **30** (1956) 184.
31. A. D. J o s e y, R. J. T u i t e, and H. R. S n y d e r, *J. Amer. Chem. Soc.,* **82** (1960) 1597.
32. D. J. Z w a n e n b u r g, J. F e i g e n, and H. W y n b e r g, *Recueil. Trav Chim. Pays-Bas,* **86** (1967) 589.
33. J. F e i j n and H. W y n b e r g, *Recueil Trav. Chim.* Pays-Bas, **89** (1970) 639.
34. M. P. C a v a and M. V. L a h s m i k a n t h a n, *Accounts Chem. Res.* **8** (1975) 139.
35. B. T a m a m u s h i, H. A k i y a m a, and S. U m e z a w a, *Bull. Chem. Soc. Japan,* **14** (1939) 318.
36. S. U m e z a w a, *Bull. Chem. Soc., Japan,* **14** (1939) 363.

## SAŽETAK

### O aromatičkoj stabilnosti bicikličkih pozicijskih izomera sastavljenih isključivo od peteročlanih heterocikla

*M. Milun i N. Trinajstić*

S pomoću novog indeksa aromatičnosti nazvanog topološka rezonancijska energija (*TRE*) proučeni su izomerni biciklički konjugirani sustavi koji se sastoje isključivo od peteročlanih heterocikla. Ovi izomeri, nazvani pozicijski izomeri, jer se razlikuju jedino po položaju σ-bivaltentnog heteroatoma, mogu se klasificirati u nekoliko skupina, ovisno o načinu anelacije. Takvu klasifikaciju podupire indeks *TRE* i postojeći eksperimentalni rezultati.