Table I

Compound	Solvent	$^1J_{^{15}NH}$ (Hz)
$CH_3CONHCH_3$	Pure	93.0
$CH_3CH_2CONHCH_3$	Pure	92.9
$(CH_3)_2CHCONHCH_3$	Pure	92.7
$(CH_3)_3CCONHCH_3$	CCl_4	92.3
$CH_3CONHCH_2COOCH_3$	Acetone	93.5
$CH_3CONHCH(C_2H_5)COOCH_3$	Acetone	92.6
$CH_3CONHCH(i\text{-}Pr)COOCH_3$	Acetone	92.9

Figure 2. AISEFT spectrum of *N*-methylacetamide (^{15}N being in natural abundance) with ^{15}N satellites corresponding to $^1J_{NH}$. Note the smallness of the residual peak corresponding to molecules containing ^{14}N.

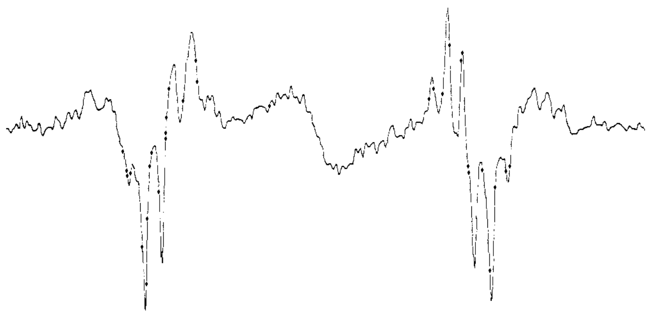

Figure 3. AISEFT spectrum of *N*-methylacetamide with irradiation frequency shifted from ^{15}N resonance. Lines down correspond to the normal undecoupled satellites. The other lines are due to incomplete decoupling and, according to the theory,[6] they appear on each side of the undecoupled peaks.

I. One notices that $^1J_{NH}$ is almost independent on the substitution, (ca. 92–93 Hz) provided that the respective position of N—H and C═O is the same. All these molecules are indeed in the trans conformation.[3,4] (The cis isomer of *N*-methylformamide is in too weak a proportion to enable the determination of the corresponding coupling.) Formamide, however, presents obviously the two arrangements and the cis coupling is seen to be smaller than the trans coupling. This is in agreement with other results obtained from ^{15}N enriched molecules.[4,5]

Another interesting feature of this method lies in the possibility to determine the nitrogen resonance frequency. A small shift of the ^{15}N frequency actually results in the appearance of an off-resonance satellite spectrum together with the normal satellite spectrum. A typical result is shown in Figure 3 for *N*-methylacetamide. It is possible to relate the observed splittings of the off-resonance spectrum to the difference between the irradiation frequency and the true ^{15}N resonance frequency.[6] Consequently two experiments carried out at two different frequencies are sufficient to obtain the ^{15}N chemical shift. For *N*-methylacetamide, we have found 80.881, 284 MHz relative to TMS resonance (the TMS resonance frequency is 90.001, 537 MHz).

In conclusion, two distinct advantages of these experiments have to be pointed out. In one hand, ^{15}N parameters are obtained with proton sensitivity (for a neat liquid in a 5-mm sample, 200 scans are sufficient to observe ^{15}N satellites). On the other hand, the elimination of strong lines arising from molecules containing ^{14}N authorizes a great number of scans without saturating the computer memories.

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A Molecular Orbital Study of the Electronic Structure and Spectrum of Rectangular (D_{2h}) Cyclobutadiene

Sir:

Cyclobutadiene (**1**) was first generated as a transient intermediate by Pettit and coworkers[1] in 1965; subsequently they went on to show that the room temperature chemistry of **1**[2] and its vicinal diphenyl derivatives[3] are characteristic of highly reactive singlet dienes.[4] More recently,[6] however, ir studies of low temperature matrix isolated cyclobutadiene, have been interpreted in terms of a square (D_{4h}) structure for **1**. This result is in apparent contradiction to the earlier work (*vide postea*), and for this reason we have employed the semiempirical MINDO/3 method[7] and *ab initio* molecular orbital theory at the 4-31G level[8] together with the equations of motion (EOM) method[9,10] in the hope of throwing further light on the nature of **1**.

In the simple Huckel MO (HMO) picture of square cyclobutadiene (see Figure 1a), two π-electrons occupy a bonding orbital (π_1) while the remaining two π-electrons are placed in doubly degenerate nonbonding molecular orbitals (π_2, π_3). On distortion of the carbon framework to a rectangular geometry, the degeneracy of π_2 and π_3 is lifted and a closed shell ground state results (Figure 1b).

The electronic states which arise from the open shell electronic configuration of D_{4h} cyclobutadiene are not well described by single determinant molecular orbital theory and, in general, at least two determinants are required to give wave functions of the proper spin and spatial symmetry in such cases.[11a] For this reason we report only our calculations for the rectangular (D_{2h}) geometry at this time; complete results will be presented elsewhere when we have completed our search of the potential hypersurface. However, it is worth noting that the ^1A_g state (Figure 1b) of rectangular cyclobutadiene is the lowest point which we have so far located on the potential hypersurface, (using the MINDO/3 and EOM methods) and lies lower in energy than the square triplet (Figure 1a) when calculated with the MINDO/3 (half-electron scheme) or *ab initio* 4-31G (RHF and UHF) methods.[11b]

The calculated equilibrium geometries for D_{2h} cyclobutadiene are given in Table I. As expected, a large alternation of bond lengths is found, in agreement with previous theoretical treatments[12] and with X-ray structural analyses of sterically crowded cyclobutadienes.[13] The term antiaromatic[14,15] is clearly justified as the degree of bond alternation

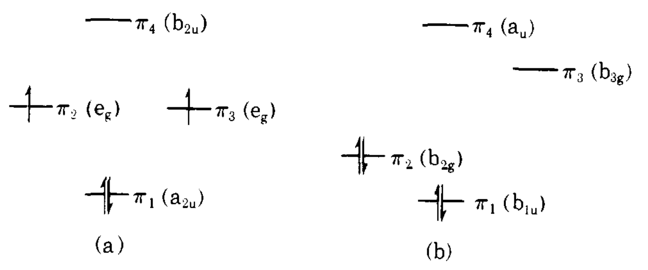
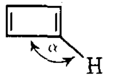


Figure 1. (a) One component of the triplet state ($^3A_{2g}$) of square (D_{4h}) cyclobutadiene (the lowest state found by MINDO/3, *ab initio*, and EOM calculations for this symmetry). (b) The ground singlet state (^1A_g) of rectangular (D_{2h}) cyclobutadiene (the ground state found by MINDO/3, and EOM calculations).

Table I. Equilibrium Geometries Calculated for the ^1A_g Rectangular Ground State of Cyclobutadiene



Method	C=C (Å)	C–C (Å)	C–H (Å)	α (deg)
MINDO/3	1.342	1.535	1.095	131.7
STO-3G	1.313	1.569	1.081	133.8
4-31G	1.323	1.581	1.067	134.7

Table II. Electronic Transitions from the ^1A_g Rectangular Ground State of Cyclobutadiene Calculated by the EOM Method

Excited state	Transition energy (eV)	Oscillator strength[a]
$^3B_{1g}$	1.12	sdf
$^1B_{1g}$	3.67	df
^1A_g	5.36	df
$^3B_{1u}$	6.11	sf
$^3B_{2u}$	6.27	sf
$^1B_{1u}$	6.67	3.30×10^{-4}
$^3B_{1u}$	6.92	sf
$^1B_{1u}$	7.92	3.55×10^{-2}
$^3B_{2g}$	8.99	sdf
$^1B_{2g}$	9.15	df
$^3B_{3u}$	9.39	sf
$^1B_{3u}$	9.75	$\sim 10^{-8}$
$^1B_{2u}$	10.19	6.27×10^{-1}
^3A_u	10.22	sdf

[a] Key: df = dipole forbidden; sf = spin forbidden; sdf = spin and dipole forbidden.

is greater than that found in nonaromatic acyclic analogs (for example, the differences in carbon-carbon bond lengths of *trans*-butadiene are calculated to be: $\Delta r = 0.134$ Å (MINDO/3) and $\Delta r = 0.171$ Å (STO-2G);[16] experimental,[17] $\Delta r = 0.121$ Å).

We have also calculated the electronic spectrum of rectangular cyclobutadiene by the EOM method, using the 4-31G basis. In the EOM calculations we have included all particle-hole pairs arising from the excitation of electrons from the two highest energy hole states to the 16 lowest energy particle states. The EOM study includes the effects of both single particle-hole and double particle-hole interactions. Further details of the EOM approach to the calculation of excitation properties of molecules may be found in papers by Williams and Poppinger[9] and McKoy and coworkers.[10] Previous calculations[9,10] by the EOM method have provided very good results for the excitation energies and oscillator strengths of a range of organic molecules, including π-electron systems.

The calculations were carried out at the geometry obtained from the 4-31G optimization given in Table I. The results of the calculations are given in Table II and include all the transitions which were found below 11 eV. So far as we can tell, the energies found for the allowed transitions in the present work are in good agreement with an earlier π-electron treatment by Allinger and Tai.[18]

In spite of the very considerable effort made to observe the electronic spectrum of matrix-isolated cyclobutadiene, it is not clear whether the species under observation is square or rectangular, or if indeed the observed bands correspond to "free" cyclobutadiene.[19] There is a growing body of evidence from ir studies, which indicates that the low-temperature matrix-isolated form of cyclobutadiene is in fact square.[6] Furthermore, this is not necessarily in disagreement with the many theoretical calculations[12] (including our own), which predict that the ground state of cyclobutadiene should be a rectangular singlet, for, as Dewar[12c] has pointed out, the conditions of formation may lead exclusively to the production of the metastable square triplet form, which, at very low temperature, may have insufficient vibrational energy to allow an intersystem crossing. Nevertheless, it is the purpose of this communication to point out that the single band, which by consensus has been ascribed to cyclobutadiene,[19] could be assigned to a transition from the rectangular ^1A_g ground state of cyclobutadiene to the first $^1B_{1g}$ state ($\pi_2 \rightarrow \pi_3$ in Figure 1b), the energy of which we calculate to be 3.67 eV. The experimental band in question was found at 301 nm (4.12 eV) by Maier and Hoppe[20] and in the range of 300-305 nm (4.06-4.13 eV) by Masamune and coworkers.[21] In the absence of more detailed information on the electronic spectrum the assignment must be regarded as tentative in the extreme, depending as it does on vibronic coupling (b_{2u} or b_{3u} vibrations) to overcome the dipole selection rule;[22] clearly, however, our present knowledge of the electronic spectrum of cyclobutadiene does not rule out the possibility of a rectangular singlet ground state.

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Polyamide Supports for Polypeptide Synthesis

Sir:

We report the preparation and use in peptide synthesis of a polyamide resin specifically designed to overcome problems inherent in the use of styrene-based polymers. The principles guiding the design of this resin have been described previously,[1] as have earlier experiments based on modification of commercial polyacrylamide.[2] In the synthesis of the stringent test sequence described below, these resins have given results clearly superior to those obtained elsewhere using the customary polystyrene support.

The cross-linked polydimethylacrylamide resin was prepared by persulfate-initiated emulsion copolymerization of a mixture of monomer, cross-linking agent, and functionalizing agent. Solutions containing freshly distilled dimethylacrylamide (5.47 g), *N,N'*-bisacryloylethylenediamine (1.1 g),[3] and ammonium persulfate (0.6 g) in water (50 ml), and cellulose acetate butyrate (3.3 g) and *N-tert*-butoxycarbonyl-β-alanyl-*N'*-acryloylhexamethylenediamine (1.35 g) in 1,2-dichloroethane (100 ml) were mixed at 52° under nitrogen and stirred at 500 rpm for 4.25 hr. The insoluble, washed resin was largely beaded but contained some amorphous polymer. The β-alanine content was 0.33 mmol/g. The resin swelled in dimethylformamide and acetic acid to approximately ten times its dry bed volume, rather more in water, but very much less in methylene chloride and other less polar organic solvents. These properties are the reverse of those of polystyrene based resins. Utility of the new resin in solid phase peptide synthesis is illustrated[4] with the decapeptide sequence residues 65–74 of acyl carrier protein. This difficult sequence has been studied previously in great detail on polystyrene,[5] but no satisfactory synthesis has hitherto been described.

The synthesis was initiated by cleavage of the butoxycarbonyl group and addition of a spacer-internal reference BOC-amino acid (leucine) as its symmetrical anhydride. The first amino acid of the sequence proper (glycine) was added as the substituted benzyl ester-activated ester derivative, Boc-Gly-$OCH_2C_6H_4CH_2CH_2COOC_6H_2Cl_3$ (2,4,5), simultaneously incorporating a labile peptide-polymer linkage. Subsequent amino acids were added as symmetrical anhydrides[6] or *p*-nitrophenyl esters (asparagine and glutamine). The side chains of aspartic acid and tyrosine were protected as the benzyl ester and 2,6-dichlorobenzyl ether,[7] respectively. One full synthetic cycle contained the following steps: (1) *t*-AmOH, 5 × 2 min; (2) AcOH, 5 × 2 min; (3) 1 *N* HCl-AcOH, 1 × 5 min, 1 × 25 min; (4) AcOH, 5 × 2 min; (5) *t*-AmOH, 5 × 2 min; (6) DMF, 10 × 2 min; (7) 10% NEt_3-DMF, 3 × 2 min; (8) DMF, 5 × 2 min; (9) coupling, sixfold excess of BOC-amino acid anhydride, DMF, 1 × 120 min; (10) DMF, 5 × 2 min. For activated ester couplings, steps 9 and 10 were replaced by: (9a) sixfold excess of 1-hydroxybenzotriazole, DMF, 1 × 5 min; (10a) DMF, 3 × 2 min; (11) coupling, sixfold excess of BOC-amino acid *p*-nitrophenyl ester, sixfold excess of 1-hydroxybenzotriazole, DMF, 1 × 240 min; (12) DMF, 5 × 2 min. Qualitative ninhydrin tests[8] for residual amine were performed during coupling steps 9 or 11 and compared with the fully deprotected resin at step 8. In all cases negative results were obtained after the reaction times indicated. Amino acid incorporations were estimated by hydrolysis of resin samples and amino acid analysis. The results are given in Figure 1 together with those obtained elsewhere[5] on polystyrene.

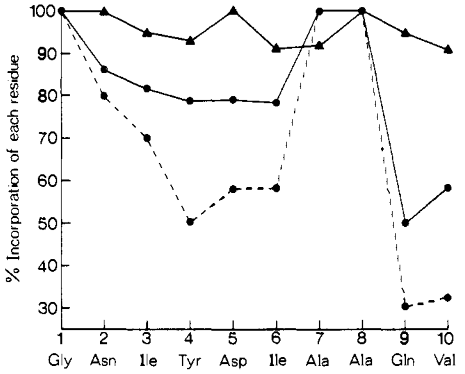

Figure 1. Amino acid incorporation during the solid-phase synthesis of acyl carrier protein, residues 65–74: ●----●, on polystyrene by an essentially standard procedure;[5] ●—● on polystyrene using double acylation and other modifications;[5] ▲—▲, present work on polydimethylacrylamide.

Eighty-eight percent of the peptide chains were retained on the final resin, an average loss of 1.4% per cycle due to acidic cleavage of the benzyl ester in agreement with the results of Gutte and Merrifield.[9] The yield of peptide-polymer from 1 g of starting resin (not taking into account the 23 analytical samples removed during the course of the synthesis) was 1.27 g (theory 1.50 g). Cleavage of the peptide-resin (190 mg) with liquid HF in the presence of anisole for 1 hr at 0° gave40.8 mg of 0.1 *M* NH_4OH soluble product (theory 39.7 mg), actual peptide content 33.3 μmol (found: Asp, 2.11; Glu, 0.99; Gly, 1.10; Ala, 1.99; Val, 0.96; Ile, 1.96; Tyr, 0.90).[10] Chromatography of an aliquot equivalent to 15.6 μM of this material on diethylaminoethylcellulose DE-52 using a linear gradient of 0.01–0.5 *M* ammonium bicarbonate, pH 8.1, gave the elution profile shown in Figure 2. Recovery of the main peak gave 7.48 μmol of peptide (48%) (found: Asp, 2.06; Glu, 1.02; Gly, 1.02; Ala, 1.97; Val, 0.97; Ile, 1.95; Tyr, 1.02). One-fifth of this material was rechromatographed under the same conditions and gave a single peak containing 0.82 μmol of peptide (55% recovery)[11] (found: Asp, 1.98; Glu, 1.03; Gly, 1.03; Ala, 1.98; Val, 1.00; Ile, 1.92; Tyr, 1.06). A single ninhydrin-reacting spot R_{Asp} 0.19 was obtained on electrophoresis at pH 6.5.

We draw attention to the following points relating to the use of the new solid support. (1) All the reactions are carried out in highly polar organic media in which both the peptide and polymer chains should be fully solvated.[1] (2) The coupling reactions appear to be very fast and a negative ninhydrin reaction is commonly obtained within a few minutes of the start. (3) Active ester couplings appear to be very sensitive to the presence of traces of formic acid which cause irreversible chain termination. Caution should therefore be exercised in the use of HCl-formic acid for deprotection.[12] We are now examining the use of dimethylacet-