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BICYCLO[5.3.1]UNDEC-1(10)-ENE BRIDGEHEAD OLEFIN STABILITY AND THE TAXANE BRIDGEHEAD OLEFIN

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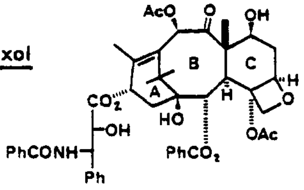
Abstract: MM2 calculations have shown how substituent and conformational effects play a role in the stabilities of systems containing the bicyclo[5.3.1]undec-I(10)-ene moiety and that the taxane diterpene skeleton which possesses this structural feature is surprisingly stable.

Considerable attention, both computational[1,2] and experimental,[3] has been given to bridgehead olefin systems recently. Our interest in the bicyclo[5.3.1]undec-1(10)-ene system stems from our synthetic work[4] directed toward the taxane diterpenes,[5] exemplified by taxol,[6] which uniquely possess this sub-structure among natural substances. Although this appears to be the smallest known naturally occurring bridgehead olefin moiety, information available from degradative work[7] suggests that the taxane A ring olefin might be extraordinarily stable, at least in a kinetic sense. As this situation could have considerable significance for the developing synthetic work in this area,[4,8] we were interested in quantitatively assessing the matter and in determining the effects of the geminal methyl substituents and the conformational restrictions imposed by the complete taxane skeleton on the strain of such a bridgehead olefin. Semi-empirical molecular mechanics calculations[9] are ideally suited for this problem. We outline here our computational results which reveal subtle influences on the stability of the bicyclo[5.3.1]undec-1(10)-ene system in variously substituted forms, and which indicate the taxane bridgehead olefin system to be remarkably unstrained.

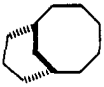
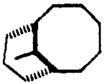
Taxol

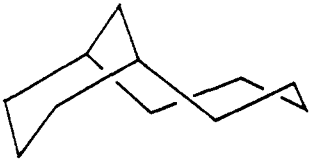


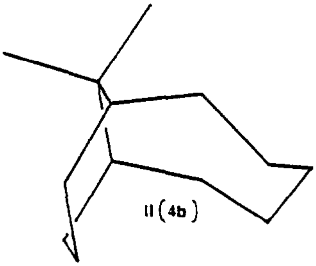
Listed in Table 1 are the energy parameters[10] for a series of bicyclo[5.3.1]undec-1(10)-enes possessing varying substitution by methyl groups on C11 together with their saturated counterparts. Values were calculated using the MM2 force field.[11] The conformations of the saturated structures are profoundly affected by the presence of the methyl groups and their stereochemistry. Hydrocarbons 1b and 3b possess unexceptional boat-chair-containing cyclooctane rings (as in I) but 2b and 4b adopt chair-chair cyclooctanes (as in II), presumably to minimize trans-annular nonbonded interactions across the eight-membered rings. This is only partially successful since the strain energies (S.E.) of the saturated structures bearing methyls syn to the larger bridge are the highest in the series. The OS values[2] (S.E. of olefin in lowest energy conformation - S.E. of alkane in lowest energy conformation) listed verify the marginally strained nature of the bridgehead olefins which possess conformations like III. In looking at the sequential introduction of methyl groups into 1a-4a, the methyl which causes the greatest increase in strain energy is the one syn to the five carbon bridge. Again, this methyl is involved in the most severe van der Waals interactions.

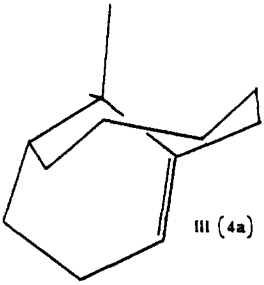
In Table 2 is listed the energy data for the structures more closely related to the taxanes.

Table 1 (kcal/mol)

	ΔH_f^0	S.E.		ΔH_f^0	S.E.	O.S.
 1a	−8.69	20.03	 1b	−35.40	18.93	1.1
 2a	−8.34	27.79	 2b	−34.68	27.06	0.7
 3a	−14.43	21.70	 3b	−40.06	21.67	0.0
 4a	−12.06	32.45	 4b	−39.04	31.08	1.4


I (1b)

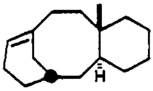
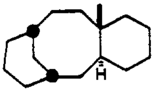
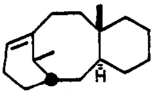
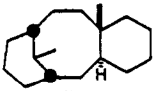
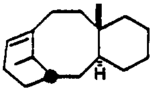
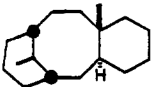
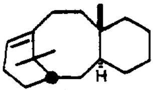
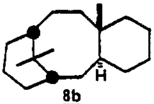

II (4b)

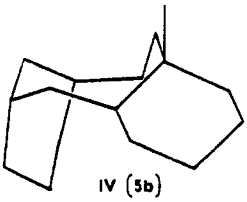

III (4a)

Here too, the saturated series is marked by two fundamentally different lowest energy conformations: hydrocarbons 5b and 7b possess conformations like IV while 6b and 8b adopt chair-chair-containing conformations like V. The olefins in this series possess taxane-related conformations like VI[12] which are clearly different from those of the 1a-4a series. Thus the C ring determines the gross conformation of the bicyclo[5.3.1]undeca(e)ne moiety in these structures and appears to impose on them conformations of higher overall strain energy than in the 1-4 series. Again, in both the saturated and olefinic series the methyl substituent which is involved in the more severe repulsive interactions is the one over the eight-membered ring. This is somewhat surprising since the A ring clearly would like to adopt a boat conformation (it does so in 5a) and thus should suffer stem/stern interactions involving its syn methyl. Indeed, in 8a the A ring is highly flattened. However, trans-annular interactions across the B ring obviously play the dominant role. Finally, the most striking result depicted in Table 2 is that all of the olefins closely related to the taxane skeleton possess negative OS values and are therefore hyperstable.[2] Evident here is the subtle effect that the C ring has on the stability of the A ring bridgehead olefin, dictating more highly strained conformations for both the saturated and unsaturated systems but reversing their relative stability.

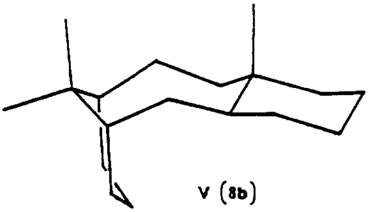
While the OS values measure the ability of the intact skeleton to accomodate bridgehead unsaturation, we were also interested in whether or not the generally higher strain associated with

Table 2 (kcal/mol)

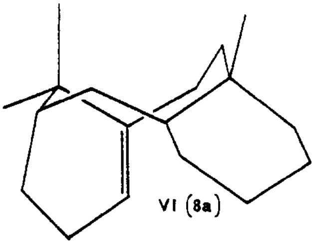
	ΔH_f^0	S.E.		ΔH_f^0	S.E.	O.S.
 5a	−23.40	30.14	 5b	−46.05	33.09	−3.0
 6a	−24.76	36.18	 6b	−47.40	39.14	−3.0
 7a	−28.19	32.75	 7b	−50.67	35.88	−3.1
 8a	−27.11	42.21	 8b	−51.20	43.72	−1.5



IV (5b)



V (8b)



VI (8a)

the geminally methylated systems might be substantially relieved upon scission of a carbon-carbon bond. The hypothetical processes of greatest significance to our ring A annulative approach to the taxanes are shown in the Scheme. Thus while it is true that strain is relieved upon breaking an A ring bond, it is not an excessive[13] fraction of the total strain inherent in 8a; wrapping the A ring carbons around the geminally substituted carbon does not greatly increase repulsive nonbonded interactions. Note that this observation is consistent with those above that the methyl syn to the larger bridge is involved in more severe van der Waals interactions than its geminal partner.

In conclusion, we have shown how the stabilities of systems containing the bicyclo[5.3.1]undec-1(10)-ene sub-structure are affected by substitution in the vicinity of the double bond and by varying conformation. Of specific importance to taxane diterpene synthesis is the demonstration by two different criteria that the taxane A ring is surprisingly unstrained despite the steric bulk of the geminally methylated ring carbon. We expect our approach to the synthesis of the taxanes to experimentally test many aspects of this computational analysis.

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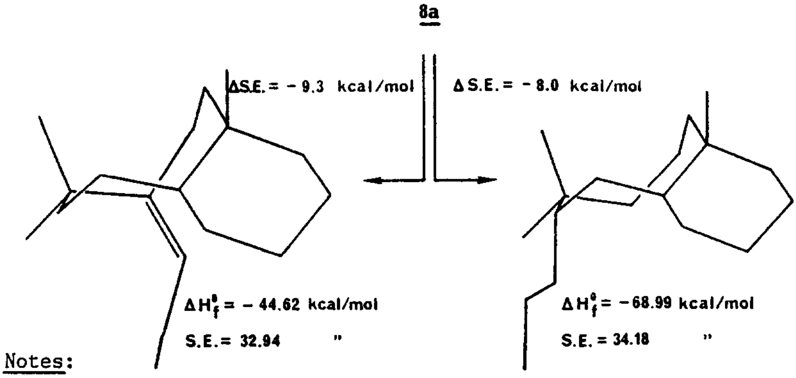
Scheme



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7. For example, the A ring is stable to base-induced retro-aldolization in taxicin I derivatives (Harrison, J.W.; Scrowston, R.M.; Lythgoe, B. J. Chem. Soc. (C) 1966, 1933.), hydrogenates less readily than a phenyl ring (Baxter, J.N.; Lythgoe, B.; Scales, B.; Scrowston, R.M.; Trippett, S. J. Chem. Soc. 1962, 2964.), and is less reactive toward epoxidation than a less substituted olefin (Dello Casa de Marcano, D.P.; Halsall, T.G. J. Chem. Soc., Chem. Comm. 1970, 1381.).
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13. To put these numbers in perspective, the relief of strain involved in converting cyclopentane to n-pentane is -6.7 kcal/mol, in converting cycloheptane to n-heptane is -7.3 kcal/mol, and in converting cyclooctane to n-octane is -10.7 kcal/mol.[9]

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