Enantiospecific Synthesis with Amino Acids. Part 2. α-Alkylation of Tryptophan: A Chemical and Computational Investigation of Cyclic Tryptophan Tautomers‡

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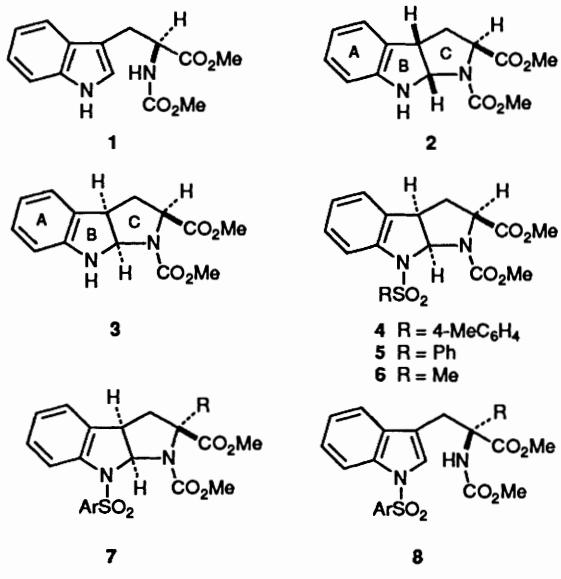
The tautomerisation of various α-substituted tryptamine and tryptophan carbamates in trifluoroacetic acid/chloroform to the corresponding hexahydropyrrolo[2,3-*b*]indoles is studied by ^{1}H NMR spectroscopy and force field calculations in an attempt to understand the thermodynamic preference of substituents at C-2 in the latter system for the *endo*-face. The calculations agree with experiment as to the thermodynamic nature of the selectivities observed, but fail to predict accurately the equilibrium ratios. It is concluded that the ratios are affected by factors not taken into account in the calculation and it is suggested that these factors may be entropic resulting from differential solvation of the *endo* and *exo* substituted systems.

N_b-Methoxycarbonyl-L-tryptophan methyl ester **1** dissolves in 85% phosphoric acid or in trifluoroacetic acid with formation of its diastereoisomeric cyclic tautomers **2** and **3**.[1] At equilibrium, at room temperature, the isomer **3** with the 2-methoxycarbonyl group *endo* to the bicyclic system predominates significantly with the exact ratio of **2**:**3** being dependent on the acid used. After work-up, sulfonylation enables isolation of the sulfonamido derivatives **4** and **5**, as single diastereoisomers, in upwards of 80% yield.[2] Significantly, under the typical work-up and sulfonylation conditions, the minor, less stable diastereoisomer **2** reverts to the ring-open form **1**, ensuring that **4**/**5** are isolated as pure diastereoisomers. This ease of preparation and isolation of pure **4**, and particularly the more highly crystalline **5**, is crucial to the success of a method developed in this laboratory for the preparation of enantiomerically pure α-alkylated derivatives of tryptophan in which **4** or **5** are deprotonated with lithium diisopropylamide and the resulting enolates quenched with standard alkyl halides to give the alkylated derivatives **7** with essentially complete retention of configuration.[2] Treatment with trifluoroacetic acid of the alkylated sulfonamides then brings about ring opening to **8** which are deprotected to simple α-alkyltryptophan derivatives of considerable interest to the pharmaceutical industry.[3] More recently we have extended this method to encompass the preparation of α-alkylated aspartic acid derivatives.[4] The present study was inspired by a desire to understand the fundamental reasons underlying the inherent stability of **3** as compared to **2** and, more pragmatically, by the wish to design conditions under which **2**, or a related substance, would be the predominant, and isolable, tautomer.



Results and Discussion

Vigorous stirring of a suspension of **1** in 85% phosphoric acid at room temperature leads after several hours to a clear viscous solution which on addition to aqueous sodium carbonate followed by extraction into dichloromethane yields **3**, contaminated with approximately 10% of **1**. Sulfonylation of this mixture with 4-toluenesulfonyl chloride or benezenesulfonyl chloride in pyridine at room temperature provides, in high overall yield, the sulfonamides **4** and **5** respectively.[1,2] The absolute configuration of **3** was confirmed by Hino[1] by reconversion to a known L-tryptophan derivative. The relative configuration of **3**, **4** and **5** with the *endo*-2-methoxycarbonyl group, inferred by Hino[1] from comparison of ^{1}H NMR chemical shifts with the related compound **9** whose structure had been determined crystallographically,[5] is readily deduced by careful inspection of the ^{1}H NMR spectra. These assignments have been confirmed crystallographically[6] on the methansulfonamide **6**.[2] The precise solution conformation of these substances is also available from detailed analysis of the ^{1}H NMR spectra. The relevant features of the ^{1}H NMR spectrum of **5** (or **4**) in deuteriochloroform are the chemical shift of the 2-methoxycarbonyl O*Me* group (δ 3.10) indicative of its shielding by the aromatic moiety of the hexahydropyrroloindole system and the ^3J coupling constants within the H-2, H-3*endo*, H-3*exo* and H-3a spin system. Specifically, H-2 (δ 4.59) is a clean doublet with J_{2-3exo} = 8.8 Hz; H-3*exo* (δ 2.45) is a ddd; H-3*endo* (δ 2.58) is a clean geminal doublet with J_{gem} = 13.06 Hz and H-3a (δ 3.66) is a triplet with $J_{3a-3exo} = J_{3a-8a}$ = 6.70 Hz. The absence of coupling between H-2 and H-3*endo*, and H-

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‡ Part 1: G. T. Bourne, D. Crich, J. W. Davies and D. C. Horwell, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1693.

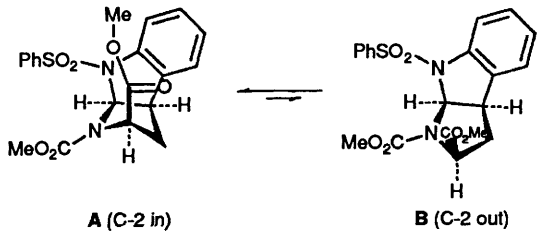
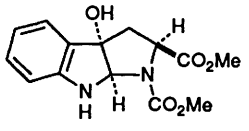


Fig. 1 Conformation of sulfonamide **5**

3*endo* and H-3a leads to the conclusion that the torsion angles (H-2)-C–C-(H-3*endo*) and (H-3*endo*)-C–C-(H-3a) are approximately 90°. The only valid interpretation of this data has the terminal five-membered ring, which we designate the C-ring, with C-3 puckered away from the *endo*-face and the C-2 methoxycarbonyl group *endo* and projected firmly in towards the concave surface as opposed to the alternative conformation with C-3 puckered in towards the concave surface but with the plane of the C-2–methoxycarbonyl bond approximately orthogonal to the plane of the aromatic ring (Fig. 1). Detailed analysis of the ^{1}H NMR spectrum of **3** is more complex owing to the existence of rotamers about the N–CO_2Me bond, nevertheless the gross features are the same with the upfield nature of the methyl ester signal apparent for both rotamers (δ C–CO_2*Me* 3.13 and 3.16). This conformation is also apparent in the crystal structure of **9** (and of **6**[6]) where the torsion angle for (N-1)-C–C-(C-3a)* is given as 33.0° which, assuming C-2 and C-3 to be perfectly tetrahedral, leads to a torsion angle for (H-2)-C–C-(H-3*endo*) of 87.0°. Similarly the torsion angle for (HO-3a)-C–C-(H-3*endo*) in **9** can be calculated to be 87.3° from the data given in the literature.



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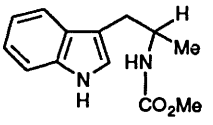
On the basis of the above observations we formulated a working hypothesis in which **3** was stabilised, *via à vis* **2**, by a non-bonding secondary orbital interaction, possibly of the π-stacking type, between the ester moiety on the *endo*-face and the aromatic ring of the pyrroloindole. This hypothesis was readily tested, and invalidated. Reaction of commercial racemic α-methyl tryptamine with methyl chloroformate gave the carbamate **10** quantitatively. This carbamate was dissolved at room temperature (297 K) in a 3:1 mixture of trifluoroacetic acid and deuteriochloroform and the system monitored by ^{1}H NMR spectroscopy. After 10 min all of the substrate had been converted to the cyclic tautomers **11** and **12** in the ratio 3.25:1. After 24 h the ratio of **11** to **12** was essentially unchanged at 3.30:1 and we conclude that this is the equilibrium ratio under these conditions. The relative configurations of **11** and **12** were readily assigned from the spectra. The major isomer **11** had δ 0.81 for the C-2 Me doublet on the concave face of the molecule shielded by the aromatic ring current, whilst the minor isomer **12** had a more normal δ 1.39 for the corresponding doublet. Under identical conditions **1** was cyclised to an equilibrium mixture of 6.2:1 in favour of **3**. In a preparative scale reaction **10** was dissolved in 85% phosphoric acid in the usual manner: standard work-up and subsequent sulfonylation with benzenesulfonyl chloride in pyridine gave, in direct analogy to the conversion of **1** to **5**, a mixture of sulfonamide **13** and recovered **10** but none of the diastereoisomeric sulfonamide **14**, reflecting the instability of the latter under the workup/sulfonylation conditions. It was not possible from the mixture of **11** and **12** in trifluoroacetic acid to assign the complete spectra unambiguously. However the obtainment of a pure sample of the sulfonamide **13** enabled complete assignment of its spectrum. Salient features of the ^{1}H NMR spectrum of **13** are the chemical shifts of the C-2 proton and methyl group at δ 4.15 and 0.71 respectively and the absence of ^3J coupling of both H-2, and H-3a with H-3*endo*: evidently this compound, and presumably **11**, adopt a conformation similar to that of **5**.

The stability of **11**, relative to **12**, clearly indicates that the stability of **3**, relative to **2**, is not primarily due to any non-bonding interaction between the ester and the aromatic ring, although a contribution from such an interaction to the total stabilisation of **3** cannot be categorically ruled out. The same experiment also eliminates any hypothesis in which **3** is stabilised *vis à vis* **2**, either under acidic or neutral conditions, by a hydrogen bond between the N-8 proton and the *endo*-methoxycarbonyl group.



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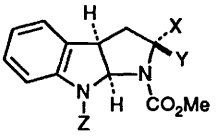


11 X = H, Y = Me, Z = H
12 X = Me, Y = Z = H
13 X = H, Y = Me, Z = $PhSO_2$
14 X = Me, Y = H, Z = $PhSO_2$

In view of the interesting, and unexpected, result observed on treatment of **10** with trifluoroacetic acid, we determined to examine the tautomerisation of the α-alkylated tryptophan derivatives **15**, **16** and **17** under the same conditions in order to compare directly the effect of alkyl and methoxycarbonyl groups on the position of the tautomeric equilibrium. All three compounds were prepared by our standard method of alkylation of the lithium enolate of **5**, followed by ring opening with trifluoroacetic acid and desulfonylation with sodium in liquid ammonia. The results of the ring closure experiments are summarised in Table 2. The major difference is between the α-methyl derivative **15**, which undergoes ring closure to an equilibrium ratio of 1.42:1 in favour of the *endo*-methoxycarbonyl compound **18** over its tautomer **21**, and the α-ethyl and isopropyl derivatives **16** and **17**, both of which lead, within the limits of experimental error, to the ring-closed tautomers in which the *endo*-isomer (**19** and **20**) is favoured over the *exo*-isomer (**22** and **23**) by the more substantial ratio of 3.76:1. The pertinent, and diagnostic, chemical shift data collected in Table 1 leave no room for doubt as to the assignment of relative configuration within the various pairs of isomers. The most obvious difference between the ^{1}H NMR spectra of **3**, **18**, **19** and **20** as recorded in Table 1 for solutions in 3:1 TFA/$CDCl_3$ compared to the spectra of **3** and related substances **4** and **5** taken in neat $CDCl_3$ is the change in chemical shift of the 2-CO_2*Me* group from δ 3.00–3.05 to δ 3.45–3.52. These chemical shifts are still significantly upfield from those of the corresponding *exo*-methoxycarbonyl derivatives under the same conditions (Table 1) and indicate shielding by the aromatic ring current. The difference between the neat $CDCl_3$ and the 3:1 TFA/$CDCl_3$ spectra is indicative of the protonated nature of the various systems under the later conditions. Evidently a methyl group competes effectively with the CO_2Me for the *endo*-position but the ethyl and isopropyl groups do so to a lesser extent. We attribute the increased preference for the

* The numbering scheme employed here corresponds to that used by Chemical Abstracts for pyrrolo[2,3-*b*]indoles.

Table 1 Pertinent chemical shift data for ring closures in $CDCl_3$/TFA (3:1)

Compound	Ester CO_2Me	H-8a	H-3a	Others
2	3.95	6.40	4.55	—
3	3.45	6.45	4.55	H-3 (*endo* and *exo*) 2.75 and 3.00
11	—	6.02	4.2	2-Me 0.81
12	—	5.97	4.2	2-Me 1.39
18	3.50	6.45	4.40	2-Me 1.80; H-3*exo* 2.70; H-3*endo* 2.80
21	3.90	6.39	4.40	2-Me 1.55; H-3 (*endo* and *exo*) 2.40 and 2.95
19	3.52	6.47	4.43	2-CH_2CH_3 1.03
22	3.95	6.43	4.43	2-CH_2CH_3 0.78
20	3.41	6.41	4.43	H-3 (*endo* and *exo*) 2.8; $CHMe_2$ 1.15 and 0.99
23	3.95	6.41	4.43	$CHMe_2$ 1.10 and 0.78

Table 2 Equilibrium ratios for ring closure in $CDCl_3$/TFA (1:3) at room temperature

Entry	Compounds	Ratio
1	**2/3**	1/6.25
2	**11/12**	3.25/1
3	**18/21**	1.42/1
4	**19/22**	3.76/1
5	**20/23**	3.79/1

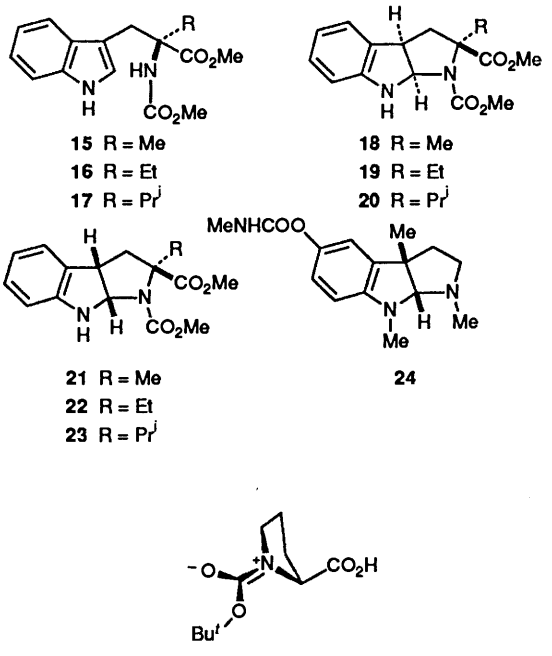


Fig. 2 Solid state conformation of *N-tert*-butyloxycarbonylproline adapted from ref. 7

methoxycarbonyl *endo* system in the pairs **19/22**, and **20/23** with respect to the pair **18/21** to a new destabilising interaction in **22** and **23** in which the larger alkyl group is forced into close proximity with, and is repelled by, the *endo* surface of the aromatic ring.

The X-ray crystal structure of *N-tert*-butyloxycarbonylproline (Fig. 2) reveals that, like **3**, **4**, **5**, **6** and **9**, it too adopts a conformation in which the CO_2H group is approximately perpendicular to the plane defined by the *N*-CO_2Bu^t group and the α-carbon.[7] If the carbamate group is more accurately represented as N(1)=C(O^-)OBu^t, it is evident that this conformational preference is the result of minimisation of $A^{1,3}$ (allylic) strain.[8] Evidently, the preference of the various *endo*-substituted pyrroloindoles described here for the conformation with C-2 puckered in rather than out can be attributed to a similar minimisation of $A^{1,3}$ strain about the N(1)$^+$=C(O^-)-OMe bond. The same argument *cannot* be used to explain the

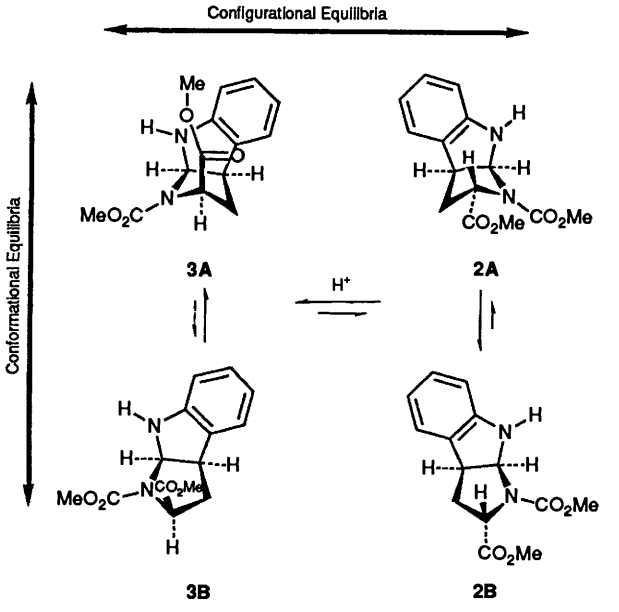


Fig. 3 Configurational and conformational equilibria of **2** and **3**

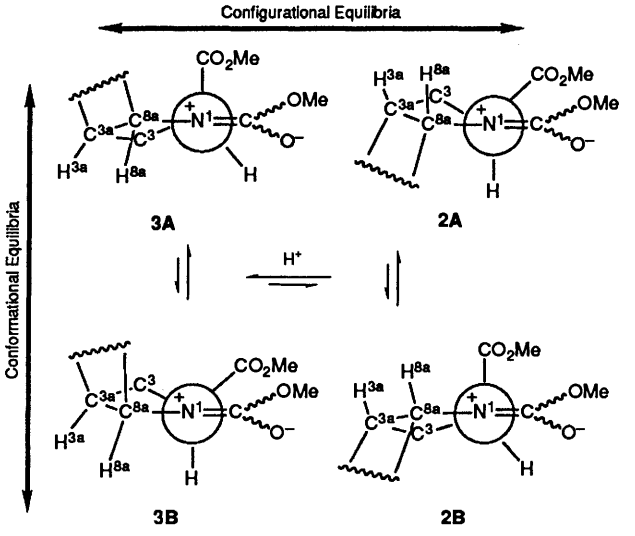


Fig. 4 Configurational and conformational equilibria of **2** and **3**: Newman projections along the N-1 to C-2 bond

thermodynamic preference for the formation of the *endo* over the *exo* substituted products. This is evident from consideration of the graphic representation (Fig. 3) or the Newman projection formulae (Fig. 4) of the various configurations (*endo* and *exo*) and their extreme conformations (C-2 in and out) available to **2** and **3**. Thus, whilst it is clear that $A^{1,3}$ strain is minimised in

3A, the experimentally observed conformation, it is also clear that such would be the case for **2B** with its CO_2Me *exo* configuration and C-2 out conformation. Furthermore, inspection of the X-ray crystal structure[9] of the calabar bean alkaloid physostigmine **24** reveals that it too adopts a conformation, closely related to that found for **5** and **9**, in which C-2 is puckered in towards the *endo* surface of the molecule. Physostigmine does not have an sp^2 centre in its terminal heterocyclic ring and as such the observed conformation of that ring cannot be the result of minimisation of allylic strain. The small differences in torsion angles between **9** and **24**, evidently result from the replacement of an sp^2 by an sp^3 centre.

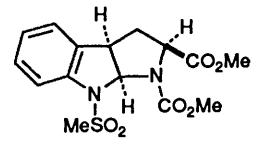
Finally we turned to force field calculations for guidance. In this endeavour we employed the COSMIC framework.[10] A simple protocol was adopted in which various structures were constructed and minimised using the COSMIC 2D-builder and molecular mechanics algorithm with partial charges generated by the semi-empirical molecular orbital program MOPAC (see Experimental section).[11]

The results for the various diastereoisomeric pairs calculated are outlined in Table 3. For each pair, calculation (Table 3) and experiment (Table 2) are in agreement on the relative stabilities of the diastereoisomers, if not on the exact degree. Thus, COSMIC's force field finds that **3** is of lower energy than **2**; **11** lower than **12**, although only slightly; and **20** lower than **23**. The breakdown of total energy into its constituent terms (Table 3) is especially revealing. For the two pairs **2** and **3**, and **20** and **23** the bond, angle and torsion components differ little. The most significant difference being found in the Van der Waals term. For the pair **11** and **12** both the torsion term and the coulombic term are *greater* for **11**. Individually they are barely significant, but in conjunction they have the effect of lowering the total energy difference between **11** and **12**. However, **11** is still favoured over **12** in the significant Van der Waals term.

We have also computed the alternative extreme conformations for the tautomers **2** and **3** in which C-2 is puckered away from the *endo*-surface of the molecule. The two extreme structures (C-2 *endo* and *exo* puckered) for both **2** and **3** are depicted in Figs. 5–8, the calculations summarised in Table 4, and the torsion angles about the C-ring in Table 5. For the endo isomer **3**, the conformation in which C-2 is puckered in towards the *endo* surface is clearly of lower energy (Table 4, entries 3 and 4). On the other hand, for the *exo*-isomer **2**, the conformation with C-2 puckered out from the *endo* surface is found to be of lower energy (Table 4, entries 1 and 2). If the coulombic term * is excluded from the calculation a different picture results for the total energy of the various conformations (Table 4, final column) in which for both **2** and **3** the lower energy conformations are those with C-2 puckered in towards the *endo*-surface of the molecule. Thus, the most significant comparison is that between the lowest energy conformations of **2** and **3** in their C-2 *endo* puckered forms. The total energy difference, with the coulombic term excluded, is found to be 2.76 kcal mol^{-1} in favour of **3** (Table 4, entries 1 and 3, last column) representing an equilibrium ratio of 107:1 in favour of **3** over **2** at 298 K.† When the coulombic term is included the total energy difference is found to be only 0.31 kcal mol^{-1} in favour of **3** (Table 4, entries 2 and 3, penultimate column) representing an equilibrium ratio of 1.69:1 at 298 K. Clearly these energy differences err significantly on either side of the experimentally derived value of 1.08 k cal mol^{-1} in 3:1 TFA/$CDCl_3$ (ratio **3**:**2** = 6.25:1 at room temperature) indicating that the experimental ratio is further influenced by factors not taken into account in the calculation. At this stage the most reasonable factor appears to be the increased entropy on formation of **3** owing to desolvation of the *endo* face of the molecule or perhaps, as suggested by a referee, differential solvation of **2** and **3** by the polar solvent.

Examination of Table 5 reveals that, of both possible conformations of both **2** and **3**, only that with the C-2 substituent on the *endo* face and with C-2 puckered in towards the *endo* face (entry 1) has the torsion angles (H-2)-C–C-(H-3*endo*) and (H-3*endo*)-C–C-(H-3a) close to 90° as found experimentally in the derived sulfonamide **5**. The calculated conformations of **2** (C-2 *endo* and *exo*) and of **3** (C-2 *endo* and *exo*) are depicted in the stereoviews of Figs. 4–7 respectively.

For the sake of completeness we have also analysed the two diastereoisomeric hypothetical methanesulfonamides **25** and **26** which correspond to **5** and its diastereoisomer. The main contributing factor to the total energy difference is again the difference in Van der Waals energy. The gas phase conformations of **25** and **26** are depicted in Figs. 9 and 10. The conformation of the C-ring with C-2 folded in toward the *endo* surface, whether the substituent is *exo* or *endo*, is particularly noteworthy. The calculated conformation of **25** corresponds to that observed in solution for **5**, depicted as **A** in Fig. 1, to the solid state conformation of a derivative (**27**[12]) of **5**, to that of **9**, and to a good approximation to that of **24**.



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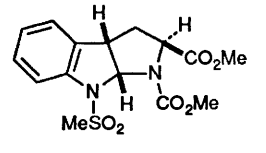

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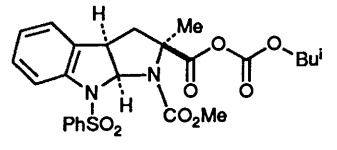

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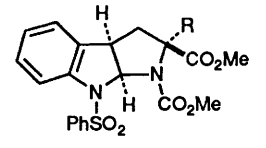

28 R = Et
29 R = Pr^i

Conclusions

The tautomeric equilibrium of **2** and **3**, taking into account alternative extreme conformations of the C-ring of both tautomers, has been examined experimentally by NMR spectroscopy and theoretically by force field calculations. Experiment and theory agree that tautomer **3** is the preferred form but not on the extent of difference. This difference of degree between theory and experiment can probably be attributed to the gas phase nature of the calculations which in turn suggests that the enhanced preference for **3** over **2** in solution is the result of increased entropy due to desolvation of the *endo* face of the molecule or of differential solvation of **2** and **3**. Clearly the experimental results have challenged the theoretical calculations to provide an adequate explanation of the system. We believe therefore, as this system is exciting, challenging and synthetically important, that further investigation is warranted. Practically, it is apparent that the balance between **2** and **3** is a fine one, affected by both the solvent and substituents. Whilst it may not be possible to tip this balance significantly in favour of **2** by simple modification of reaction conditions it should prove possible to do so by minor adaptation of the substituents. Studies in this direction in our laboratory have already provided very promising results and we hope, in the near future, to be able to describe a system for the α-alkylation of tryptophan with inversion of configuration.

* This term appears disproportionately large, possibly as the result of the imprecise nature of using partially derived Mulliken charges in a molecular mechanics calculation.

† 1 cal = 4.184 J.

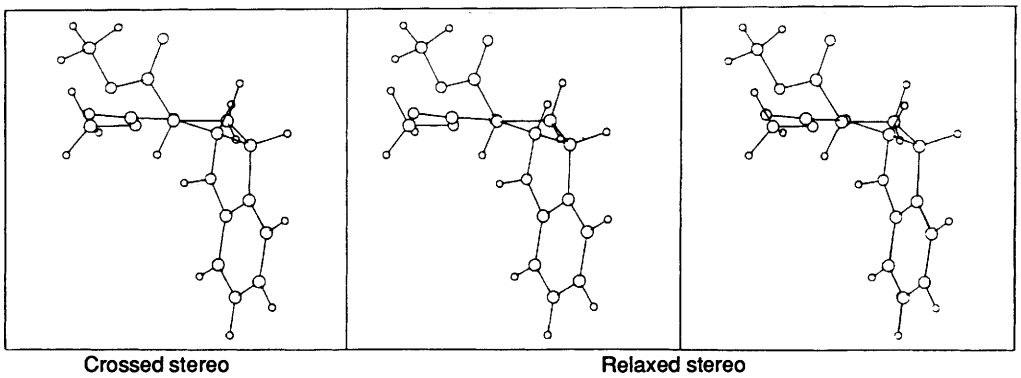

Fig. 5 C-2*endo* conformation of **2**

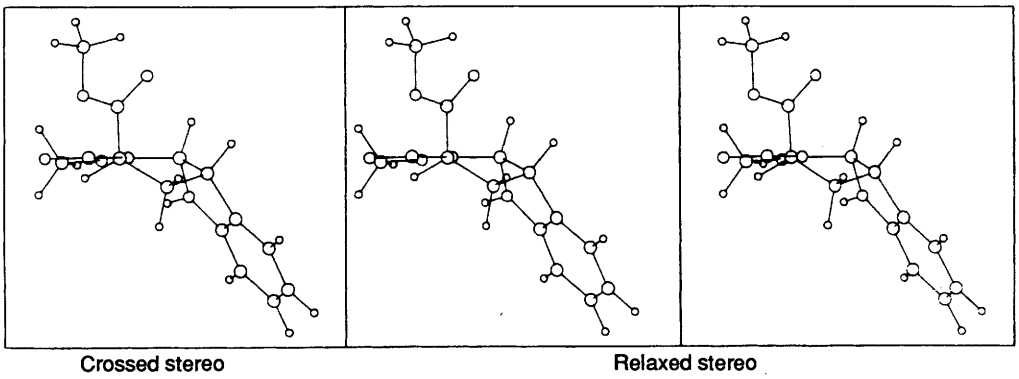

Fig. 6 C-2*exo conformation of* **2**

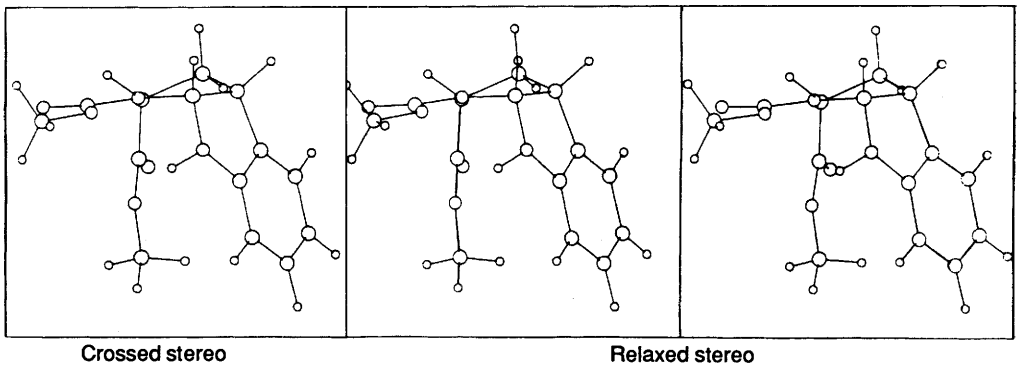

Fig. 7 C-2*endo* conformation of **3**

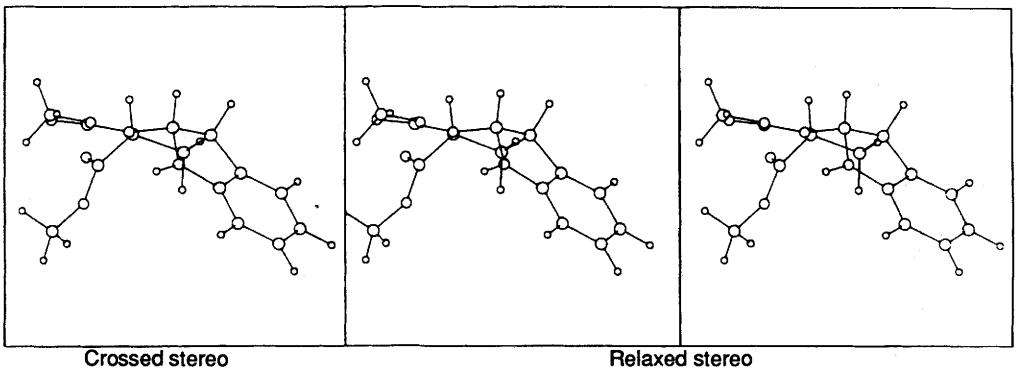

Fig. 8 C-2*exo conformation of* **3**

Experimental

General.—The general experimental details are as in Part 1[2] with the addition that 300 MHz ^{1}H NMR spectra were obtained on a Bruker AC300 instrument. *J* Values are given in Hz. Computational work was carried out on a Vax 64/20 computer.

(±)-1-(3-*Indolyl*)-2-*methoxycarbamoylpropane* **10**.—Commercial (±)-α-methyltryptohan (349.2 mg, 2.00 mmol) and sodium carbonate (264 mg) were dissolved in a two-phase system comprising water (2 cm^3) and dichloromethane (4 cm^3). This mixture was stirred vigorously at room temperature and a solution of methyl chloroformate (216 mg, 2.2 mmol) in dichloromethane (1 cm^3) added. The stirring was continued for 4 h at room temperature before the phases were allowed to separate out. After removal of the organic layer the aqueous

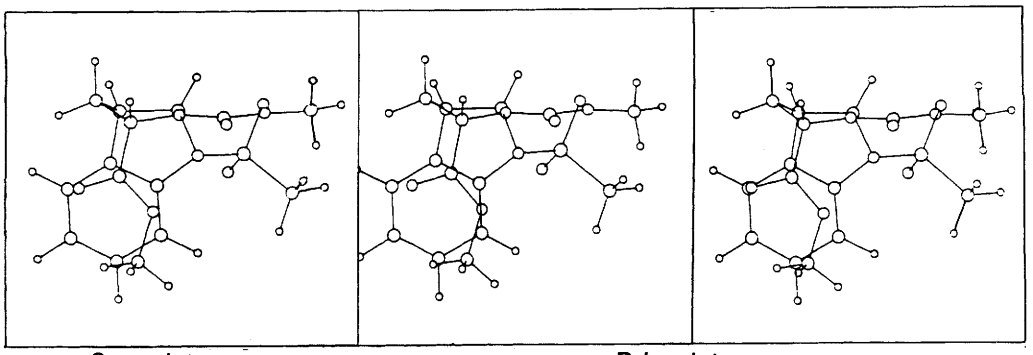

Fig. 9 Conformation of **25**

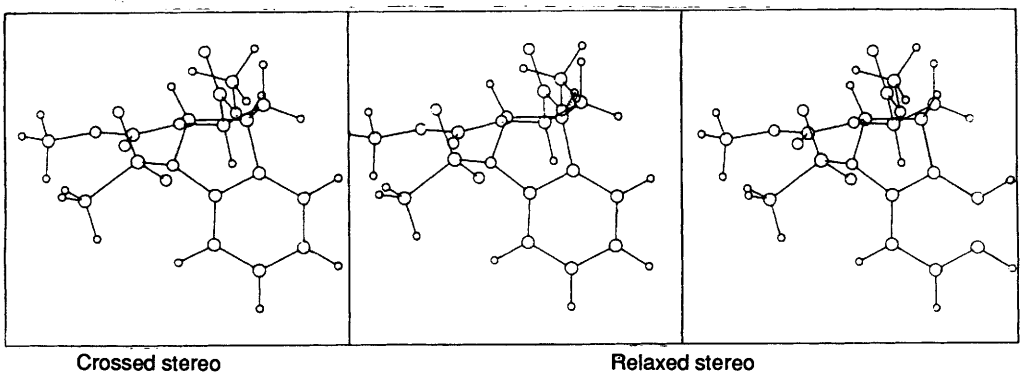

Fig. 10 Conformation of **26**

Table 3 COSMIC energy components (kcal mol^{-1})

Entry	Compound	Total energy	Coulombic	Van der Waals	Bonds	Angle	Torsion
1	2[a]	4.06	−14.09	−2.06	0.63	12.42	7.16
2	3[a]	0.62	−14.77	−5.06	0.61	12.61	7.24
3	11	4.02	−13.37	−2.41	0.61	11.87	7.32
4	12	4.14	−14.09	−1.44	0.62	12.47	6.58
5	20	9.40	−6.61	−5.73	1.12	13.18	7.44
6	23	13.12	−5.71	−3.43	1.27	13.56	7.44
7	25	5.74	−12.40	−2.57	0.74	12.80	7.18
8	26	7.09	−13.45	0.31	0.74	12.25	7.23

[a] C-2 *endo* puckered conformers.

Table 4 COSMIC energy components (kcal mol^{-1}) for alternative conformations of **2** and **3**

Entry	Compound	Coulombic	Van der Waals	Bonds	Angle	Torsion	Total energy	Total energy excluding coulombic term
1	**2** C-2 *endo* puckered	−14.09	−2.06	0.63	12.42	7.16	4.06	18.15
2	**2** C-2 *exo* puckered	−18.27	−2.31	0.65	12.74	8.12	0.93	19.20
3	**3** C-2 *endo* puckered	−14.77	−5.06	0.61	12.61	7.24	0.62	15.39
4	**3** C-2 *exo* puckered	−13.81	−2.06	0.61	12.80	7.89	5.44	19.25

Table 5 COSMIC torsion angles for alternative conformations of **2** and **3**

Compound	(H-2)-C–C-(H-3*exo*)	(H-2)-C–C-(H-3*endo*)	(H-3*exo*)-C–C-(H-3a)	(H-3*endo*)-C–C-(H-3a)	(H-3a)-C–C-(H-8 a)
3 C-2 *endo* puckered	32.9	−88.3	−36.5	84.8	18.8
3 C-2 *exo* puckered	−36.3	−156.9	26.2	146.6	−8.4
2 C-2 *endo* puckered	−157.2	−36.1	36.4	−84.9	−20.7
2 C-2 *exo* puckered	−87.8	33.3	−26.4	−147.2	4.9

phase was treated with 15% aqueous sodium carbonate (4 cm^3) and further extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give essentially pure *title compound* as a colourless glass (460 mg, 100%) which rapidly darkened on standing in air. The compound was characterised by δ_H(200 MHz) 1.15 (3 H, d, *J* 6.56, 3-Me), 2.9 (2 H, m, 1-H), 3.66 (3 H, s, CO_2Me), 4.1 (1 H, m, 2-H), 4.6 (1 H, bs, carbamate NH), 6.9–7.8 (5 H, m) and 8.2 (1 H, bs, indole NH) (Found: M^+, 232.1205. Calc. for $C_{13}H_{16}N_2O_2$: M^+, 232.1212).

(±)-*Methyl* (2R,3aR,8aS)-2-*Methyl*-8-*phenylsulfonyl*-1,2,3,-3a,8,8a-*hexahydropyrrolo*[2,3b]*indole*-1-*carboxylate* **13**.—The tryptamine derivative **10** (460 mg) was dissolved in 88% H_3PO_4 with stirring at room temperature over 16 h. The reaction mixture was then added dropwise into a vigorously stirred mixture of 15% aqueous sodium carbonate (200 cm^3) and dichloromethane (200 cm^3). The organic phase was then separated off and the aqueous phase further extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) filtered and evaporated to give crude **11** (459 mg) in admixture with starting material. This mixture was dissolved in pyridine (0.5 cm^3) at room temperature and treated with benzenesulfonyl chloride (425 mg, 2.31 mmol) and further pyridine (2 cm^3). After stirring for 3 h at room temperature the reaction mixture was diluted with water (100 cm^3) and extracted thoroughly with ethyl acetate. The extracts were washed sequentially with water and brine then dried ($MgSO_4$) and evaporated *in vacuo*. The reaction mixture (698 mg) consisted of a 4:5 ratio of **10** and **13** as judged by 200 MHz ^1H NMR spectroscopy representing a yield of 48% of **13**, overall from **10**. A sample of **13** was isolated pure by chromatography on silica gel [eluent light petroleum–ethyl acetate (1:1)]. It had m.p. 57–59 °C; δ_H(400 MHz) 0.71 (3 H, d, *J* 6.84, 2-Me), 1.84 (1 H, d, *J* 13, 3*endo*-H), 2.37 (1 H, dt, *J* 13, 8, 3*exo*-H), 3.50 (1 H, t, *J* 8, 3a-H), 3.72 (3 H, s, CO_2Me), 4.15 (1 H, m, 2-H), 6.18 (1 H, d, 8a-H) and 6.8–8.5 (9 H, m) (Found: M^+, 372.1146. Calc, for $C_{19}H_{20}N_2O_4S$: M^+, 372.1143).

Dimethyl (2S,3aR,8aS)-2-*Ethyl*-8-*phenylsulfonyl*-1,2,3,3a,8,-8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **28**.—The hexahydropyrroloindole **5** (1.00 g, 2.4 mmol) was dissolved in tetrahydrofuran (THF) (10 cm^3) and cooled to −78 °C under a nitrogen atmosphere. Lithium diisopropylamide (LDA) (2.64 cm^3 of 1 mol dm^{-3} in THF; 2.64 mmol) was added resulting in the formation of a yellow enolate which was quenched, after 10 min, by addition of ethyl iodide (0.23 cm^3, 2.9 mmol). After warming to room temperature the volatiles were removed *in vacuo* and the residue taken up in ethyl acetate (15 cm^3), the resultant solution was extracted with 1 mol dm^{-3} HCl (2 × 10 cm^3), dried ($MgSO_4$), filtered and evaporated to give the crude product (1.58 g). Recrystallisation from methanol gave the *title compound* as a white crystalline solid (1.02 g, 96%) with m.p. 130–131 °C; $[\alpha]_D$ = +94.7 (*c* = 0.55, $CHCl_3$); δ_H(300 MHz) 0.80 (3 H, t, *J* 7.3, 2-CH_2CH_3), 1.88 (2 H, m, CH_2CH_3), 2.33 (1 H, dd, *J* 13.5 and 6.05, 3*exo*-H), 2.47 (1 H, d, *J* 13.5, 3*endo*-H), 3.00 (3 H, s, 2-CO_2CH_3), 3.33 (1 H, bt, *J* 6.5, 3a-H), 3.63 (3 H, s, 1-CO_2CH_3), 6.21 (1 H, d, *J* 6.3, 8a-H) and 6.95–7.61 (9 H, m) (Found: C, 59.33; H, 5.41; N, 6.30; S, 7.21. $C_{22}H_{24}N_2O_6S$ requires: C, 59.44; H, 5.44; N, 6.30; S, 7.21%).

Dimethyl (2S,3aR,8aS)-2-(1-*Methylethyl*)-8-*phenylsulfonyl*-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]*indole*-1,2-*dicarboxylate* **29**.—A solution of **5** (3.00 g, 7.2 mmol) in THF (30 cm^3) at −78 °C, under a nitrogen atmosphere, was treated with LDA (7.92 cm^3 of 1 mol dm^{-3}, 7.9 mmol) and after 10 min with isopropyl iodide (0.86 cm^3, 8.64 mmol). After stirring for 15 h at −78 °C the reaction mixture was allowed to warm to room temperature and then worked up as for the lower homologue **28**. The crude reaction mixture (3.48 g) was purified by chromatography on silica gel [eluent light petroleum–ethyl acetate (1.8:1)] to give the *title compound* as a white crystalline solid (1.72 g, 51.3%) with m.p. 121–122 °C (MeOH); $[\alpha]_D$ = +90.1 (*c* = 0.55, $CHCl_3$); δ_H(300 MHz) 0.76 [3 H, d, *J* 6.6, 2-$CH(CH_3)CH_3$], 0.93 [3 H, d, *J* 6.8, 2-$CH(CH_3)CH_3$], 2.18 (1 H, dd, *J* 13.3 and 7.6, 3*exo*-H), 2.47 (1 H, bd, *J* 13.3, 3*endo*-H), 2.86 [1 H, m, 2-$CH(CH_3)CH_3$], 2.94 (3 H, s, 2-CO_2Me), 3.27 (1 H, bt, *J* 6.9, 3a-H), 3.67 (3 H, s, 1-CO_2Me), 6.13 (1 H, d, *J* 6.37, 8a-H) and 6.95–7.50 (9 H, m) (Found: C, 60.52; H, 5.94; N, 6.08; S, 6.92. $C_{23}H_{26}N_2O_6S$ requires: C, 60.25; H, 5.71; N, 6.11; S, 6.99%).

(αS)-α-*Ethyl*-N_b-*methoxycarbonyltryptophan Methyl Ester* **16** [*and* (αS)-1-*Benzenesulfonyl*-α-*ethyl*-N_b-*methoxycarbonyltryptophan Methyl Ester*].—The ethyltetrahydropyrroloindole derivative **28** (0.95 g, 2.1 mmol) was stirred at room temperature in trifluoroacetic acid (4 cm^3) under nitrogen for 1 h. The volatiles were removed *in vacuo* and the oily residue taken up in ethyl acetate (10 cm^3) and washed with 1 mol dm^{-3} NaOH (2 × 5 cm^3), dried and evaporated to give the essentially pure N-1 sulfonyltryptophan (*N*-1-$PhSO_2$-**16**) as an oil (0.95 g, 100%) with δ_H 0.79 (3 H, s, α-CH_2CH_3), 1.92 (1 H, m, α-CH_2CH_3), 2.53 (1 H, m, α-CH_2CH_3), 3.18 (1 H, d, *J* 14.6, β-CH_2), 3.63 (3 H, s, CO_2Me), 3.6 (3 H, s, $NHCO_2Me$), 93.74 (1 H, d, *J* 14.6, β-CH_2), 5.60 (1 H, s, NH) and 7.15–7.95 (9 H, m). This substance, without further purification, was dissolved in refluxing liquid ammonia (*ca.* 100 cm^3) and THF (3 cm^3) under nitrogen and treated portionwise with sodium metal (182 mg, 7.9 mmol) after which the reaction mixture exhibited the characteristic intense blue colour of ammonia-solvated electrons. After addition of solid ammonium chloride (5 g) the ammonia was allowed to evaporate and the residue taken up in ethyl acetate (20 cm^3) and washed with water (3 × 10 cm^3). The organic phase was dried ($MgSO_4$) and evaporated down to give the crude product (1.63 g) from which the *title compound* was isolated by crystallisation from methanol as a white crystalline solid (560 mg, 87%) with m.p. 105–107 °C; $[\alpha]_D$ = +124.0 (*c* = 0.65, $CHCl_3$); δ_H(300 MHz) 0.83 (3 H, t, *J* 7.3, α-CH_2CH_3), 2.01 (1 H, α-CH_2CH_3), 2.56 (1 H, m, α-CH_2CH_3), 3.29 (1 H, d, *J* 14.6, β-CH_2), 3.66 (3 H, s, CO_2Me), 3.69 (3 H, s, $NHCO_2Me$), 3.76 (1 H, d, *J* 14.6, β-CH_2), 5.63 (1 H, bs, α-NH), 6.90 (1 H, d, *J* 2.1, 2-H), 7.08 (1 H, dd), 7.15 (1 H, dd), 7.32 (1 H, d), 7.52 (1 H, d) and 9.02 (1 H, bs, 1-NH) (Found: C, 63.20; H, 6.73; N, 9.28. $C_{16}H_{20}N_2O_4$ requires: C, 63.14; H, 6.62; N, 9.20%).

(αS)-α-(1-*Methylethyl*)-N_b-*methoxycarbonyltryptophan Methyl Ester* **17** [*and* (αS)-1-*Benzenesulfonyl*(α(-1-*methylethyl*)-N_b-*methoxycarbonyltryptophan Methyl Ester*].—The 2-isopropylpyrrolindole **29** (1.5 g, 3.27 mmol) was converted to the N-1-sulfonyltryptophan (*N*-1-$PhSO_2$-**17**), as described for the lower homologue above, by dissolution in trifluoroacetic acid (6 cm^3) and concentration after 1 h at ambient temperature. The so-obtained ring-opened tautomer was a white foam (1.47 g, 98%) with δ_H 0.92 [3 H, d, *J* 7.0, 2-$CH(CH_3)CH_3$], 1.1 [3 H, d, *J* 6.8, 2-$CH(CH_3)CH_3$], 2.70 [1 H, m, 2-$CH(CH_3)CH_3$], 3.37 (1 H, bd, *J* 14.6, β-CH_2), 3.84 (1 H, bd, *J* 14.6, β-CH_2), 3.60 (3 H, s, CO_2Me), 3.64 (3 H, s, $NHCO_2Me$), 5.71 (1 H, bs, αN-H) and 7.17–7.93 (9 H, m). Without further purification this substance was desulfonylated by treatment with sodium (250 mg, 10.9 mmol) in liquid ammonia (*ca.* 100 cm^3) essentially as described for the lower homologue **16** above. Recrystallisation of the crude extracts (1.7 g) from methanol gave the *title product* as a white crystalline solid (913 mg, 90%) with m.p. 105–106 °C; $[\alpha]_D$ = +107.3 (*c* = 0.7, CH_2Cl_2); δ_H(300 MHz) 0.97 [3 H, d, *J* 6.9, 2-$CH(CH_3)CH_3$], 1.18 [3 H, d, *J* 6.8, 2-$CH(CH_3)CH_3$], 2.74 [1 H, m, 2-$CH(CH_3)CH_3$], 3.54 (1 H, bd, *J* 14.6, β-CH_2), 3.66 (3 H, s, CO_2Me), 3.68 (3 H, s, $NHCO_2Me$), 3.88 (1 H, bd, *J* 14.6, β-

CH_2), 5.76 (1 H, bs, αN-H), 6.89 (1 H, d, *J* 2.0, 2-H), 7.01 (1 H, t), 7.16 (1 H, t), 7.29 (1 H, d), 7.59 (1 H, d) and 8.38 (1 H, bs, 1-NH) (Found: C, 64.23; H, 6.95; N, 8.39. $C_{17}H_{22}N_2O_4$ requires: C, 64.13; H, 6.97; N, 8.80%).

Ring Closure Experiments in Trifluoroacetic Acid.—The carbamate to be studied (20 mg) was dissolved at room temperature in a 3:1 v:v mixture of trifluoroacetic acid and deuteriochloroform (0.5 cm^3) in a 5 mm diameter NMR tube. ^1H NMR spectra were recorded, at room temperature (297 K) with a 300 MHz instrument, at regular intervals until no further change was observed.

Representative Procedure for Molecular Modelling.—All structures were constructed within the 2D-build menu of the molecular modelling framework, COSMIC.[10]* An initial 3D-conformation was achieved by steepest descent minimisation (see ref. 10 for parameter sets) until the maximum derivative was less than 0.01 kcal mol^{-1}. The semi-empirical molecular orbital program MOPAC[11] (AM1, Version 5) was employed to obtain partial derived atomic charges. The conformational preference of the structure was determined by employing a fully relaxed two-bond rotation about the N1–CO_2Me and C2–CO_2Me bonds using the SPIN01 option in COSMIC. This entailed energy minimisation at 15° increments from 0–360° for both bonds while maintaining a force constant of 100 kcal mol^{-1} on the defined torsions. The lowest energy structure obtained was then re-minimised using COSMIC's Quasi Newton–Raphson algorithm until the maximum derivative was less than 0.01 kcal mol^{-1}. Partial charges were recalculated with MOPAC and applied, before final re-minimisation to determine the components of the energy.

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* COSMIC 91 includes improvements in the parametrization of the force field for hydrocarbons and conjugated systems.

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