This investigation was supported by the National Cancer Institute (1-CM-53741).

Registry No.—**1b**, 2579-67-1; **2b**, 61752-20-3; **3a**, 61752-21-4; **3a** HCl, 61752-22-5; **3b**, 61752-23-6; **4**, 61752-24-7; **4** free base, 61752-25-8; **5**, 61752-26-9; **6**, 61752-27-0; **7**, 61752-28-1; **8**, 61752-29-2; **8** free base, 61752-30-5; **9**, 61752-31-6; **10**, 61752-32-7; chloroacetic anhydride, 541-88-8; 6-(2-chloro-1-hydroxyethane)-2,11-diacetoxy-10-thoxynoraporphine, 62139-41-7.

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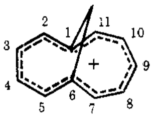
Electronic Structure of the Bicyclo[5.4.1]dodecapentaenylium Cation

Robert C. Haddon[1a]

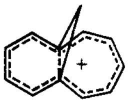
Research School of Chemistry, The Australian National University, P.O. Box 4, Canberra, A.C.T. 2600, Australia

Received December 20, 1976

The structure of the bicyclo[5.4.1]dodecapentaenylium cation (**1**) has been the subject of some discussion in the recent literature. Vogel and co-workers[1b] have formulated the ion in terms of a perturbed [11]annulenium system (**1a**), whereas Masamune and co-workers[2] have suggested a benzohomotropenylium structure (**1b**). In a timely x-ray crystallographic study, Destro, Pilati, and Simonetta[3] have concluded that **1** is quite similar to the neutral bridged [10]annulenes, on the basis of the 1–6 distance, which was found to be 2.299 Å.



1a



1b

Table I. Perturbed Bond Orders and Bond Lengths of 1,6-Methano[10]annulene (2)

Bond i–j	Torsional model[a,e] δp_{ij}	Homoaromatic interaction model[b,e] δp_{ij} (units of $\delta\beta_{16}$)	δr_{ij}[c,d]
1–2	−0.00601	−0.0631	−0.015
2–3	0.00384	0.0852	0.017
3–4	0.00433	−0.0442	−0.009

[a] Equation 2. [b] Equation 3. [c] Equation 4. $\bar{r}(2) = 1.400$ Å. [d] Reference 9. [e] Correlation coefficient for zero intercept regression analysis: 0.327 (torsional), 0.993 (homoaromatic), 0.995 (bivariate analysis).

In this communication we report a reinvestigation of the ion using the perturbational molecular orbital (PMO) theory,[4] as previously employed[5] in our general study of homoaromaticity.[6] In particular, we focus on the experimental bond lengths found for **1a** by Simonetta and co-workers.[3] In the treatment we adopt the peripheral (annulene) π-electron framework as reference system. In the presence of perturbations $\delta\beta_{kl}$ (to the resonance integrals of bonds k–l), the i–j bond order is changed by an amount δp_{ij}, where[5]

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}\, \delta\beta_{kl} \qquad (1)$$

and $\pi_{ij,kl}$ is the mutual bond polarizability.

We consider specifically two perturbations to the electronic structure of the peripheral π-electron system which might be responsible for the variations in bond length observed in the bridged annulenes.[7] In the first case we allow for the dislocations in overlap which must occur in these systems, due to the pπ orbital misalignment. Following Heilbronner and coworkers[8] we introduce this factor as a perturbation to the resonance integrals (β_{kl}), which in this treatment take the value $\beta \cos\theta_{kl}$ (where θ_{kl} is the torsional angle about the bond k–l), thus $\delta\beta_{kl} = (\cos\theta_{kl} - 1)\beta$. In the second model account is taken of the possibility of a 1–6 homoaromatic interaction[5] ($\delta\beta_{kl} = \delta\beta_{16}$, where $\delta\beta_{16}$ is in units of β). Thus from eq 1 we obtain

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}(\cos\theta_{kl} - 1) \qquad (2)$$

(torsional model)

and

$$\delta p_{ij} = \pi_{ij,16}\delta\beta_{16} \qquad (3)$$

(homoaromatic interaction model)

The results of these two perturbation schemes take slightly different forms, as the torsional angles (θ_{kl}) are directly available from crystallographic studies,[3,9] whereas the value of the homoaromatic interaction resonance integral ($\delta\beta_{16}$) is unknown (within the present context). Thus the δp_{ij} are obtained explicitly in the first case but only within a multiple of $\delta\beta_{16}$ in the second scheme. We adopt the well-known proportionality between bond lengths and bond orders[10] in the analysis (note, however, that we are considering perturbations to these quantities, rather than absolute values). Within the framework of this approximation, an increase in bond order is expected to lead to a decrease in bond length. We define

$$\delta r_{ij} = \bar{r} - r_{ij} \qquad (4)$$

where $\bar{r}$ is the mean peripheral bond length. In such circumstance short bonds have positive δr_{ij}, and if the correlation between bond orders and bond lengths is valid there should be a direct proportionality between the δp_{ij} and δr_{ij}.

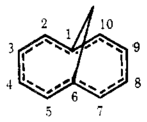
As a test of the scheme, we first analyze the x-ray crystallographic structure[9] of 1,6-methano[10]annulene (**2**)[11] in terms of the two perturbations discussed above. The results are presented in Table I, and it is immediately apparent that there is a strong correlation between the perturbed bond orders of the homoaromatic interaction model and the experimentally

Table II. Perturbed Bond Orders and Bond Lengths of the 1,6-Methano[11]annulenium Cation (1)

Bond i–j	Torsional model[a,e] δp_{ij}	Homoaromatic interaction model[b,e] δp_{ij} (units of $\delta\beta_{16}$)	δr_{ij}[c,d]
3–4	0.00805	−0.0342	0.008
4–5	0.00020	0.0819	0.027
5–6	−0.01246	−0.0374	−0.030
6–7	0.01677	−0.0501	0.013
7–8	−0.01660	0.0286	−0.031
8–9	0.00807	−0.0059	0.018

[a] Equation 2. [b] Equation 3. [c] Equation 4. $\bar{r}(1) = 1.397$ Å. [d] Reference 3. [e] Correlation coefficient for zero intercept regression analysis: 0.659 (torsional), 0.050 (homoaromatic), 0.959 (bivariate analysis).

observed variations in bond length. A bivariate regression analysis shows that the agreement is slightly improved if the torsional perturbations are also included. Nevertheless the results indicate that the small variations in the perimeter bond lengths of **2** originate primarily from the transannular 1–6 homoaromatic interaction.



2

In Table II we report the results of a similar analysis on the 1,6-methano[11]annulenium cation (**1**), and it is surprising to find that the homoaromatic interaction model, which was successful in the previous case, here completely fails (by itself) to reproduce the variations in bond lengths observed[3] for this molecule. On the other hand, reference to Table II shows that the torsional model performs quite well in this case; in particular the signs of the variations are all correctly reproduced. In fact, only the shortened bonds (positive δp_{ij} and δr_{ij}) are incorrectly ordered, and of these the most seriously in error appear to be 4–5 and 6–7, which are calculated to have increases in bond order which are too small and too large, respectively. Interestingly, the largest corrections to the bond orders from the homoaromatic interaction model occur for just these two bonds, and are of the correct sign to bring the perturbed bond orders into line with the experimental results. It would therefore seem that the slight misalignment of the pπ orbitals around the periphery of **1** is mainly responsible for the variations in bond length, together with a smaller, but important, contribution from the 1–6 homoaromatic interaction.

Why then is the 1–6 homoaromatic interaction more important for **2** than **1**? Of a number of possible explanations the most likely seems to be a reduction in the 1–6 overlap for **1** (note that the transannual interaction is calculated[5] to be slightly more favorable in **2**). Although the 1–6 distance is slightly longer in **1** (2.299 Å)[3] than in **2** (2.25 Å),[9] the variation in transannular overlap probably arises from the differing angles of the pπ orbitals at the 1 and 6 positions. We note that the dihedral angles of the bonds to the 1,6 atoms are 34.0° in **2**,[8,9] but only 24.9 and 16.3 in **1**.[3] Thus in the case of **2** the pπ orbitals at these positions should be bent further under the ring (anti to the bridge), and therefore will overlap more effectively (note that in **2** these orbitals lie in a symmetry plane and therefore point directly toward one another). In addition the "elastic ribbon principle", first enunciated by Heilbronner and co-workers,[8] may well be more effective in improving the peripheral overlap (at the expense of the transannular interactions) in a carbocation where the necessary polarization functions will be more accessible than in a neutral molecule.

Table III. Perturbed Charge Densities of the 1,6-Methano[11]annulenium Cation (1)

Position i	Torsional model[a] $\delta\xi_i$	Homoaromatic interaction model[b] $\delta\xi_i$ (units of $\delta\beta_{16}$)
4	−0.00471	−0.0572
5	0.00641	−0.0917
6	0.00025	−0.0131
7	−0.00183	0.1132
8	0.00838	−0.0062
9	−0.01347	0.1099

[a] Equation 6. [b] Equation 7.

Finally we consider the effects of the above perturbations ($\delta\beta_{kl}$) on the charge densities (ξ_i) of **1**. The perturbed charge densities $\delta\xi_i$ take the form[5]

$$\delta\xi_i = -\sum_{kl} \pi_{i,kl}\,\delta\beta_{kl} \tag{5}$$

where $\pi_{i,kl}$ is the atom-bond polarizability. Note that the $\delta\xi_i$ (unlike electron densities) are positive for increased cationic character (and vice versa). Thus

$$\delta\xi_i = -\sum_{kl} \pi_{i,kl}\,(\cos\theta_{kl} - 1) \tag{6}$$

(torsional model)

and

$$\delta\beta_i = -\pi_{i,16}\,\delta\beta_{16} \tag{7}$$

(homoaromatic interaction model)

The results of this analysis are presented in Table III. Vogel and co-workers[12] have drawn attention to the sensitivity of the ^{13}C NMR chemical shifts in the bridged annulenes to stereochemical factors (as against electronic effects). It is therefore not without misgivings that we compare our perturbed charge densities with the ^{13}C NMR chemical shifts observed for **1** by Masamune and co-workers.[2] Normally, of course (in the absence of nonplanarity and variations in hybridization), ^{13}C NMR chemical shifts can be used to obtain quite detailed information on π-electron charge distributions.[13] Nevertheless, it is clear that the perturbed charge densities derived from the homoaromatic interaction model bear a strong resemblance to the interpretation of the ^{13}C NMR chemical shifts of the ion given by Masamune and co-workers,[2] that is, transfer of electron density to positions 4(3), 5(2), and 8(10), with excess positive charge located at 7(11) and 9. The torsional perturbations appears to have little influence on the charge densities.

Acceptance of these data, of course, requires a dichotomy in the behavior of the bond orders and charge densities of **1**, the former depending mainly on the torsional angles, with the latter apparently being determined by the 1–6 homoaromatic interaction. There are at least three possible explanations for this divergence. (1) The ^{13}C NMR chemical shifts in **1** are not (primarily) determined by charge densities, and the agreement with the homoaromatic interaction model is purely fortuitous. (2) Nontransferability of parameters, that is, distinct properties require the consideration of different perturbations, to which they are especially sensitive. (3) The molecular structure of **1** is different in the solution[2] and solid[3] states. In this connection it is interesting to note that Vogel[1] has drawn attention to the similarity of the UV spectra observed for **1** and the benzotropenylium cation (where the 1–6 interaction is, of course, well developed).

Perhaps more than anything, the results of this study highlight the complex interplay of perturbations which determine the electronic structure of the bridged annulenes. Similar conclusions have been drawn by other authors.[8,14]

Registry No.—1, 29534-58-5; 2, 2443-46-1.

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(7) Note that the inductive effect of the bridge group cannot affect the bond orders of 2 ($\pi_{i,kl} \equiv 0$ for alternant hydrocarbons). Even for 1 none of the properties examined in this study showed any obvious relationship to inductive perturbations by the bridge[8] (as calculated[5] via the quantities $\pi_{i,k}$ and $\pi_{i,kl}$).

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Efficient Preparation of N^{α}-Formylamino Acid *tert*-Butyl Esters

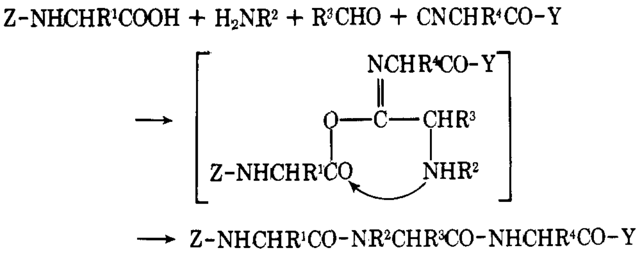
Michinori Waki and Johannes Meienhofer*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received December 30, 1976

The formyl group has been a very useful amino-protecting group in peptide synthesis,[1] and could serve in combination with the selectively removable *tert*-butyl ester group in synthesizing suitably protected trifunctional amino acid derivatives. This study has been concerned with the development of an efficient procedure for preparing N^{α}-formylamino acid *tert*-butyl esters with minimal or no racemization. These compounds can be readily converted into isocyano acid *tert*-butyl esters required as one of the starting materials in four-component condensations (FCC). The FCC method of Ugi et al.[2] offers a unique and interesting new approach to peptide synthesis. In this reaction a carboxylic acid, an amine, and an aldehyde are combined with an isonitrile, such as an isocyano acid ester, to produce a tripeptide (Scheme I). Several known isocyano acid methyl (Y, OCH_3) and ethyl (Y, OC_2H_5) esters have been used in four-component condensations,[3] but *tert*-butyl isocyanoacetate[4-6] is the only known *tert*-butyl ester [Y, $C(CH_3)_3$] of an α-isocyano acid. These esters may be prepared by dehydration of intermediate N^{α}-formylamino acid esters.

Scheme I



Z = NH_2 protecting group
R^1, R^4 = amino acid side chain
R^2, R^3 = alkyl, aryl
Y = COOH protecting group

Known procedures for the preparation of N^{α}-formylamino acids proved to be unsatisfactory for producing their respective *tert*-butyl esters. The synthetic route to the preparation of N^{α}-formylglycine *tert*-butyl ester by treatment of *tert*-butyl chloroacetate with formamide[6] is not applicable to optically active amino acids without racemate resolution. Attempts at preparing *tert*-butyl esters of N^{α}-formylamino acids by the acid-catalyzed isobutylene procedure[7] provided the desired products, but only in very low yields. Standard N^{α}-formylation of amino acids or esters by formic acid and acetic anhydride[8] was incompatible with the *tert*-butyl ester group. However, the use of dicyclohexylcarbodiimide for the preparation of N^{α}-formylamino acid benzyl esters, reported by Thomas,[9] offered a route compatible with the *tert*-butyl protecting groups. We wish to describe a modified procedure for the efficient preparation of N^{α}-formylamino acid *tert*-butyl esters in high yields using formic anhydride[10] in pyridine.

Thus, dropwise addition of a preformed mixture consisting of formic acid (4 equiv) and dicyclohexylcarbodiimide (2 equiv) in chloroform at 0 °C to a solution of leucine *tert*-butyl ester in pyridine produced N^{α}-formylleucine *tert*-butyl ester (2) in 87% yield after purification by silica gel column chromatography, which removed a small amount of the side product 1,3-dicyclohexyl-1′,3′-diformylurea. The absence of racemized product was ascertained by converting **2** into N^{α}-formylleucine by treatment with trifluoroacetic acid and comparison of the product with an authentic sample[11] obtained by an independent procedure.[8] Other compounds prepared by our procedure are listed in Table IA.

The use of equivalent amounts or smaller excesses of reagents, i.e., 2 or 3 equiv of formic acid and 1 or 1.5 equiv of dicyclohexylcarbodiimide, resulted in considerably lower yields of **2** (28 or 57%, respectively). Attempts to prepare compound **2** by the isobutylene method[7] afforded the product in unacceptably low yields (17%).

The isocyano acid *tert*-butyl esters **5** and **6** were obtained from **1** and **2**, respectively, by dehydration with phosgene[3,13] followed by silica gel column chromatography in overall yields of 84 and 85% based on the starting amino acid *tert*-butyl esters.

Experimental Section

Amino acid *tert*-butyl esters were purchased from Bachem Inc., Marina Del Rey, Calif. Ester hydrochlorides were converted into free amines prior to use.[14] All optically active amino acids were of the L configuration.

***N*-Formylglycine *tert*-Butyl Ester (1).** A 2 M solution of formic acid in $CHCl_3$ (80 mL) was added dropwise with stirring and ice-bath cooling to a solution of dicyclohexylcarbodiimide (16.51 g, 80 mmol) in $CHCl_3$ (100 mL). The mixture was further stirred for 5 min, and then added with stirring over a period of 30 min into an ice-cold solution of glycine *tert*-butyl ester (5.25 g, 40 mmol) in pyridine (100