# Computer Calculations as an Aid to Drug Design: More Stable Compounds related to Thromboxane $A_2$

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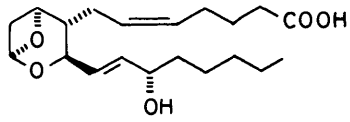
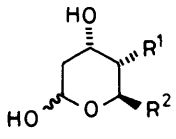
Semi-empirical SCF-MO calculations, mainly using the MNDO program, have been used to determine the smallest possible change that can be made to the bicyclic ring system of thromboxane $A_2$ in order to increase its stability. The bicyclic system 2,6-dioxabicyclo[3.1.1]heptane is predicted to be more stable with respect to its hydrolysis product when one or more oxygen atoms are replaced by sulphur, the order of stability being 2,6-dithiabicyclo[3.1.1]heptane > 2-oxa-6-thia analogue > 6-oxa-2-thia-analogue > 2,6-dioxabicyclo[3.1.1]heptane. These predictions are qualitatively in agreement with observations on the stability of synthetic monothia- and dithia-analogues of thromboxane $A_2$. The optimised geometries for these bicyclic systems imply a considerable flattening of the end of the six-membered ring that is remote from the bridge, but a consideration of n.m.r. data for a monothia-analogue suggests that the optimisation overestimated the extent of flattening of the six-membered ring.

Thromboxane $A_2$ ($TXA_2$) is a highly potent inducer of blood platelet aggregation and of the contraction of arterial smooth muscle.[1] It is a very labile compound, its half-life in aqueous medium having been estimated to be *ca.* 30 s.[1] It is hydrolysed to thromboxane $B_2$ (**1**). There is considerable interest in the synthesis of analogues and antagonists of $TXA_2$ and most synthetic approaches have been designed to produce stable compounds for example by replacing one or both of the ring oxygen atoms by methylene.[2]

The lability of $TXA_2$ is clearly due to the strained bicyclic ring system and it is proposed that computer calculations be used to find the smallest change that could be made to the bicyclic ring system that would result in an increase in stability.



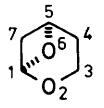
$TXA_2$



(**1**)

$R^1 = CH_2CH{=}^{Z}CH(CH_2)_3COOH$

$R^2 = CH{=}^{E}CHCH(OH)(CH_2)_4CH_3$

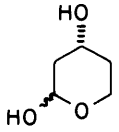


(**2**)

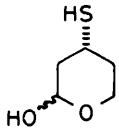
(**3**)

(**4**)

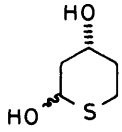
(**5**)



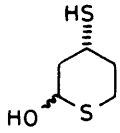
(**6**)



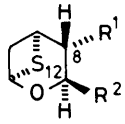
(**7**)



(**8**)

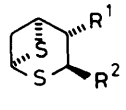


(**9**)

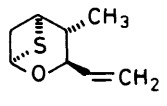


(**10**)

(methyl ester)



(**11**)



(**12**)

Results and Discussion

Chemical intuition suggested that the smallest change that could be made to the bicyclic ring system (**2**) to improve stability would be to replace one of the oxygen atoms by a sulphur atom. The 6-thia-analogue (**3**) was first studied because this atom substitution was expected to release more strain than replacing the oxygen atom of the six-membered ring.† Also the synthetic routes envisaged lead more easily to 6-thia- than to 2-thia-analogues. The 2-thia-analogue (**4**) and the 2,6-dithia-analogue (**5**) have also been studied.

Semi-empirical SCF-MO calculations have been used to calculate the enthalpy of formation of the unknown bicyclic compounds (**2**)—(**5**) and their hydrolysis products (**6**)—(**9**). Although these products would actually exist in solution as mixtures of configurational and conformational isomers the calculations were performed on the diequatorial isomers.

Since the MINDO/3 program[4] is not fully parameterised for sulphur it could only be used for the sulphur-free compounds (**2**) and (**6**). MNDO[5] was used for all eight compounds. Trial bond angles and torsion angles were measured to ±5° using molecular models and the geometry was then optimised. The enthalpies of formation and the calculated enthalpy change for hydrolysis of each bicyclic compound are shown in the Table. Although these calculations do not take into account the entropy changes and solvation energies it was hoped that in the comparison of the same reaction for the four bicyclic compounds these factors would at least partially cancel. There is a clear trend; as the oxygen atoms are replaced by sulphur the hydrolysis becomes less exothermic. Indeed the figures suggest

† The CCC bond angle in thietane is larger and closer to the tetrahedral value than it is for oxetane.[3]

**Table.** Enthalpies (kcal mol $^{-1}$) calculated using MNDO[a]

| Bicyclo[3.1.1]heptane derivative | $\Delta H$ | | Hydrolysis product $\Delta H$ | Enthalpy of hydrolysis[b] $\Delta H$ |
|---|---|---|---|---|
| 2,6-Dioxa | −62.6 (−73.7) | (6) | −148.6 (−156.4) | −18.0 (−14.7) |
| 6-Thia-2-oxa | −20.5 | (7) | −102.4 | −13.2 |
| 2-Thia-6-oxa | −21.2 | (8) | −95.0 | −5.8 |
| 2,6-Dithia | −17.0 | (9) | −49.0 | +36.4 |

[a] Figures in parentheses were calculated using MINDO/3. [b] Calculated using $\Delta H_f$ −68 for $H_2O$.

that the hydrolysis of the dithiabicyclo[3.1.1]heptane is endothermic. The MNDO program has been claimed to be superior to MINDO/3 but four-membered ring hydrocarbons were less satisfactorily handled by MNDO. It is hoped that any errors inherent in the calculations affect the enthalpies of hydrolysis to a similar extent. The *rates* of hydrolysis of the bicyclic acetals will depend on the activation energies but the enthalpies of hydrolysis would afford a guide to the effects of substitution of sulphur for oxygen on reactivity if the transition states resembled to a significant extent the hydrolysis products.

Thus it is predicted that monothia- and especially dithia-analogues of $TXA_2$ would be more stable, relative to the hydrolysis products, than $TXA_2$ itself. This prediction is supported by recent observations on synthetic analogues. After these calculations had been completed, Ohuchida *et al.*[6] reported the synthesis of the monothia-analogue (**10**) of $TXA_2$. This compound (**10**) was very sensitive to acid and attempts to hydrolyse the methyl ester under basic conditions resulted in opening of the thietane ring. The synthesis of the dithia-analogue (**11**) of $TXA_2$ was also reported by the same laboratory.[7] Although the free acid was not very stable the sodium salt was stable and was formed in high yield (>90%) from the methyl ester by alkaline hydrolysis. These qualitative observations thus support the above prediction that replacing one and especially two of the oxygen atoms in the bicyclic system of $TXA_2$ would increase its stability.

The optimised geometry for these bicyclic compounds is also of interest since synthetic analogues of antagonists of $TXA_2$ may need to resemble the shape of the $TXA_2$ bicyclic ring system to produce optimum biological activity. It was observed that in the optimisation of the geometry of 2,6-dioxabicyclo-[3.1.1]heptane the last 13 kcal mol$^{-1}$ of energy was gained at the expense of a flattening of the six-membered ring, the torsion angle C(5)C(4)C(3)O(2) being decreased from −42.6 to −4.1°. The optimised conformation was thus derived from the original chair by a flattening of the end remote from the four-membered ring. A similar flattening of the chair occurred during the optimisation of the monothia- and dithia-analogues. The optimised bond lengths and angles are reported in Supplementary Publication No. SUP 23934 (6 pp.).* The optimised conformation may be compared with that deduced from proton coupling constants, the key coupling constant, $J_{8,12}$ 8 Hz, having been reported[6] for the monothia-analogue (**10**) of $TXA_2$. To calculate the dihedral angle for these protons use was made of the modified Karplus equation of Haasnoot *et al.*[8] This equation includes a correction for the electronegativity and orientation of substituents. With Huggin's electronegativity values a coupling constant of 8 Hz corresponds to a dihedral angle (defined as in ref. 8) of −146°. This angle is −180 and −120° in a perfect chair and a flattened chair, respectively. This implies that the six-membered ring has a conformation which is less flattened than is implied by the MNDO optimisation. Since the thia-analogue (**10**) has on the six-membered ring neighbouring alkyl substituents which might influence the extent of flattening of the ring MNDO calculations were applied to the unknown compound (**12**) which is a better model for (**10**). However, the optimised conformation had very similar torsion angles to those for the unsubstituted compound. For example, the torsion angle C(5)C(4)C(3)O(2) was 2.6°. Thus it appears that the MNDO program, like MINDO/3, underestimates eclipsing interactions and overestimates the flattening of rings.[5b]

* For details of Supplementary Publications see Instructions for Authors (1984),. *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

## Acknowledgements

I am indebted to Dr. T. W. Bentley for introducing me to MINDO/3 and MNDO, to Dr. G. L. Reed, Brunel University, and Mr. D. Evans, Swansea, for assistance with the use of computer facilities, and to Mr. M. J. Williams for a user-friendly microcomputer program.

## References

1 M. Hamberg, J. Svensson, and B. Samuelson, *Proc. Natl. Acad. Sci. U.S.A.*, 1975, **72**, 2994.
2 R. J. K. Taylor in 'Prostaglandins and Thromboxanes', eds. R. F. Newton and S. M. Roberts, Butterworth, Sevenoaks, 1982, p. 132.
3 R. Livingstone in 'Rodd's Chemistry of Carbon Compounds', ed. S. Coffey, Elsevier, Amsterdam 1973, 2nd. edn., vol. IV A, p. 2.
4 R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 1975, **97**, 1285, 1294, 1302, 1307, 1311.
5 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, (*a*) 4899; (*b*) 4907.
6 S. Ohuchida, N. Hamanaka, S. Hashimoto, and M. Hayashi, *Tetrahedron Lett.*, 1982, **23**, 2883.
7 S. Ohuchida, N. Hamanaka, and M. Hayashi, *J. Am. Chem. Soc.*, 1981, **103**, 4597.
8 C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

*Received 7th December* 1983; *Paper* 3/2161